0163-4984/(Online) 1559-0720/07/117(1–3)–039 $30.00

Role of Zinc in Regulation of Arterial Blood Pressure and in the Etiopathogenesis of Arterial Hypertension

SŁAWOMIR TUBEK

Faculty of Physical Education and Physiotherapy, Institute of Technology, Opole, and Clinic of Cardiology, Medical Academy, Wrocław, Prószkowska Str. 70, 45-758 Opole, Poland (slawomir.tubek@hipokrates.org)

Received June 9, 2006; Accepted August 14, 2006

ABSTRACT

Increased gastrointestinal absorption and urinary excretion of zinc has been confirmed in experimental and clinical studies on primary arterial hypertension as a result from changes of intracellular and extracellular zinc content. In arterial hypertension, the levels of zinc in serum, lymphocyte, and bone decrease while increasing in heart, erythrocytes, kidney, liver, suprarenal glands and spleen. These changes result in the loss of zinc homeostasis that leads to various degrees of deficiency, not entirely compensated by nutritional factors or increased absorption in the gastrointestinal tract. Loss of zinc homeostasis can be both cause and effect of high blood pressure. In the present review, the role of zinc metabolism changes and its mechanisms in arterial hypertension are discussed.

Index entries: Zinc; blood pressure; arterial hypertension.

INTRODUCTION

Changes in the distribution of zinc between the extracellular and intracellular spaces have been confirmed in arterial hypertension. To date, however, the significance of such changes is still mostly unknown. Zinc is involved in organic changes that develop in patients with hypertension and its deficit is known to reduce the response to hypotensive factors. Zinc

*Author to whom all correspondence and reprint requests should be addressed.

is also known to exert a protective effect against the evolution of arterial hypertension resulting from exposure to heavy metals.

Clinical and laboratory data suggest that zinc participates in blood pressure regulation and in the pathogenesis of hypertension. Evidence includes the negative correlation between arterial blood pressure and zinc content in serum and higher zinc concentration in the red blood cells in patients suffering from primary arterial hypertension and in subjects with type A personality, who are at risk of circulatory system diseases *(1,2).* Higher zinc levels in erythrocytes and heart muscle have been found in a strain of spontaneously hypertensive rats (SHRs) *(1–5).* All of these observations point out that the influence of zinc on the regulation of arterial blood pressure is not a simple process, but one that involves several systems at different physiological levels.

Zinc exerts an inhibiting effect on the ATP-dependent calcium pump that catalyzes the outpour of calcium ions from the cell *(6).* An excess of zinc inside the cell could lead to a rise of the free Ca^{2+} level in the smooth muscular layer of vessels, causing an increase of the arterial wall tension. Reduced activity of Ca^{+2}ATP-ase was found in erythrocytes of SHRs. Zinc also facilitates the release of calcium from the sarcoplasmic and endoplasmic reticules *(3).* Furthermore, the inhibition of 1,4,5-triphosphoinositol-5-phosphatase activity ($InsP_3$) by zinc was also demonstrated *(7).* Such an inhibiting effect could cause accumulation of $InsP_3$ and increased release of intracellular calcium, leading to increases of the arterial muscular layer tension and the proliferation of smooth muscle cells often found in the arteries of SHRs *(3,4,8).* On the other hand, extracellular zinc produces a blocking effect on the calcium channel *(9).*

The zinc content in human erythrocytes and in the erythrocytes, spleen, and liver of mice is genetically determined. This evidence supports the fact that diffrences in zinc content in tissues between SHRs and Wistar–Kyoto rats (WKY) also depend on genetic factors. In SHRs, higher concentrations of zinc in the heart, erythrocytes, kidneys, liver, suprarenal glands, and spleen were observed. Except for the last three, these differences were statistically significant, suggesting a general tendency to increased zinc intracellular content in SHRs in comparison with WKY rats. In extracellular space, the zinc concentrations were practically the same, although the zinc content in bones was lower in SHRs in comparison to WKY rats *(3,4,10,11).* It can be assumed that there is a faulty mechanism or mechanisms that regulate the intracellular zinc concentration in SHRs.

Increases of intracellular zinc were observed in young SHRs, in which signs of heart muscle hypertrophy appeared as early as the prehypertensive period *(12,13).* The induction of hypertension in Wistar rats by DOCA + sodium chloride resulted in heart muscle hypertrophy, but the elevation of zinc was insignificant *(4).* In the sodium-sensitive Dahl rats strain, large sodium intakes caused a significant rise of zinc in the heart muscle after the development of aterial hypertension *(14).*

The zinc concentrations in the serum of SHRs were higher than in those with nephrogenic hypertension (RH) or normotensive (NT) rats, which did not show significant differences in their serum zinc *(15).*

In Sprague–Dawley rats, nutritional zinc deficit results in lowering of the systolic arterial blood pressure and the levels of angiotensin-converting enzyme activity (ACE) in serum *(16).* It is well known that drugs ihibiting ACE lower arterial blood pressure, so it can be assumed that this is related to zinc deficiency. This hypothesis would explain the observed direct correlation between high nutritional zinc intake and incidence of chronic hypertensive disease *(16–18).* In another study, a zinc deficit was found to result in the reduction of the vasodilatation reaction to bradykinin and prostacycline, which probably results from impairment of their receptor sites *(19).*

In these studies, the decrease of activity of ACE in serum was accompanied by a rise of its activity in the aorta wall, but its activity in lungs remained unchanged. The rennin activity in serum did not change or showed insignificant increases. In vitro studies revealed a significantly higher activity of ACE in zinc-deficient rats that were administered zinc directly into the bloodstream. Such an observation suggests that although zinc deficient, the ACE synthesis intensifies and so does the total ACE concentration in serum; yet, a large number of enzyme molecules show reduced activity or are totally inactive *(16).* Because administration of zinc to a control group of normally fed rats also elevated the activity of ACE, it can be assumed that there is a pool of inactive ACE molecules in the blood; thus, zinc might be one of the factors involved in the feedback mechanism that controls the activity of ACE in serum *(16).*

In in vitro studies, zinc intensifies norepinephrine-induced vasopression. Yet, such a phenomenon, observed in SHRs, did not occur in normotensive WKY rats *(4).* Intensified dopamine release from pheochromocytoma cells of rats being under the influence of zinc was also confirmed *(20).* Also in vitro, low zinc concentrations increased the release of catecholamine from bovine adrenal glands, but high zinc concentrations acted inversely, probably by blocking the calcium channel *(21).*

Furthermore, zinc was demonstrated to modulate the influence of aldosterone on Na^+/H^+ exchange *(22).* A close relationship was found between the zinc content in erythrocytes and the activity of carbonic anhydrase *(23,24).* According to the theory on the role that arterial chemoreceptors and tissue oxygen supply play in the pathogenesis of hypertension, the higher zinc content in erythrocytes could have triggered an increase of carbonic anhydrase activity such as it occurs in acidosis as a response to a false signal of oxygen deficiency in tissues. Experimental zinc deficiency in rats caused the activity of carbonic anhydrase to decrease by about 40%. The defense reaction against such decline is polyglobulia *(25,26).* It can be assumed that the rise of hematocrit values found in arterial hypertension and the positive correlation between blood pressure and hemoglobin concentration are responses to the same signal; that

is, the rise of carbonic anhydrase activity as a signal of cytosol acidification mentioned above is a false signal of the lack of oxygen in tissues.

As for any biologically active substance, the biological effects of zinc depend on its concentration, among other factors. Zinc(II) ions are known to have a regulating effect on H^+ transfer into the cell *(22,27).* If the increase of extracellular Zn^{2+} slows down the H^+ transfer into the cell to prevent excessive acidification of the cytoplasm and the converse, the following hypothesis can be put forth.

In the case of an increased level of zinc ions in the extracellular compartment, the intracellular rise of pH lowers the sympathicotonia. This favors the parasympathetic system, which causes a decrease of ventilation and arterial blood pressure drop as a mechanism to inhibit alkalization of the intracellular environment. In patients with low blood pressure, there is a tendency to higher serum zinc concentrations and an inclination to vasovagal reactions *(28,29).*

Under conditions of lower zinc in the extracellular space, the lower pH of cytosol raises sympathicotonia, which elevates blood pressure and, by hyperventilation, increases oxygen intake. Simultaneously, tissue acidification from flow autoregulation intensifies blood flow in microcirculation. This causes increased tissue oxygenation, which, with time, activates the defense mechanisms against oxygen excess, initially leading to a functional and, later, a structural decrease of microcirculation net. In arterial hypertension, one can observe both the drop of zinc content in serum and the rise of sympathicotonia and hyperventilation, originating a rise of circulating blood volume related to hyperperfussion of microcirculation, which then goes back to the initial volume and reduced microcirculation net *(1,3,5,30–38).*

Zinc also stimulates the activity of the endothelin-converting enzyme, responsible for endothelin-1 synthesis, the central vasoconstricting factor produced by endothelium. Higher peroxide concentrations were measured in sera of SHRs. Peroxide inhibits the activity of this enzyme by removing Zn^{2+} from its catalytic center. Zinc replacement has been shown to restore the enzyme's activity *(39–41).*

Another zinc-dependent metal peptidase is the neutral endopeptidase responsible for the degradation of the atrial natriuretic factor (ANF), a cardiac hormone that regulates salt and water balance in body fluids and blood pressure. The ANF inhibits hypertrophy of heart muscle and of the muscular layer of the vessels *(42,43).* Administration of an inhibitor of vasopeptidase resulted in a decline of arterial blood pressure and restriction of hypertensive changes in heart muscle. The results were even more favorable than those following treatment with an ACE blocker *(44).*

The vasoactive intestinal peptide (VIP) promotes vasodilatation and protects cells against possible toxic effects of excessive zinc *(45).* Decreased VIP concentrations in serum and increased transcription of this peptide in the brains of SHRs were reported *(46,47).* In spontaneously hypertensive hamsters (SHHs), administration of VIP in lyposomes caused vasodilata-

tion and a drop of arterial blood pressure *(48,49).* The protective effect by VIP against intracellular zinc accumulation and its hypotensive activity demonstrate that it takes part in maintaining zinc metabolism homeostasis.

Another factor in the regulation of arterial blood pressure involving zinc is the heme–oxygenase–carbon monoxide system, which, upon activation, decreases arterial blood pressure. Blocking of this enzyme by zinc–protoporphyrin IX (ZnPP-IX) in SHRs led to a rise in blood pressure *(50,51).* ZnPP-IX can also inhibit the nitrogen oxide vasodilatation effect *(52).*

Ma et al. showed that intravenous administration of zinc sulfate to dogs with an open chest under general anesthesia resulted in a drop of both the systolic and diastolic blood pressure, accompanied by bradycardia and decrease of heart index, with unchanged total peripheral resistance, suggesting that in this case, hypotension results from the depressive influence of zinc sulfate the on heart muscle *(53).*

It was stated that increasing the zinc–copper ratio (e. g., by decreasing the copper content in diet) led to hypercholesterolemia. It is then possible that impaired regulation of intracellular zinc, apart from increasing blood pressure, could be an independent factor for intensified atherosclerosis evolution *(54).*

Both zinc deficiency and zinc excess impaired the function of copper–zinc superoxide dismutase and, in this way, might impair endothelium-dependent relaxation in experimental animals and in humans *(55–58).* Zinc deficiency aggravated hypertension in SHRs *(56),* but did not change blood pressure levels in NT rats *(58).* Excessive zinc intake elevated systemic blood pressure in NT rats *(59).* Those observations were connected with the function of the above-mentioned dismutase.

The results from animal experiments are consistent with observations made in human subjects. The idea of a primary, genetically determined defect of intracellular zinc content regulation in the course of circulatory system diseases is justified both by high zinc content in erythrocytes of young NT individuals with type A personality (which also depends on genetic factors) and by the high incidence of hypertension in their family *(2,4).*

There is an increasing number of articles suggesting that the onset of hypertension can be predicted in adults who had left ventricle muscle hypertrophy in their childhood, again suggesting a genetic factor in hypertension that agrees well with results obtained using SHRs *(60).*

The use of diuretics or ACE blockers as treatment for hypertension causes changes in urinary zinc excretion, decrease of zinc in erythrocytes, and increase in leucocytes *(61–65).* It is widely known that effective hypotensive treatment leads to regression of left ventricle muscle hypertrophy. Is there any relation between these two phenomena? It is also well documented that zinc is one of the major growth stimulators for some cell lines, such as T-lymphocytes *(4,66).* Is zinc also a growth factor for cardiomiocytes? A reduction of heart muscle protein synthesis was reported in zinc-deficient rats, but this is not thought to be a specific but rather a general effect of zinc deficiency *(67).* In newborn SHRs, heart muscle

hyperplasia was accompanied by increased DNA synthesis, which is known to require zinc ions *(68)*.

Based on experimental and epidemiological studies, it was suggested that increased dietary zinc could result in the elevation of arterial blood pressure and, eventually, to hypertension *(16–18,53)*. At the other end, low dietary zinc resulted in atherosclerosis, evolution of arterial hypertension, and diabetes *(69)*.

In a short-time study on healthy, NT, properly nourished individuals undergoing additional zinc supplementation, there was a dose-dependent rise of plasma rennin activity and serum aldosterone levels, without significant changes in blood pressure *(53)*.

In a study published in 2001, the author confirmed increased gastrointestinal (GI) tract absorption of zinc in arterial hypertension *(70)*. Earlier, Wang et al. discussed the side effects of steroid therapy in hypertension and diabetes in a study of the influence of dexametasone on zinc absorption, which increased during this therapy *(71)*. There were no change in zinc absorption after administration of clopamide, but urinary zinc excretion was intensified *(72)*.

The increase of zinc absorption in the GI tract in arterial hypertension can be related to primary and secondary changes. Assuming that zinc is a trace element that elevates blood pressure, then intensified zinc excretion with urine would come as a response to a pressure regulation mechanism. In that case, the increased absorption of zinc in the alimentary tract would occur to compensate the larger zinc loss. It can also be argued that the increase of zinc absorption in the alimentary tract is a primary phenomenon, triggering the pressure mechanisms that result in high blood pressure. Both of these assumptions are not mutually exclusive and each performs its particular role in the evolution of primary arterial hypertension.

It has been shown that the Cd–Zn ratio in serum is higher in people suffering from arterial hypertension. This and other evidence show that zinc has an antagonistic effect to the hypertensive activity of cadmium *(73–75)*.

The changes in distribution of zinc in the body in hypertension can be considered as a possible defense mechanism to lower blood pressure. The role of zinc in the rennin–angiotensin–aldosterone system (RAAS) can be considered in this regard. In the author's own studies, significantly higher zinc was determined in serum from hypotense subjects, in comparison to hypertensive individuals. This fact could be related to the regulating function of ACE *(76)*.

Zinc and magnesium are phosphodiesterase activators *(77)*. In this context, the increase of intracellular zinc could have been considered as a mechanism to restrict adrenergic stimulation and, more generally, to counteract the factors that elevate the concentration of cyclic adenosine-3′,5′-monophosphate (cAMP) in smooth and heart muscle cells *(77)*.

Endogenous ouabaine from the adrenal cortex plays an important role in arterial blood pressure control. About half of the patients suffering from primary arterial hypertension have higher concentrations of endogenous

ouabaine *(78–81).* Ouabaine produces a vasoconstrictive effect and, depending on the dose, produces whether inhibiting or stimulating the effect on aldosterone excretion by angiotensin II *(82).* It is also a natridiuretic factor whose excretion is controlled by adrenaline and angiotensin II *(81).* As an inhibitor of the sodium pump, Na^+/K^+-ATP-ase, it most probably takes part in the pathogenesis of hypertension *(78–81).* The ouabaine dependence of zinc efflux from lymphocytes was shown in one of our own studies *(30).* This efflux is affected by hypertension and drugs used in its treatment *(83,84).* Together with data about the involvement of the RAAS in the regulation of zinc metabolism and zinc involvment in feedback mechanisms between RAAS components, all of these facts suggest that ouabaine is part of the zinc metabolism *(16,30,53).*

Zinc-protoporphirine (ZnPP-IX), which increases in dialyzed patients with iron deficiency, could also be responsible for increased blood pressure values. With proper iron supplementation, the ZnPP-IX concentrations decrease and so does arterial blood pressure *(85).*

Arterial hypertension or hypotension was not found in families with genetically determined higher serum zinc *(86).* High zinc concentrations in blood serum were observed in one patient with ceroidlipofuscinosis, renal artery stanosis, and arterial hypertension. These concentrations and the high values of blood pressure were lowered after effective precutaneous angioplasty of the stenosed renal artery *(87).*

There are some reports of acute toxicity of zinc compounds. In one case, hypotension was reported in zinc phosphide poisoning *(88).* In another case, arterial hypertonia was seen after intoxication with zinc chloride *(89).* The toxic symptoms are probably the result of the compound, and not only to zinc.

To summarize the known facts about the role that zinc plays in the regulation of arterial blood pressure and in the etiology of hypertension, it is necesary to ask the following questions:

1. What are the changes in zinc metabolism that occur in subjects with arterial hypertension?
2. Are these changes primary or secondary?
3. What is the significance of these changes in relation to arterial blood pressure regulation?
4. Is zinc itself—whether in excess or deficit—a causal agent of arterial hypertension?

Question 1. Experimental and clinical studies have confirmed increases in the GI absorption and urinary excretion of zinc in primary arterial hypertension, resulting from decreases of zinc in the extracellular compartment and changes of zinc intracellular compartment. The zinc content in serum, lymphocytes, and bone decrease with a concurrent increase in heart, erythrocytes, kidneys, liver, suprarenal gland and spleen. In general, the increase of urinary zinc in hypertension leads to greater zinc deficit in the organism because the loss of zinc is not fully compensated by the observed increase of its absorption from the GI tract.

Question 2. The loss of homeostasis that results from the changes mentioned earlier can be classified both as primary and secondary changes; that is, it might be considered to be the cause (primary) or the result of (secondary) increased arterial blood pressure. The following hypotheses can be put forth:

(a) *Primary cause.* Primary defect of zinc excretion on kidney level: acidification of cytoplasm. The increase of urinary zinc loss might be the result of kidney malfunction, followed by disrupted zinc homeostasis and increased blood pressure as a result of the acidification of cytoplasm. The origin might be in malfunction of the alimentary tract, which would lead to increased zinc absorption, saturating or exceeding the zinc pump capacity and leading to intracellular accumulation of the element, followed by a rise of arterial blood pressure and progressive loss of zinc homeostasis. Alternatively, the problem might concern the zinc membrane pumps, which would also result in intracellular increases with the same results as above. Secondary, zinc dyshomeostasis causes intracellular accumulation of calcium and intensification of pressure mechanisms.

(b) *Secondary cause.* The loss of zinc homeostasis could be also considered as secondary to hypertension, related to the activation of various pressure mechanisms.

Question 3. The changes in zinc metabolism might be considered at the origin of increases or decreases of blood pressure. The flow of zinc from cells into extracellular space occurs against a concentration gradient and is regulated by the physiological zinc level outside the cells *(90).*

Low zinc concentrations in serum can be considered as a mechanism to lower blood pressure in hypertension by affecting activities of the ACE, the endothelin-converting enzyme and neutral endopeptidase. The higher zinc concentration in erythrocytes is associated with an increase of carbonic anhydrase activity to increase the cytoplasm's pH. These are reasons for sympathetic system and RAAS activation. On the other hand, low zinc concentration in extracellular space means less efficient blocking of calcium channels, favoring the inflow of calcium ions into the cell and its accumulation, leading to increased tension and hypertrophy of the smooth muscular layer and heart vessels.

The role of zinc in the regulation of arterial blood pressure is multilevel. It can be assumed that in the first stage of hypertension, the changes in zinc metabolism are of compensative nature, trying to lower blood pressure. With time, continuation of these changes results in the loss of zinc homeostasis, which becomes part of the mechanism that promotes high blood pressure.

Question 4. Changes in zinc metabolism caused by endogenous and exogenous factors could lead to arterial hypertension. In this article, plau-

sible mechanisms and hypotheses on the role of zinc in increasing or modulation pressure reactions are presented.

If the zinc intake is too low, deficiency would lead to hypotensive mechanisms dysfunction, increase of arterial blood pressure, and aggravating loss of zinc homeostasis (Hypothesis 1). Excessive zinc intake can lead to intensified zinc absorption after breaking the intestinal barrier, which might cause intracellular zinc accumulation, enzymes and signaling processes dysfunction, followed by a rise of arterial blood pressure and progressing to the loss of zinc homeostasis (Hypothesis 2).

REFERENCES

1. W. R. Harlan, J. R. Landis, L. R. Schmouder, N. G. Goldstein, and L. C. Harlan, Blood lead and blood pressure. Relatioship in the adolescent and adult U. S. population, *JAMA* **253,** 530–534 (1985).
2. G. Frithz and G. Ronquist, Increased red cell content of zinc in essential hypertension, *Acta Med. Scand.* **205,** 647–649 (1979).
3. J. G. Henrotte, M. Santarromana, G. Franck, and R. Bourdon, Blood and tissue zinc levels in spontaneously hypertensive rats, *J. Am. Coll. Nutr.* **9,** 340–344 (1990).
4. J. G. Henrotte, M. Santarromana, G. Franck, P. Guicheney, R. Boulu, and R. Bourdon, High cardiac zinc levels in spontaneously hypertensive rats, *J. Hypertens.* **10,** 553–559 (1992).
5. G. Vivoli, M. Bergomi, S. Rovesti, M. Pinotti, and E. Caselgrandi, Zinc, copper and zinc- or copper-dependent enzymes in human hypertension, *Biol. Trace Element Res.* **49,** 97–106 (1995).
6. G. Vezzoli, A. A. Elli, G. Tripodi, G. Bianchi, and E. Carafoli, Calcium ATPase in erythrocytes of spontaneously hypertensive rats of the Milan strain, *J. Hypertens.* **3,** 645–648 (1985).
7. M. J. Berridge, Regulation of ion channels by inositol triphosphate and diacyl-glycerol, *J. Exp. Biol.* **124,** 323–335 (1986).
8. I. G. Macara, Oncogenesis, ions and phospholipids, *Am. J. Physiol.* **248,** C3–C11 (1985).
9. J. Cortijo, J. V. Esplugues, and B. Sarria, Zinc as a calcium antagonist; a pharmacological approach in strips of rat aorta, *IRCS Med. Sci. Cancer* **13,** 292–293 (1985).
10. P. Darlu, J. M. Lalouel, J. G. Henrotte, and D. C. Rao, A genetic study of red blood zinc concentration in man, *Hum. Heredity* **33,** 311–318 (1983).
11. J. G. Henrotte, M. Santarromana, and M. Pia, Genetic factors regulating zinc concentrations in mics spleen and liver: relationship with the H-2 complex, *Immunogenetics* **25,** 408–410 (1987).
12. B. Bucher, P. Travo, and J. C. Stoclet, Smooth muscle cells hyperthrophy and hyperplasia in the thoracic aorta of spontaneously hypertensive rat, *Cell. Biol. Int. Rep.* **8,** 567–577 (1984).
13. J. Kunes, S. C. Pang, and M. Cantin, Cardiac and renal hyperplasia in newborn spontaneously hypertensive rats, *Clin. Sci.* **72,** 271–275 (1987).
14. M. S. Clegg, F. Ferrell, and C. L. Keen, Hypertension-induced alternations in copper and zinc metabolism in Dahl rats, *Hypertension* **9,** 624–628 (1987).
15. H. F. Loyke, Copper and zinc in experimental hypertension, *Biol. Trace Element Res.* **29,** 45–49 (1991).
16. H. Dahlheim, C. L. White, J. Rothemund, N. von Lutterotti, I. C. Jacob, and J. Rosenthal, Effect of zinc depletion on angiotensin I-converting enzyme in arterial walls and plasma of the rat, *Miner. Electrolyte Metab.* **15,** 125–129 (1989).

17. N. V. Davydenko, I. P. Smirnova, E. A. Kvasha E. A. I. M. Gorbas, and A. V. Koblianskaia, Interrelatioship between dietary intake of minerals and prevalence of hypertension, *Vopr. Pitan.* **6,** 17–19 (1995).
18. N. V. Davydenko, I. P. Smirnova, E. A. Kvasha, and I. M. Gorbas, The relationship between the copper and zinc intake with food and the prevalence of ischaemic heart disease and its risk factors, *Lik. Sprava* 5–6, 73–77 (1995).
19. J. D. Browning, P. G. Reeves, and B. L. O'Dell, Zinc deficiency in rats reduces the vasodilatatory response to bradykinin and prostacyclin, *J. Nutr.* **117,** 490–495 (1987).
20. S. Koizumi, M. Ikeda, K. Inoue, K. Nakazawa, and K. Inoue, Enhancement by zinc of ATP-evoked dopamine release from rat phe ochromocytoma PC12 cells, *Brain Res.* **673,** 75–82 (1995).
21. M. T. Vega, C. Villalobos, B. Garrido, et al., Permeation by zinc of bovine chromaffin cell calcium channels: relevance to secretion, *Pflugers Arch. – Eur. J. Physiol.* **429,** 231–139 (1994).
22. M. Gekle, S. Silbernagl, and S. Wunsch, Non-genomic action of the mineralocorticoid aldosterone on cytosolic sodium in cultured kidney cells, *J. Physiol.* **511,** 255–263 (1998).
23. T. Kondo, N. Tanigochi, K. Taniguchi, I. Matsuda, and M. Murao, Inactive form of erythrocyte carbonic anhydrase B in patients with primary renal tubular acidosis, *J. Clin. Invest.* **62,** 610–617 (1978).
24. D. Mafra and S. M. Cozzolino, Erythrocyte zinc and carbonic anhydrase levels in nondialyzed chronic kidney disease patients, *Clin. Biochem.* **37,** 67–71 (2004).
25. A. Boznański, Zachowanie się jonów cynku w osoczu i krwinkach czerwonych w przebiegu cukrzycy insulinozależnej klinicznie wyrównanej, Doctoral thesis, Medical Academy, Wrocław (1982) (in Polish).
26. I. Puscas, L. Sturzu, and G. Buzas, Effect of $ZnSO_4$ upon gastric acid secretion and carbonic anhydrase, *Int. J. Clin. Pharmacol. Ther. Toxicol.* **23,** 609–614 (1985).
27. M. Gekle, N. Golenhofen, H. Oberleithner, and S. Silbernagl, Rapid activation of Na^+/H^+ exchange by aldosterone in renal epthelial cell requires Ca^{2+} and stimulation of a plasma membrane proton conductance, *Proc. Natl. Acad. Sci. USA* **93,** 10,500–10,504 (1996).
28. S. Tubek, Selected zinc metabolism parameters in women with arterial hypotension, *Biol. Trace Element. Res.*, in press.
29. S. Tubek, Activity of zinc ions efflux from lymphocytes, serum zinc concentration and zinc content in lymphocytes in persons with arterial hypotension and hypertension, *Post. Med. Klin. Dośw.* **3,** 257–261 (1994) (in Polish).
30. S. Tubek. The zinc content in lymphocytes and the activity of zinc ions efflux from lymphocytes in primary arterial hypertension, *Biol. Trace Element Res.* **107,** 89–99 (2005).
31. J. Przybylski, The role of arterial chemoreceptors and tissue oxygen supply in primary arterial hypertension pathogenesis, based upon investigations carried out on animal model (SAH), Qualifying thesis., Medical University of Warsaw, Warsaw, pp. 24–42, 85–167 (1991) (in Polish).
32. A. Trzebski, M. Tafil, M. Żółtowski, and J. Przybylski, Increased sensitivity of the arterial chemoreceptor drive in young men with mild hypertension, *Cardiovasc. Res.* **16,** 163–171 (1982).
33. N. Kaplan, *Clinical Hypertension,* 6th ed., William & Wilkins, Baltimore, pp. 97–98 (1994).
34. P. M. Hutchins and A. E. Darnell, Observations of derceased number of small arterioles in spontaneously hypertensive rats, *Circ. Res.* **34(Suppl. 1),** 161–168 (1974).
35. R. L. Prewitt, S. S. Cardoso, and W. B. Wood, Prevention of arteriolar rarefaction in the spontaneously hypertensive rat by exposure to simulatd high altitude, *J. Hypertens.* **4,** 735–742 (1986).
36. A. W. Cowlay, Assesment of the contributions of autoregulatory mechanisms to the antihypertensive actions of beta-adrenergic therapy, *Hypertension* **6,** 137–144 (1984).

37. B. Flokow, Physiological aspects of primary hypertension, *Physiol. Rev.* **62,** 347–354 (1982).
38. L. R. Prewitt, I. I. H. Chen, and R. Dowell, Development of microvascular rarefaction in the spontaneously hypertensive rat, *Am. J. Physiol.* **243,** H243–H450 (1982).
39. S. Lopez-Ongil, V. Senchak, M. Saura, et al., Superoxide regulation of endothelin converting enzyme, *J. Biol. Chem.* **275,** 26,423 –26,429 (2000).
40. P. M. Cummins, E. J. Cotter, and P. A. Cahill, Hemodynamic regulation of metallopeptidases within the vasculature, *Protein Pept. Lett.* **11,** 433–442 (2004).
41. F. A. De Lano, R. Balete, and G. W. Schmid-Schonbein, Control of oxidative stress in microcirculation of spontanously hypertensive rats, *Am. J. Physiol.:Heart Circ. Physiol.* **288,** H805–H812 (2005).
42. C. V. Maniu, D. M. Meyer, and M. M Redfield, Hemodynamic and humoral effects vasopeptidase inhibition in canine hypertension, *Hypertension* **40,** 528–534 (2002).
43. M. W. Taal, V. D. Nenov, W. Wong, et al., Vasopeptidase inhibition affords greater renoprotection than angiotensin-converting enzyme inhibition alone, *J. Am. Soc. Nephrol.* **10,** 2051–2059 (2001).
44. R. Corti, J. C. Burnett Jr., J. L. Rouleau, F. Ruschitzka, and T. F. Luscher, Vasopeptidase inhibitors: a new therapeutic concept in cardiovascular disease? *Circulation* **104,** 1856–1862 (2001).
45. I. Divinski, L. Mittelman, and I. Gozes, A femtomolar acting octapeptide interacts with tubulin and protects astrocytes zinc intoxication, *J. Biol. Chem.* **279,** 28,531–28,538 (2004).
46. K. Mori, S. Asakura, H. Ogawa, S. Sasagawa, and M. Takeyama, Decreases in substance P and vasoactive intestinal peptide concentrations in plasma of stroke-prone spontaneously hypertensive rats, *Jpn. Heart J.* **34,** 785–794 (1993) (abstract).
47. R. V. Peters, R. T. Zoeller, A. C. Hennessey, E. G. Stopa, G. Anderson, and H. E. Albers, The control of circadian rhythms and the levels of vasoactive intestinal peptide mRNA in the suprachiasmatic nucleus are altered in sponateously hypertensive rats, *Brain Res.* **639,** 217–227 (1994).
48. H. Suzuki, Y. Noda, X. P. Gao, et al., Encapsulation of VIP into liposomes restores vasorelaxation in hypertension in situ, *Am. J. Physiol.* **271,** H282–H287 (1996).
49. I. Rubinstein, H. Ikezaki, and H. Onyuksel, Intratracheal and subcutaneous liposomal VIP normalize arterial pressure in spontaneously hypertensive hamsters, *Int. J. Pharm.* **316,** 144–147 (2006).
50. E. A. dos Santos, G. A. Yamaguishi, and J. C. Heimann, Effect of the heme/heme oxygenase pathway on the relationship between salt consumption and blood pressure, *J. Hypertens.* **16,** 1965–1969 (1998).
51. T. Seki, M. Naruse, K. Naruse, et al., Roles of heme oxygenase/carbon monoxide system in genetically hypertensive rats, *Biochem. Biophys. Res. Commun.* **241,** 574–578 (1997).
52. H. J. Vermann, G. R. Haenen, D. K. Stevenson, and A. Bast, Reduction of the NO-mediated response in the rat aorta by metalloporphyrins, *Can. J. Physiol. Pharmacol.* **6,** 457–461 (2000).
53. M. Calero, A. Sampalo, J. E. Millan, J. Freire, A. Senra, and E Zamora, Changes in the activity of plasma renin and aldosterone induced by a pattern of increasing administration of zinc sulphate in normotensive individuals, *Med. Clin. (Barc),* **92,** 729–732 (1989) (abstract).
54. P. Saltman, Trace elements and blood pressure, *Ann. Intern. Med.* **98(Pt. 2),** 823–831 (1983).
55. C. E. Gracia, C. M. Kdcoyne, C. Cardillo, R. O. Cannon 3rd, A. A. Quyyumi, and J. A. Panza, Effect of copper-zinc superoxide dismutase on endothelium-dependent vasodilation in patients with essential hypertension, *Hypertension* **26,** 863–868 (1995).
56. M. Sato, H. Yanagisawa, Y. Nojima, J. Tamura, and O. Wada, Zn deficiency aggravates hypertension in spontaneously hypertensive rats: possible role of Cu/Zn-superoxide dismutase, *Clin. Exp. Hypertens.* **24,** 355–370 (2002).

57. S. A. Cebeci, P. A. Kocaturk, and G. O. Kavas, Hypertension: does impaired endothelium-dependent relaxation affect superoxide scavenging? *Biol. Trace Element Res.* **90,** 239–249 (2002).
58. M. Sato, N. Kurihara, K. Moridaira, et al., Dietary Zn deficiency does not influence systemic blood pressure and vascular nitric oxide signaling in normotensive rats, *Biol. Trace Element Res.* **91,** 157–172 (2003).
59. H. Yanagisawa, M. Sato, M. Nodera, and O. Wada, Excessive zinc intake elevates systemic blood pressure levels in normotensive rats: potential role of superoxide-induced oxidative stress, *J. Hypertens.* **22,** 543–550 (2004).
60. L. T. Mahoney, R. M. Schieken, W. R. Clarce, and R. N. Laner, Left ventricular mass and exercise responses predict future blood pressure. The Muscatine Study, *Hypertension* **12,** 206–214 (1998).
61. A. Golik, D. Modai, J. Weissgarten, et al., Hydrochlorothiazide-amiloride causes excessive urinary zinc excretion, *Clin. Pharmacol. Ther,* **42,** 42–44 (1987).
62. A. Golik, D. Modai, Z. Averbukh, et al., Zinc metabolism in patients treated with captopril versus enalapril, *Metabolism* **39,** 665–667 (1990).
63. A. Golik, Z. Averbukh, M. Cohn, et al., Effect of diuretics on captopril-induced urinary zinc excretion, *Eur. J. Clin. Pharmacol.* **38,** 359–361 (1990).
64. M. Pęczkowska, Influence of angiotensin I converting enzyme inhibitors on selected parameters of zinc metabolism, *Pol. Arch. Med. Wewn.* **96,** 32–38 (1996).
65. M. Koren-Michowitz, V. Dishy, R. Zaidenstein, et al., The effect of losartan and losartan/hydrochlorothiazide fixed-combination on magnesium, zinc, and nitric oxide metabolism in hypertensive patients: a prospective open-label study, *Am. J. Hypertens.* **18,** 358–363 (2005).
66. S. Ripa and R. Ripa, Zinc and immune function, *Minerva Med.* **86,** 315–318 (1995).
67. I. Dorup and T. Clausen, Effects of magnesium and zinc deficiencies on growth and protein synthesis in skeletal muscle and the heart, *Br. J. Nutr.* **66,** 493–504 (1991).
68. S. V. Walter and P. Hamet, Enhanced DNA synthesis in heart and kidney of newborn spontaneously hypertensive rats, *Hypertension* **8,** 520–525 (1986).
69. R. B. Singh, M. A. Niaz, S. S. Rastogi, S. Bajaj, Z. Gaoli, and Z. Shoumin, Current zinc intake and diabetes and coronary artery disease and factors associated with insulin resistance in rural and urban populations of North India, *J. Am. Coll. Nutr.* **17,** 564–570 (1998).
70. S. Tubek, Increased absorption of zinc from alimentary tract in the primary arterial hypertension, *Biol. Trace Element Res.* **83,** 31–38 (2001).
71. Z. Wang, S. A. Atkinson, F. P. Bertolo F. P., S. Polberger, and B. Lonnerdal, Alternations in intestinal uptake and compartmentalization of zinc in response to short-term dexamethasone therapy or excess dietary zinc in piglets, *Pediatr. Res.* **33,** 118–124 (1993).
72. M. J. du-Preez and Lockett, Effect of clopamide, a thiazide diuretic, on copper and zinc levels in hypertensive patients, *J. Am. Coll. Nutr.* **10,** 34–39 (1991).
73. M. Łapiński, K. Kuczyńska, B. Wocial, and W. Januszewicz, Rola magnezu, kadmu i cynku w patogenezie nadciśnienia tętniczego pierwotnego [The role of magnesium, cadmium and zinc in etiopathogenesis of arterial hypertension], *Pol. Tyg. Lek.* **41,** 941–945 (1986) (in Polish).
74. H. M. Perry, M. W. Erlanger, and E. F. Perry, Limiting conditions for the induction of hypertension in rat by cadmium, *Trace Subst. Environ. Health* **10,** 459–467 (1977).
75. H. M. Perry, M. W. Erlanger, and E. F. Perry, Inhibition of cadmium-induced hypertension in rats, *Sci. Total Environ.* **14,** 153–166 (1980).
76. S. Tubek, Activity of zinc ions efflux from lymphocytes, serum zinc concentration and zinc content in lymphocytes in persons with arterial hypotension and hypertension, *Post. Med. Klin. Dośw.* **3,** 257–261 (1994) (in Polish).

77. R. Gryglewski and E. Kostka-Trąbka, *Leki betaadrenolityczne,* PZWL, Warsaw, p. 32 (1983) (in Polish).
78. M. P. Blaustein, J. Zhang, L. Chen, and B. P. Hamilton, How does salt retention blood pressure? *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **290,** R514–R523 (2006).
79. P. Manunta, M. Ferrandi, E. Messaggio, and P. Ferrari, A new antihypertensive agent that antagonizes the prohypertensive effect of endogenous ouabain and adducin, *Cardiovasc. Hematol. Agents Med. Chem.* **4,** 61–66 (2006).
80. W. Schoner and G. Scheiner-Bobis, Endogenous cardiac glycosides: hormones using the sodium pump as signal transducer, *Semin. Nephrol.* **25,** 343–351 (2005).
81. W. Schoner, N. Bauer, J. Muller-Ehmsen, et al., Ouabain as a mammalian hormone, *Ann. NY Acad. Sci.* **986,** 678–684 (2003).
82. L. V. Rossoni, L. Dos Santos, L. A. Barker, and D. V. Vassallo, Ouabaine changes arterial blood pressure and vascular reactivity to phenylephrine in L-NAME-induced hypertension, *J. Cardiovasc. Pharmacol.* **41,** 105–116 (2003).
83. S. Tubek, Effect of aldosterone receptor blockade by spironolactone on zinc efflux rate constans from lymphocytes of patients with arterial hypertension, *Post. Med. Klin. Dośw.* **3,** 27–33 (1994).
84. S. Tubek, Zinc ions efflux from lymphocytes *in vitro* in the presence of a calcium and magnesium ionic environment and its changes following administration of verapamil, *Biol. Trace Element Res.* in press.
85. G. Kurp, Bedeutung der Zink–Protoporphyrin–Bestimmung für die Steuerung der Eisensubstitution bei Hämodialysepatienten mit renaler Anämie, Doctoral thesis, Münster (Westfalen) University (2005).
86. J. C. Smith, J. A. Zeller, E. D. Brown, and S. C. Ong, Elevated plasma zinc: a heritable anomaly, *Science* **193,** 496–498 (1976).
87. S. Tubek, A case of renovascular hypertension with high serum zinc concentration and ceroidlipofuscinosis with genom 46,*XY*,9gh+, *Pol. Arch. Med. Wew.* **101,** 59–63 (1999).
88. S. N. Chugh, H. K. Aggarwal, and S. K. Mahajan, Zinc phosphide intoxication symptoms: analysis of 20 cases, *Int. J. Pharmacol. Ther.* **36,** 406–407 (1998).
89. P. E. McKinney, J. Brent, and K. Kulig, Acute zinc chloride ingestion in a child: local and systemic effects, *Ann. Emerg. Med.* **23,** 1383–1387 (1994).
90. S. Devergnas, F. Chimienti, N. Naud, et al., Differential regulation of zinc efflux transporters ZnT-1, ZnT-5 and ZnT-7 gene expression by zinc levels: a real-time RT-PCR study, *Biochem. Pharmacol.* **68,** 699–709 (2004).