REVIEWS

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Membrane Zinc Transporters Znt-1 and Znt-5 in Circulatory System Pathophysiology

Transportery błonowe cynku ZnT-1 i ZnT-5 w patofizjologii układu krążenia

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Abstract

The paper presents current information concerning the significance of membrane zinc transporters in circulatory system pathophysiology. The presence of ZnT-1, ZnT-3, ZnT-5 and ZnT-7 carriers in the heart has been reported. Two of these – ZnT-1 and ZnT-5 – reveal a relationship with some cardiac conditions. ZnT-1 occurs in the cellular membrane, and ZnT-5 in the membrane of cell organelles, including the Golgi apparatus. Elucidating the role of ZNT-1 and other proteins in intracellular zinc contents could have useful implications for the treatment of cardiovascular diseases (**Adv Clin Exp Med 2011, 20, 1, 87–91**).

Key words: membrane zinc transporters, ZnT–1, ZnT–5, circulatory system diseases.

Streszczenie

W pracy przedstawiono aktualne dane dotyczące roli błonowych transporterów cynku w patofizjologii układu krążenia. W sercu stwierdza się obecność nośników ZnT–1, ZnT–3, ZnT–5 i ZnT–7. Dwa z nich: ZnT–1 i ZnT–5, wykazują związek z patologiami układu krążenia. ZnT–1 występuje w błonie komórkowej, a ZnT–5 w błonach organelli komórkowych, w tym aparatu Golgiego. Wyjaśnienie roli ZnT–1 i innych białek wpływających na wewnątrzkomórkowe stężenie cynku może mieć istotne znaczenie praktyczne w leczeniu chorób układu sercowo-naczyniowego (**Adv Clin Exp Med 2011, 20, 1, 87–91**).

Słowa kluczowe: transportery błonowe cynku, ZnT-1, ZnT-5, choroby układu krążenia.

Zinc (Zn) is an essential element in the organism, where it plays numerous functional and structural roles. The human organism has developed efficient mechanisms of zinc homeostasis, so the clinical symptoms of zinc deficit are rarely encountered. Pathological processes such as arterial hypertension, diabetes mellitus, obesity or ischemia cause zinc dyshomeostasis: excessive zinc accumulation in cells, which leads to mitochondrial dysfunction and impairment of energy production. Zn is considered to be the main toxic factor in hypoxic neurons, leading to their death. Taking these considerations into account, there must be efficient mechanisms of homoeostasis in normal physiological conditions to prevent excessive intracellular zinc accumulation. This is what actually happens: Free zinc levels are increased in extracellular space, while the global amount of zinc is much higher in intracellular space. Zinc efflux from cells takes place against the concentration gradient and electrochemical gradient [1, 2].

Therefore, physiologically, in order to maintain the proper intracellular zinc level, an increase in the zinc level in serum (which means potentially higher zinc influx to the cell) must be accompanied by increases in its efflux. In fact, zinc efflux from cells is influenced by increased zinc influx into the cell [3]. There is a positive correlation between serum zinc levels and the efflux rate constants of total and ouabain-dependent lymphocyte zinc from healthy subjects [4].

So far, 24 protein carriers participating in transmembrane zinc transport have been identified on the cell membrane level, including 10 proteins shifting zinc from cytoplasm outside the cell (ZnT-1 – a cell membrane transporter) or to inner structures, mainly into the endoplasmic reticulum (the remaining transporters) [5].

The presence of ZnT-1, ZnT-3, ZnT-5 and ZnT-7carriers in the heart has been reported. A correlation between two of them – ZnT-1 and ZnT-5 – and circulatory system pathologies has been observed. ZnT-1 occurs in cell membranes, while ZnT-5 occurs in the membranes of cell organelles, including the Golgi apparatus [5].

In instances of a genetic lack of ZnT-1 in mice, embryonic lethality was observed, whereas the lack of one allele did not result in clinical changes in experimental animals. An increase in ZnT-1 atrial myocytes in the course of atrial fibrillation, and a functional correlation between ZnT-1 and L-type calcium channels were also observed [6, 7].

Experimental studies on rats with chronic hyperaldosteronism have also revealed increased ZnT-1 expression in cardiomyocytes, which decreased after spironolactone use [8, 9]. In Wistar-Kyoto rats, Zn inhalation caused no significant changes in ZnT-1 expression in the lung or liver, but zinc increased cardiac ZnT-1 at 24th hours, indicating a possible zinc-specific cardiac effect [10].

In the case of ZnT-5, however, it was observed that a genetically conditioned absence results mainly in rapid cardiac deaths in male rats in the course of bradyarrhythmia. This is related to myocyte dysfunction in the heart conduction system resulting from the lack of ZnT-5 [11].

During atrial fibrillation, atrial muscle myocytes have an increased ZnT-1 level, which suggests the activation of mechanisms lowering zinc accumulation in cells. Increased expression of mRNA for ZnT-1 has been observed in the atrial muscles of patients with atrial fibrillation, especially in obese subjects [6]. It can be therefore be concluded that the abnormal bioelectrical function of the myocytes and their excessive tension results in an increase in Zn ion influx into the cell, with a secondary increase in ZnT-1 synthesis as a protective mechanism reducing the toxic effect of excessive intracellular Zn.

A close correlation has been observed between ZnT-1's participation in electrical remodeling in the heart and L-type voltage dependent calcium channels (LTCC) [7]. Therefore, the higher the ZnT-1 expression, the lower the LTCC activity.

Decreased LTCC activity observed in the atria can be considered as the main cause underlying patients' susceptibility to atrial fibrillation [7]. Thus, it could be also suggested that higher ZnT-1 expression would result in reduced calcium overload in cardiomyocytes.

In a comparison of obese and normal subjects with arterial hypertension, differences have been noted in the Zn efflux from lymphocytes. In these patients, a spironolactone block of aldosterone receptors resulted in increased zinc content in lymphocytes and increased zinc ion efflux from lymphocytes – i.e., activity reversing the changes in zinc metabolism that occur in arterial hypertension. There was a positive correlation between zinc efflux and its level in the cell. A difference in the reaction of normal and obese subjects to spironolactone was also observed: In obese subjects, the activity of zinc efflux from lymphocytes was on virtually the same level during a one-week observation, whereas it increased in normal subjects [12].

A similar direction of intracellular Zn changes influenced by aldosterone and spironolactone was observed in experimental rats with chronic hyperaldosteronism, in which increased ZnT-1 expression decreasing under the influence of spironolactone was found [8, 9].

On the basis of ZnT-1 behavior in atrial fibrillation, it can be assumed that the same phenomenon will take place in ventricular myocytes when their tension is increased (e.g. increased pre-load or sympathetic tension), both in a normal myocardium and in the course of cardiectasia. It may be assumed that the higher the ZnT-1 activity, which is most probably genetically conditioned, the lower the activity of toxic intracellular Zn accumulation will be, and the slower the development of changes during the course of pathological processes involving the circulatory system (e.g. myocardial ischemic damage, atherosclerosis, arterial hypertension).

Different levels of severity of disturbances in various organs in different patients who are exposed to harmful factors of similar intensity and duration can be explained by variations in genetically determined Zn efflux from cells.

Animal studies indicate that there are genetic differences – e.g. a Zn deficit in the diet results in a different reaction in spontaneously hypertensive rats (increased arterial blood pressure) than in Wistar-Kyoto rats (no such reaction) [13].

Observations show that the higher the zinc level in the extracellular environment, the higher the ZnT-1 activity [5, 14, 15]. It can therefore be assumed that the lower the ZnT-1 expression, the faster the progress of cardiomyopathy (including hypertensive cardiomyopathy), the more extensive the infarct size, the higher the frequency of cardiac arrhythmias (a possible role of ZnT-5?) and the higher the mortality related to cardiac condi-

tions. Earlier observations revealed a correlation between zinc deficit (low serum zinc level, Zn-s) and these phenomena [16–19]. Animal studies have indicated the possibility that prior zinc administration may considerably reduce the area of myocardial necrosis following closure of the coronary artery [20].

Other medicines influencing the renin-angiotensin-aldosterone system, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, will probably have a similar effect on ZnT-1 expression. Their beneficial effects on organic functional changes are related to the effect of zinc metabolism [21]. With regard to the circulatory system, this affects cardiomyocytes and myocytes, as well as vascular endothelial cells [22–28].

If zinc were to be used as a therapeutic agent, it should be administered intravenously (e.g. in the form of zinc sulphate), which would quickly increase its serum level and lead to increased ZnT-1 activity. Oral administration would not be of much use, due to a lack of increased zinc absorption from the alimentary tract.

Rapidly increasing temporary fluctuations in serum zinc levels may influence the nephrotoxicity of contrast agents used in imaging studies [29]. This may be related to a delayed adaptive mechanism connected with ZnT-1 activity.

In primary arterial hypertension, increased absorption of zinc from the alimentary tract has been recorded, which may testify to a deficit or an increased demand for this element [30]. Determining ZnT-1 expression in (e.g.) lymphocytes, along with the curve of zinc absorption from the alimentary tract, could provide a good indication of whether we are dealing with zinc deficit or dyshomeostasis. Zinc dyshomeostasis manifesting itself in the course of arterial hypertension may accelerate the development of atherosclerosis, accelerate the ageing process and predispose the individual to develop type II diabetes and left ventricular failure [31].

Regulating changes in zinc metabolism and lowering the level of dyshomeostasis will be possible to achieve, depending on the primary cause, through the administration of medicines directly or indirectly influencing zinc metabolism. Taking into account the toxic effect of excessive intracellular Zn^{2+}, an essential element will be to improve membrane function and the efficiency of zinc efflux into the extracellular space. Since excessive intracellular Zn^{2+} disrupts the mechanisms of oxygen metabolism, it also diminishes zinc efflux from the cell, and a vicious circle begins. The use of agents affecting intracellular oxygen metabolism, such as pyruvates, decreases zinc accumulation and improves cell survival [32].

It may be argued that the main focus of pharmacological and non-pharmacological activities aimed at achieving or maintaining zinc homeostasis should be the regulation of zinc metabolism by reversing zinc redistribution in the body.

However, with regard to the statement above concerning effective homeostasis mechanisms, chronic zinc supplementation seems to be a rather marginal problem in the population, except in cases of chronic dietary zinc deficiency. In certain justified cases, temporary zinc supplementation during a relative deficit may have a positive metabolic result, although extensive clinical studies are required. In experimental studies, an increase or decrease in zinc content in extracellular space had an ambiguous effect on the activation or inhibition of mRNA synthesis of particular ZnT transport proteins that condition effective zinc efflux from the cell [5]. Moreover, zinc supplementation should also be considered in relation to other microelements in the diet [33].

Currently, intensive studies are being conducted concerning the effect of zinc on metabolism. In these studies zinc is treated as an element regulating the physiological process of ageing and preventing some conditions, especially arterial hypertension, atherosclerosis, impaired immunity and type 2 diabetes. The role of membrane proteins transporting zinc is of particular importance in these studies, since this element plays an important role in maintaining the integrity and function of endothelial cells [31, 33–36].

It may be supposed that the same direction of ZnT-1 changes as in atrial fibrillation (which may be treated as an emergency situation) will occur in other chronic processes in the circulatory system, such as arterial hypertension, atherosclerosis and ischemic cardiomyopathy (post-inflammatory or toxic), as well as in the physiological ageing process. Due to the gradually increasing insufficiency of processes regulating zinc efflux from cells and its intracellular distribution (mainly with regard to the amount and activity of ZnT-1, but also ZnT-5), a slow process of intracellular zinc accumulation takes place (growing Zn dyshomeostasis), which may be aggravated by zinc deficit. That process may be accompanied by progressive circulatory insufficiency or cell sensitivity to hypoxia [37, 38].

Zn-T functions may also influence the toxicity of other elements, e.g. cadmium [39], as well as the ageing process [40].

Explaining the role of ZnT-1 and other proteins affecting the extracellular zinc level appears to be a promising area of study that may be of great importance in the future treatment of diseases of the circulatory system.

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