ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LIX, N 2, 115 SECTIO D 2004

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Magnesium role in cardiovascular diseases

Magnesium is one of the beneficial microelements in human physiology. It is in the second main group of the periodic system and it activates more than 300 enzymes (which belong to phosphatase, dehydrogenase, synthetase, cyclase cluster), thereby it influences on many intracellular processes (4, 5, 7, 9, 18).

Cardiovascular disorders are one of the worst plagues in most industrial countries. For the worst are recognized arteriosclerosis, myocardial infraction, arrhythmias and ischaemic heart disease. Their causes are: sedentary lifestyle, a diet with too much animal fatty acid, smoking and too much stress. Results of many studies suggest that magnesium is an important factor for treatment of these disorders.

MAGNESIUM CONNECTION WITH CALCIUM, SODIUM, POTASSIUM AND ECG

Magnesium activates calcium pump and sodium pump. Sodium pump causes transport of Na^+ ions outside the cell and brings K^+ ions to the inside of the cell (three Na^+ ions are exchanged on two K^+ ions) (14). In case of Na^+ ions this pump, acting against concentration gradient, causes formation of bioelectric potential in both sides of plasma membrane (3), which is very important in maintaining the volume of the cell and also in transport of some substations to the inside of the cell.

Calcium pump causes transport of two Ca^{2+} ions to extracellular matrix (11) and thereby helps to maintain the same, constant, low concentration of calcium in the rest phase of the cell. The correct acting of Ca^{2+}/Mg^{2+} ATP-ase is very valid, especially in patients with heart diseases, because the release of calcium from sarcoplasmic reticulum causes a systole of muscle and elimination of Ca^{2+} ions from cytoplasma causes a diastole.

Magnesium is a major regulator in distribution of Ca^{2+} ions to and from the cell not only by ATP--ase working, but because it is a natural blocker of calcium channels (it competes with them in metrication through membrane) (7, 8, 11, 15). Furthermore, low concentration of calcium inside the cell is regulated indirectly by replacement of three extracellular Na^+ ions into one intracellular Ca^{2+} ions through sodium--calcium exchanger. This exchanger works in the same time as calcium pump but energetic cost of calcium transport by this exchanger is covered by sodium pump, which generates necessary Na^+ ions gradient (17, 20).

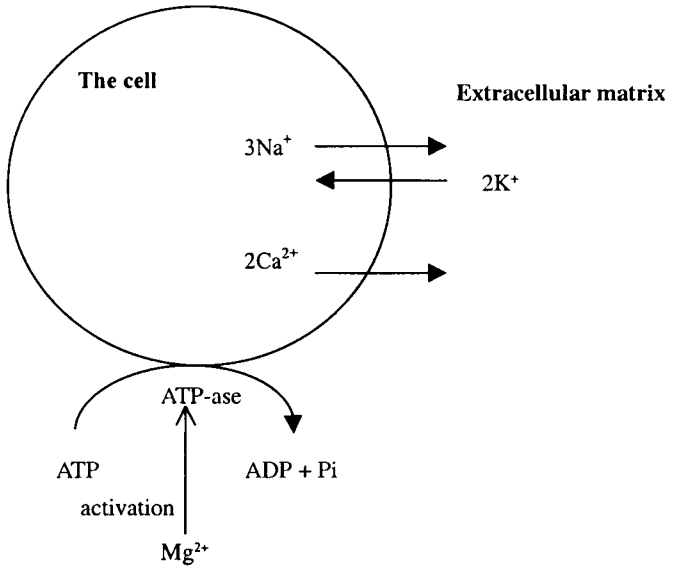

Fig. 1. The influence of magnesium on sodium and calcium pump. Disintegration of one ATP molecule into ADP and Pi, accompanies an efflux of three Na^+ and two Ca^{2+} ions from the cell. In the same time two K^+ ions get to the cell

Because magnesium influences bioelectric potential, it acts also on the cardiac conduction system and changes ECG curve (11). Deficiency of magnesium causes tall and pointed T wave (21), occurrence of U wave, elongation of QT (11, 16) and depression or elevation of ST segment (2, 3). Delivery of magnesium leads to elongation of the QRS duration (11, 12), elongation of PR interval (21) and shortens QT with parallel elongation of sinus period (21). Magnesium inhibits work of sinus node, elongates the return of sinus rhythm and elongates the conduction of sinoatrial node. The application of magnesium also inhibits atrioventricular conduction (21).

MAGNESIUM AND LIPIDS

Several epidemiologic studies have shown that magnesium is connected with triglycerides level in the human body, especially with HLD-cholesterol, which is an independent risk factor for coronary artery disease (14). High dietary magnesium values are correlated with high serum HLD-C (high density lipoprotein cholesterol) and low serum total lipid levels (12). Deficiency of magnesium acts conversely – there is observed a decrease of HLD-cholesterol and increase of the content of cholesterol in VLDL fraction (very low density lipoprotein) and also in LDL fraction (low density lipoprotein) (9,17). In consequence, it may lead to the development of arteriosclerosis, coronary artery disease, carotid disease and ischemic stroke (14). The increase of triglycerides concentration and non-esterified cholesterol in effect of hypomagnesaemia, is caused by lower activity of lecithin: cholesterol acetyltransferase (LCAT), which regulates the exchange of esterified cholesterol from HDL for triglycerides, present in VLDV.

DIGITALIS, DIURETICS AND MAGNESIUM

Glycosides of digitalis are given in treatment disorders, which cause congestion of the heart by increasing its systoles. But on the other hand, they inhibit Na^+/K^+ ATP-ase activated by magnesium, by blocking its dephosphorylation (20). It leads to the increase of Na^+ ions inside the cell and to the decrease of the sodium gradient, which causes decline of the speed of Ca^{2+} releasing from the cell by a sodium-calcium exchanger. The consequence of it is high concentration of calcium inside the cell, which increases contraction of the heart muscle and blood vessels (20). Furthermore, on the kidney level, digitalis inhibits returnable absorption of Mg^{2+} ions, which intensifies hypomagnesaemia. Magnesium deficiency suppresses digitalis elimination with urine, which leads to its high concentration in serum and organism intoxication. Additional diuretics (spread applied in hypertension) increase potassium and magnesium loss with urine and lead to ventricular arrhythmias. Thus, during digitalis and diuretics treatment, it is very important to supplement the lack of magnesium (11).

MAGNESIUM AS CARDIOPROTECTOR

Among the cardiovascular consequences of magnesium deficiency we may discern: multifocal necrosis with Ca^{2+} accumulation (ischaemic heart disease), cardiomyopathy, increased sensitivity to cardioglycerides, intensified tendency to platelet aggregation, increase of coronary and peripheral vascular resistance, arrhythmias, tachycardia, repolaryzation disturbance and ventricular arrhythmias (5, 6, 9, 13). Lack of magnesium stimulates the increase of epinephrine and norepinephrine release and it simultaneously intensifies the action of Ca^{2+} on muscle fibre. Catecholamine inducing activation of phospholipase C, releases Ca^{2+} bond with endoplazmatic reticulum, by what they preserve intracellular increase of Ca^{2+} caused by hypomagnesemia (9).

Arterial blood pressure – systolic arterial blood pressure whose responses to the systolic phase of ventricle are higher in big arterial than diastolic arterial blood pressure. Property values in adult increase with age. It has been suggested that higher dietary dose of magnesium inhibits pressure rise because it influences on resistant blood vessels and dilates blood vessels (12). The inverse correlation between magnesium serum level, magnesium erythrocytes level and arterial blood pressure has been showed (17, 20). Magnesium by competition with Ca^{2+} ions, increases systolic activity of the unstriped muscle of the cell wall (11).

Arteriosclerosis – is one of the main reasons of death of people above 65 years of age. The main causes of this disease are: agglomeration of cholesterol and its esters and others lipids inside the cell membrane, accumulation of mucopolysaccharides, focal hyperplasia of connective tissue, calcification, which leads to the thickening of the arterial wall and stenosis of its lumen. Too high consumption of animal fat and carbohydrates, lack of magnesium in a diet and its deficiency in the organism increase the risk of arteriosclerosis development (11, 17). This correlates with cholesterol which is deposited in the wall of blood vessels. Hypomagnesaemia reduces activity of lipoprotein lipase, which leads to higher concentration of triglycerides and total cholesterol in serum (9, 11).

Arrhythmias – in proper conditions, the rhythm of the heart is sinus (as a result of conduction in sinus nod) and regular (about equal intervals between the next stimulation and systole, rest frequency 60–80/min.). There are two groups of patients predisposed to ventricular arrhythmias: patients with myocardial infarction and patients with ischaemic heart disease. Magnesium deficiency increases the probability of tachycardia with ventricular fibrillation, torsade de pointes (8), ventricular tachyarrhythmias as consequences of digitalism, flutter and atrial fibrillation (6), multifocal atrial arrhythmias.

The beneficial influence of magnesium on these disorders is due to: stable action of magnesium on the cell membrane, which inhibits sodium current, suppressing the answer of blood vessel walls to

catecholamine, elongating static refraction, antagonistic action to calcium, increasing of ventricular fibrillation sensitivity threshold (19).

Myocardial infarction (MI) – is the consequence of advanced arteriosclerosis progress of the coronary artery. Many authors have suggested the correlation between hypomagnesemia and acute myocardial infraction (3, 11). Some of them in autopsy of the heart studies of patients who died because of MI, have noticed low concentration of K^+ ions and Mg^{2+} ions in cells (3). Other authors who examined animals, have observed that after closing of the arterial lumen there was efflux of K^+, Mg^{2+} ions and influx of Na^+, Ca^{2+} ions to damaged heart cells (13). The consequences of it were: higher lactic acid production, lower blood pH and arrhythmias (3). It has been shown that intravenous application of magnesium suppressed frequency of ventricular arrhythmias and possibly mortality after MI (13, 16, 19). Beneficial influence of magnesium in MI treatment is correlated with inhibiting calcium channels (13, 19, 21), with increasing of arterial circulation and with suppressing action on catecholamine release, which causes arrhythmias and which with lack of K^+ ions causes danger of ventricular arrhythmias (19). Moreover, magnesium corrects the ratio of requirement and utilization of provided to the heart oxygen (17, 19) and changes its energetic reserves.

Ischaemic heart disease – cardiovascular system does not supply oxygen and minerals to tissues and cells and does not remove CO_2 and other metabolism products. Patients with chronic heart function (CHF) have lower serum Mg^{2+} concentration. They very often die because of ventricular arrhythmias which lead to sudden heart death (2, 10). Arrhythmias are the consequences of bioelectrical heart instability, caused by ions deficiency (especially Mg^{2+} and K^+). Improper diet with low Mg^{2+} content, chronic treatment of digitalis (which is inhibitor of ATP-ase) and diuretic agents may cause or deteriorate ions deficiency in the organism (2,11). Hyperaldosteronism, induced during stimulation of renin-angiotensin-aldosterone system, very often accompanies patients with CHF. It causes systoles of vessels, sodium and water retention and increases magnesium and potassium loss with urine, which leads to acute ischaemic disease. Magnesium deficiency in patients with CHF is very often responsible for hypopotassemia resistant to supplementation. Potassium provided to the organism, because of the small activity of sodium pump being a result of magnesium lack, is not able to get into the cell (19).

REFERENCES

1. Bastida S. et al.: Selected trace elements and minerals in cord blood: association with lipids and lipoproteins at birth. Acta Paediatr., 89, 120, 2000.
2. Bogdan M. et. al.: Congestive heart failure and ventricular arrhythmias in relation Mg, K, Na in serum and erythrocytes. Kard. Pol., 38, 417, 1993.
3. Bogdan M., Nartowicz E.: Serum concentration and erythrocyte contents of magnesium. Potassium and sodium in patients with acute myocardial infraction. Kard. Pol., 38, 263, 1993.
4. Bogucka K.: Magnesium ions homeostasis in animal cells. Post. Bioch., 42, 178, 1996.
5. Boguszewska A. et al.: Magnesium and calcium concentrations in plasma in ischeamic heart disease and myocardial infraction. Annales UMCS, sect. D, 58, 96, 2003.
6. Frick M. et al.: The effect of oral magnesium, alone or as an adjuvant to sotalol, after cardioversion in patient with persistent atrial fibrillation. Europ. Heart J., 21, 1177, 2000.
7. Jones N. A., Jones S. D.: Management of life-threatening autonomic hyper-reflexia using magnesium sulphate in a patient with a high spinal cord injury in the intensive care unit. Br. J. Anaesth., 88, 434, 2002.
8. Khan J. A.: Long QT-syndrome: diagnosis and management. Am. Heart J., 143, 7, 2002.

9. Kittel M., Rewerski W.: The role of magnesium in the body. Pol. Tyg. Lek., 43, 822, 1988.
10. Klevay L. M., Milne D. B.: Low dietary magnesium increases supraventricular ectopy. Am. J. Clin. Nutr., 75, 550, 2002.
11. Lichodziejewska B., Kłoś J.: The magnesium ion in cardiology. Kard. Pol., 38, 126, 1993.
12. Maehama T. et al.: Management of automatic hyper-reflexia with magnesium sulfate during labor in woman with spinal cord jury. Am. J. Obst. Gynecol., 183, 492, 2000.
13. Manz M. et al.: Effect of magnesium on sustained ventricular tachycardia. Herz, 22 (suppl. 1), 51, 1997.
14. Maron D. J.: The epidemiology of low levels of high-density lipoprotein cholesterol in patients with and without coronary artery disease. Am. J. Cardiol., 86 (suppl. 12A), 11L, 2000.
15. Niżanowska-Błaż T. et al.: Serum magnesium level in children from the province of Rzeszów. Wiad. Lek., 46, 120, 1993.
16. Parikka H. et al.: Decreases by magnesium of QT dispersion and ventricular arrhythmias in patients with acute myocardial infraction. Europ. Heart J., 20, 111, 1999.
17. Pasternak K.: Magnesium in human physiology. Biul. Magnezol., 4, 480, 1999.
18. Sassaki S. et al.: Magnesium status in patients with cardiovascular diseases. Rinsho Byori, 47, 396, 1999.
19. Skotnicki A. B.: Antistress – cardioprotective effects of magnesium. Probl. Lek., 31, 3, 1992.
20. Stryer L. Biochemistry, 4th edition. PWN, Warszawa 1999.
21. Szyszka A., Kaźmierczak E.: Electrophysiologic effects of magnesium. Kard. Pol., 38, 131, 1993.

SUMMARY

Magnesium is one of the four major cations in the human body and the second most abundant within the cell. Observational studies have shown the fundamental role of magnesium in treatment of different cardiovascular disorders, connected with magnesium deficiency. As co-factor of many enzymes, especially those involved in phosphate transfer, it plays a role in regulation of intracellular reactions in the organism. By influence on sodium pump and calcium pump, it regulates flowing of Na^+, Ca^{2+}, K^+ ions through channels in cell membrane and therefore: decreases lack of K^+ ions, protects the cell from Ca^{2+} ions overloading, inhibits sodium influx into the cell, equalizes pH of cell by maintaining the correct level of acidosis, increases bioelectrical potential and supplies energy for calcium pump and sodium pump. Moreover, magnesium controls the level of triglycerides (rebuilds integration of cell membrane), attends in local autonomic control of circulation, which helps to maintain the balance of peripheral movement, corrects activity of conduction and stimulogenic system of the heart. Still carried out intensive research into the influence of magnesium on the human organism function may show unknown so far aspects of this element action on the cardiovascular system.

Rola magnezu w chorobach sercowo-naczyniowych

Magnez jest jednym z czterech głównych kationów występujących w organizmie człowieka i drugim obecnym w komórce. Badania doświadczalne wskazały na istotną rolę magnezu w leczeniu różnych schorzeń układu sercowo-naczyniowego, związanych z jego niedoborem. Jako kofaktor wielu enzymów (szczególnie tych związanych z przenoszeniem fosforu) bierze udział w regulacji

wewnątrzkomórkowych reakcji w organizmie. Poprzez wpływ na pompę sodową i wapniową reguluje przepływ jonów Na^+, K^+, Ca^{2+} przez błonę cytoplazmatyczną, przez co: obniża niedobór jonów K^+, chroni komórkę przed przeładowaniem jonami Ca^{2+}, hamuje napływ jonów Na^+ do komórki, wyrównuje pH komórki poprzez utrzymanie odpowiedniego poziomu kwasicy, zmienia potencjał bioelektryczny i dostarcza energii do pompy sodowej i wapniowej. Ponadto magnez reguluje poziom trójglicerydów (odbudowuje integralność błony komórkowej), bierze udział w miejscowej autoregulacji krążenia krwi, co przyczynia się do utrzymania równowagi przepływu obwodowego oraz poprawia czynność układu bodźcotwórczego i przewodzącego serca. Prowadzone intensywne badania w zakresie wpływu magnezu na funkcjonowanie organizmu człowieka mogą ujawnić nieznane jeszcze dotychczas aspekty działania tego pierwiastka na układ sercowo-naczyniowy.