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REVIEW PAPER

BIOCHEMISTRY OF MAGNESIUM

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Abstract

Magnesium is essential for biochemical functions of cells. Since Mg^{2+} has a relatively low ionic radius in proportion to the size of the nucleus (0.86 versus 1.14 f Å for Ca^{2+}), it shows exceptional biochemical activity. Due to its physicochemical properties, intracellular magnesium can bind to the nucleus, ribosomes, cell membranes or macromolecules occurring in the cell's cytosol. It is indispensable for the nucleus to function as a whole and for the maintenance of physical stability as well as aggregation of rybosomes into polysomes able to initiate protein synthesis. Mg^{2+} can also act as a cofactor for ribonucleic acid enzymes (ribozymes) capable of specifically recognizing and cleaving the target mRNA. As an essential cofactor in NER, BER, MMR processes, Mg^{2+} is required for the removal of DNA damage. An activator of over 300 different enzymes, magnesium participates in many metabolic processes, such as glycolysis, Krebs cycle, β-oxidation or ion transport across cell membranes. Mg^{2+} plays a key role in the regulation of functions of mitochondria, including the control of their volume, composition of ions and ATP production.

Key words: magnesium, DNA repair process, enzyme, metabolic cycle, cellular respiration, calcium ion transport, potassium ion transport.

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Abstrakt

Magnez jest składnikiem niezbędnym dla zasadniczych funkcji biochemicznych komórki. Ponieważ Mg^{2+} ma relatywnie mały promień w stosunku do wymiarów jądra (0.86 i 1.14 Å odpowiednio dla Mg^{2+} i Ca^{2+}), wykazuje dużą aktywność biochemiczną. Dzięki właściwościom fizykochemicznym śródkomórkowy Mg^{2+} może wiązać się z jądrem komórkowym, rybosomami, błonami komórkowymi oraz makromolekułami cytosolu komórki. Magnez jest niezbędny dla funkcjonowania jądra komórkowego jako całości oraz utrzymania fizycznej stabilności i agregacji rybosomów do polisomów zdolnych do biosyntezy białka. Odgrywa on również rolę kofaktora katalitycznych cząsteczek RNA (rybozymów), odpowiedzialnych za specyficzne rozpoznawanie i fragmentację docelowego mRNA. Jako kofaktor w procesach: NER, BER, MMR, przyczynia się do usuwania uszkodzeń DNA. Magnez, będąc aktywatorem ponad 300 różnych enzymów, uczestniczy w przebiegu wielu szlaków metabolicznych, takich jak glikoliza, cykl Krebsa, β-oksydacja czy transport jonów poprzez błony komórkowe. Odgrywa on ponadto bardzo ważną rolę w regulowaniu funkcji mitochondriów, łącznie z regulacją ich wielkości, kompozycją jonów, a także bioenergetyką i regulacją produkcji ATP.

Słowa kluczowe: magnez, proces naprawy DNA, enzym, cykl metaboliczny, oddychanie wewnątrzkomórkowe, transport jonów wapnia, transport jonów potasu.

INTRODUCTION

The involvement of magnesium ions (Mg^{2+}) in metabolic processes is governed not only by their abundance in nature or relative amount in living organisms but also by their physicochemical characteristics.

Since Mg^{2+} has a relatively low ionic radius in proportion to the size of the nucleus (0.86 versus 1.14 f Å for Ca), it shows exceptional biochemical activity. Ionized Mg^{2+} usually coordinates with 6-7 molecules of H_2O, as in the case of $MgCl_2 \cdot 6\ H_2O$ or $Mg_2SO_4 \cdot 7\ H_2O$, while Ca and Ba combine with 1 or 2 mols of H_2O ($BaCl_2$ and $CaCl_2$ respectively). In comparison to calcium (Ca), the most abundant cation in the human body, Mg^{2+} displays higher affinity for oxygen donor ligands, that is negatively charged carboxylates and phosphates or enolate moieties (Wolf, Cittadini 2003). Mg-water coordination occurs in a typical octahedral conformation and thereby magnesium exhibits slower water exchange than other ions. Consequently, it is much bigger and more stable in comparison to Ca in biological systems (Wolf, Cittadini 2003, Wedekind et al. 1995)

Considering stereochemical properties, nickel (Ni) most closely resembles Mg^{2+} (it has atoms of the same size of and identical water exchange constant). However, Ni^{2+} cannot compete with Mg^{2+} in living organisms both due to its paucity and tendency to bind nitrogen rather than oxygen.

At the cellular level, magnesium ions compete not only with Ca but also with protons or amines ($-NH_2^+$). Protons are usually present in concen-

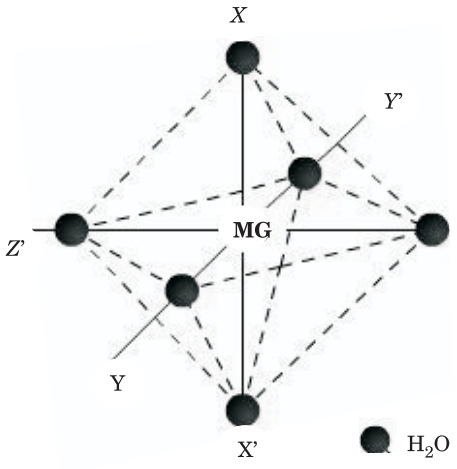


Fig. 1. Octahedral magnesium complexes (WOLF, CITTADINI 2003)

trations below 10^{-7} M at pH 7 and link up to phosphate groups with a pKa of 6.5, which is significantly lower than that of Mg-phosphate complexes. This suggests that Mg^{2+} is removed from ATP when pH falls to 6.0, causing significant modifications of Mg-dependent reactions:

$$Mg \cdot ATP + H^+ \leftrightarrow H \cdot ATP + Mg^{2+}$$

Polyamines, organic derivatives of ammonia, exhibit high-affinity binding of polyanions, for instance nucleic acids, and dislodge Mg^{2+} bound therein (WOLF, CITTADINI 2003).

Due to its physicochemical properties, intracellular magnesium can bind to the nucleus, ribosomes, cell membranes or macromolecules occurring in the cell's cytosol.

Magnesium and DNA

More than half the magnesium contained in the nucleus is closely associated with nucleic acids and free nucleotides. Since nucleic acids are polyanions, they require counterions in order to neutralize negatively charged phosphate groups (WOLF, CITTADINI 2003, ANASTASSOPOULOU, THEOPHANIDES 2002). The intracellular concentrations of Na and Ca are low, therefore the binding of the metal with nucleic acids is dominated by K^+ and Mg^{2+}. Free Mg^{2+} is the winner in this competition because it has more positive charges (+ II and +I for Mg and K, respectively) and higher hydration energy (WOLF, CITTADINI 2003).

In Mg-DNA interactions, metal ions interact with purine bases at the N7 site and pyrimidine bases at the N3 site by forming chemical bonds,

Mg-N7 and/or Mg-N3. They also interact with the negatively charged oxygen atoms of phosphate groups of nucleotide chains (ANASTASSOPOULOU, THEOPHANIDES 2002). These interactions play a significant role in the stabilization of the secondary and tertiary structure of DNA.

The pathway of binding divalent metal ions to guanosino-5-monophosphate is shown in Figure 2. The intrinsic structure of this complex results from the fact that one of the coordinated water molecules may be substituted by the N7 coordination site of the nucleotide or be hydrogen-bound to it, while another one may be involved in a hydrogen bond with O6, and yet others form more hydrogen bonds (ANASTASSOPOULOU, THEOPHANIDES 2002).

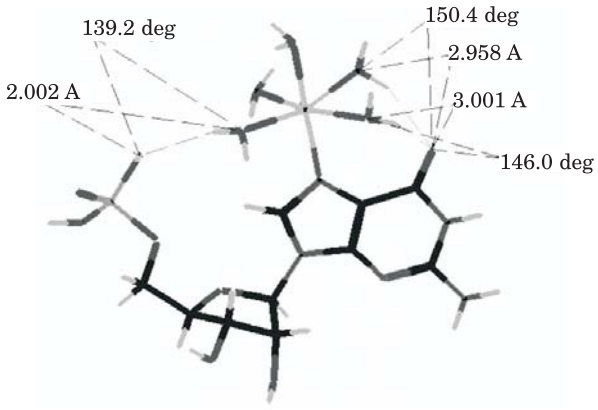


Fig. 2. Structure of magnesium hydrate complex with guanosino-5- monophosphate (the broken lines show hydrogen bonds together with the hydrogen bond distances and angles) (ANASTASSOPOULOU, THEOPHANIDES 2002)

Whether or not Mg^{2+} acts as a gene regulator remains unclear. Since the bioactivity of this cation is remarkable, it is reasonable to think that magnesium may act as a competitor to polyamines, which are currently recognized as potential regulators of the cell cycle (WOLF, CITTADINI 2003).

$$DNA^*(Mg^{2+})\ n + m\text{-polyamine}^{x+} \longleftrightarrow (DNA^*\ polyamine^{x+})\ m + nMg^{2+}$$

Magnesium ions can affect the cellular cycle also in the form of Mg-ATP. This complex plays a key part in a phosphorylation cascade catalyzed by protein kinases. Alternatively, due to its capability to directly interact with proteins, Mg^{2+} can modulate histone phosphorylation (WOLF, CITTADINI 2003).

Irrespective of the above mechanisms, magnesium is indispensable for the functioning of the cell nucleus as a whole as it is involved in the activation of enzymes important for DNA repair (endonuclease) (WOLF, CITTADINI 2003, HARTWIG 2001, WOLF et al. 2003), replication (topoisomerase II (WOLF,

CITTADINI 2003, WOLF et al. 2003), polimerase I (WOLF, CITTADINI 2003) and transcription (rybonuclease H) (WOLF, CITTADINI 2003). Mg^{2+} is crucial for the physical integrality of double-stranded DNA.

In ribosomes, Mg^{2+} is associated with rRNA or proteins, which are essential for the maintenance of physical stability as well as aggregation of these structures into polysomes able to initiate protein synthesis. Cowan has shown that magnesium deficit leads to the cleaving of a ribosomal complex (COWAN 1995). Since the only function performed by ribosomes is protein biosynthesis, it is the presence of Mg^{2+} in ribosomes that conditions the shape of RNA structures by stimulating the transformation of amino acids into active forms, polypeptide synthesis and stabilization of a protein structure.

Moreover, magnesium can also act as a cofactor for ribonucleic acid enzymes (ribozymes) capable of specifically recognizing and cleaving the target mRNA. Ribozymes are chiefly used in steered therapy of neoplastic diseases (JOŚKO, KNEFEL 2003). It is believed that two metal ions (mostly Mg^{2+}, although Mn^{2+}, Zn^{2+}, Ca^{2+}, Co^{2+} or Na^{+} are also possible) are necessary for catalytic activity of hammerhead ribozymes. One metal ion activates the attacking hydroxyl group, and the other stabilizes the negative charge of the oxygen atom of the released group (ADAMALA, PIKUŁA 2004). While one experiment with minimal hammerhead domains has demonstrated that the efficiency of catalysis is highly dependent on the concentration of magnesium ions, another one has shown that this efficiency can be increased at low magnesium concentration through stabilization of catalytically active conformation by tertiary interactions between helices I and II. Apart from these electrostatic interactions, both free Mg^{2+} as well as the GTP-Mg complex play an important role in tubulin polymerization and, consequently, in chromosome segregation during mitosis (HARTWIG 2001).

Role of magnesium in genomic stability

In 1976 LOEB et al. noted that magnesium ions are indispensable for DNA replication fidelity. Although Co^{2+}, Mn^{2+} and Ni^{2+} ions can be substituted for Mg^{2+}, such an exchange causes a considerable decrease in the fidelity of the discussed process. A metal ion (A) binds to the 3'-hydroxyl group of a new synthesis strand, leading to the lowering of its pKa and thereby facilitating an attack on the á-phosphate of “arriving” dNTP. Another metal ion (B) facilitates the leaving of the â- and ă-phosphates as well as phosphodiester bond formation (HARTWIG 2001).

Role of magnesium in DNA repair processes

Damage to DNA can be caused by exogenous factors (e.g. ultraviolet or electromagnetic radiation, high temperature, viruses, polycyclic aromatic hydrocarbons, radiotherapy or chemotherapy) or endogenous factors (mainly

ROS – reactive oxygen species). In order to lower the frequency of mutation, cells have developed many different DNA-repair systems.

Nucleotide excision repair (NER) is an evolutionarily conserved DNA repair pathway, which repairs DNA damaged by various environmental mutagens. Photodimers, pirymidine, adducts as well as some of the damage repaired in the course of base excision repair (BER) can be removed from DNA (SANCAR 1994). The repair process is dependent on coordinated action of more than 20 different proteins. The majority of them are engaged in damage recognition and incision at both sides of the defect. Magnesium acts as a cofactor practically at every NER stage. Results of *in vitro* investigations have shown that this mechanism is completely inhibited in the case of absence and very high concentrations of magnesium. Experimental data have confirmed that the DNA-damage recognition protein UV-DDBP, the helicase XPD and the nuclease XPG are all magnesium-dependent. The element is required not only in enzymatic incision of DNA, but also in the processes of polymerization and ligation (HARTWIG 2001).

Reactive oxygen forms, normal products of cellular metabolism, lead to a wide variety of DNA modifications: destabilization of a DNA helix as well as degradation of protein-DNA crosslinks. Additionally, they are a major contributor to the oxidation of purine and pyrimidine bases, the damage of pentose ring, the hydrolysis of amine – or N-glycosidic bonds and phosphodiester bonds, hydrolytic deamination and methylation of oxygen or nitrogen atoms of DNA bases. At the extracellular level, ROS impair the function of blood platelets and induce protein, lipid or nucleic acid oxidation resulting in tissue destruction in many organs (CERIELLO, MOTZ 2004). It is believed that a mature organism can produce about 2 kilograms of superoxide anions per year, which can be transformed to H_2O_2 by dismutation reaction (ROSZKOWSKI 2002).

Endogenous damages of DNA are mainly repaired by the BER mechanism. According to current models, BER begins with a removal of modified nitrogenous base by a specific N-glycosidase generating an AP site, which is repaired by AP-endonucleases cleaving the phosphodiester bond at the AP 5' side and leaving a 3' hydroxy terminus, making the action of DNA polymerase and ligase possible (ROSZKOWSKI 2002). Contrary to DNA glycosidases, enzymes involved in later stages of BER always require magnesium. In hydrolytic nucleases, which are metal-ion-dependent (mainly magnesium-dependent), metal interacts with a substrate or is directly involved in cleavage of the phosphate-oxygen bond. In human apurinic/apyrimidinic endonuclease (HAP1), single magnesium ion combines with a defined Glu residue in the active center and aids the attack on the P-O3' bond by polarization of the P-O bond, perhaps by correctly orientating the phosphate group rather than directly participating in the nucleolysis reaction. HAP can also be activated by manganese or nickel ions, but its activity is considerably lower (by 50 and 90% respectively). Other examples of magnesium-dependent endonucle-

ases in BER include apurinic/apyrimidinic endonuclease, whose activity is associated with the 5-hydroxymethyluracil-DNA glycosylase, flap-endonuclease-1 (FEN-1) and a structure-specific endonuclease involved in DNA replication and DNA repair (HARTWIG 2001).

The third system, mismatch repair (MMR), has evolved to correct errors occurring during DNA replication or recombinaton of genes. Impairment of MMR leads to genomic instability, which creates favourable conditions for induction and development of carcinogenic processes. The most frequent mutations in the MMR system are those of genes from the MLH gene family. Constitutive mutations involving one allele of the MLH1 gene lead to tumor predisposition syndrome – hereditary nonpolyposis colorectal cancer (HNPCC type II) (COOK 2000) and can also be connected with Turcot syndrome. Additionally, the role of this gene in carcinogenic processes in other organs, especially in breast cancer, is also investigated (BRYŚ et al. 2004).

A study conducted by BAN and YANG (1998) has shown that MutL gene of *E. coli* is absolutely Mg-dependent and, in absence of magnesium ions, hydrolysis of the MutL-ATP complex can be observed. High homology between MHL and MutL suggests that magnesium is also indispensable for the activity of human MHL genes. Moreover, double-stranded DNA break repair induced by ionizing radiation or formed during meiosis has also been found to be Mg-dependent (HARTWIG 2001).

Magnesium and enzymes

An activator of over 300 different enzymes, magnesium participates in many metabolic processes, including transformation of proteins, lipids, carbohydrates and nucleic acids as well as electrolyte transport across cell membranes (WOLF, CITTADINI 2003).

Magnesium can originally bind to a substrate (by chelatation), producing a complex that is the correct substrate for enzyme or directly attach to enzyme, creating active structure able to affect a substrate. However, these mechanisms are combined with each other because ATPase affects the correct substrate (ATP-Mg) only if it is activated by another Mg^{2+} ion.

The general mechanisms of Mg^{2+} action as a cofactor can be described as follows (WOLF, CITTADINI 2003):

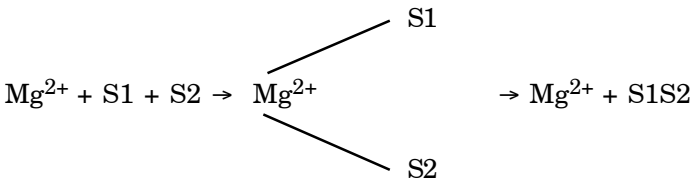
A. Magnesium is engaged in stabilization of an intermediate product:

$$Mg^{2+} + S \rightarrow Mg^{2+} - Y \rightarrow Mg^{2+} + P$$

B. Magnesium stabilizes a product leaving group:

$$Mg^{2+} + SX \rightarrow Mg^{2+} - XS \rightarrow Mg^{2+} X + S$$

C. Magnesium binds two reactive substrates simultaneously and facilitates reaction through the proximity effect:



The majority of enzymes can be also activated by metal ions other than Mg^{2+}, although such a replacement leads to reduced efficiency of enzymatic reaction.

Magnesium in metabolic cycles

In higher organisms, metabolic processes such as glycolysis, Krebs cycle, β-oxidation, active transport of ions or electrochemical coupling are regulated by Mg-dependent enzymes. The main domain of magnesium action is the activation of enzymes responsible for formation, storing and using of high-energy compounds. All reactions involving ATP require the presence of magnesium ions (Touyz 2004). An Mg^{2+} ion, coupled with oxygen atoms of phosphorus groups located at â and ă positions, protects APT molecules from enzymatic hydrolysis, while the dislocation of Mg^{2+} in the direction of á and â positions facilitates the hydrolysis of terminal phosphorus groups. Magnesium in the form of β, γ-Mg-ATP complex binds to active centers of many enzymes. The complexes of Mg-ATP are essential for catalytic activity of, e.g., phosphotransferases (kinases), nucleotidylotransferases and ATPases (Cowan 1995).

Magnesium ions activating adenylate cyclase control cyclic adenosine monophosphate (cAMP) synthesis. Adenylate cyclase activtion is crucial for the control of anaphylactic reactions because high intracellular cAMP and cGMP concentrations slow down or stop degranulation of mast cells. Consequently, the accessibility of magnesium to the enzyme can modulate cyclic nucleotide metabolisms in cells. Since Mg^{2+} deficit stimulates histamine release from mast cells by inhibition of cAMP production, it is believed that magnesium reduces the hypersensitivity reactions (Błach et al. 2007).

Perfect confirmation of the key role of cellular magnesium is glycolysis, especially in human erythrocytes, as many enzymes involved in this process are Mg-dependent. Moreover, removing extracellular Mg^{2+} or chelating intracellular Mg^{2+} markedly inhibits glycolysis and limits glucose transport by erythrocytes (Laughlin, Thompson 1996).

Numerous literature data suggest some correlation between glucose transport and changes in intro- or extracellular Mg^{2+} level resulting from hormonal stimulation of β-pancreatic islets (Henquin et al. 1983, Fagan, Romani 2000), hepatocytes (Fagan, Scarpa 2002, Gaussin et al. 1997) or cardiomyocytes (Romani et al. 1993, Romani, Scarpa 1990, Romani et al. 2000).

An increase in catecholamine or glucagon leads to secretion of glucose and Mg^{2+} from liver cells into the extracellular compartment (GAUSSIN et al. 1997). The presence of glucose transport inhibitors (ROMANI, SCARPA 1990) and the absence of extracellular Na^{+}, which hampers magnesium extrusion, also impair glucose output by liver cells. TORRES et al. (2005) have reported that hepatocytes from starved rats (after overnight fasting) accumulated approximately fourfold more Mg^{2+} than liver cells from fed animals. This clearly indicates that diminution of intrahepatic cellular glycogen or glucose level causes decreased ability of catecholamine or glucagon to mobilize Mg^{2+} from the hepatocyte.

In cardiac myocytes, parallel accumulation of glucose and Mg^{2+} is induced by insulin (HARTWIG 2001, ROMANI et al. 1993, 2000). Insulin acts as an endogenous regulating factor of Mg^{2+} homeostasis. Flux concentrations of blood or tissue magnesium are dependent on the amount of insulin released from pancreatic islets and insulin immunity of tissues (ROMANI et al. 2000). Also in this case, the absence of extracellular glucose or the presence of glucose transport inhibitors hamper Mg^{2+} transportation, lower extracellular Mg^{2+} content and break the transport of glucose to myocytes (ROMANI et al. 1993). Some correlation between glucose and Mg^{2+} transport/utilization in rats rendered diabetic by streptozotocin injection has been confirmed by FAGAN et al. (2004). Rats experienced a 10% and 20% decrease in the liver magnesium level after 4 and 8 weeks, respectively, after the onset of the disease. CEFARATTI et al. (2004) have confirmed dminished accumulation of Mg^{2+} in liver blisters isolated from rats with experimental diabetes.

Since Mg^{2+} accumulation directly or indirectly influences protein kinase C activation, it is possible that in diabetic patients the enzymatic action is disturbed. TANG et al. (1993) have also observed selective alterations in the expression PKC and marked differences in the distribution of the various isoforms between membrane and cytosol fractions of hepatocytes with streptozotocin-induced animals.

Similar modifications in the distribution of PKC as well as the reduction of cell magnesium content have been observed in tissues of ethanol-fed rats (YOUNG et al. 2003). The total magnesium concentration in animal hepatocytes of the examined group was 26.8 ± 2.4 nM mg^{-1} proteins versus 36.0 ± 1.4 nM mg^{-1} proteins for the control group. In comparison to the control conditions, the Mg^{2+} level in hepatocytes from EtOH-treated samples did not increase following stimulation of protein kinase C by vasopressin or analogs of diacilglicerol (DAG). Moreover, the stimulation of α- or β-adrenoreceptors in alcohol supplemented animals, did not elicit Mg^{2+} extrusion from liver cells to the extacellular space.

KIMURA et al. (1996) have shown that in Mg-deficient rats concentration of blood glucose and plasma insulin both in overnight fasted and non-fasted individuals as well as in response to oral sucrose loading are impaired. After 8 weeks of low-Mg^{2+} diet, translocation of insulin-stimulated glucose trans-

porter 4 (GLUT4) to the adipocyte plasma membrane was significantly reduced. In addition, phosphorylation of insulin receptor was lower in Mg-deficient animals. On the other hand, wortmannin (WT) or another PI 3-kinase inhibitor blocked the insulin-stimulated activity of Na^+/Mg^{2+} exchange (Ferreira et al. 2004).

These data may suggest that Mg^{2+} absence induces alterations in glucose metabolism by reducing intestinal glucose absorption or glucose assimilation in liver and/or other tissues (Kimura et al. 1996).

Magnesium and cellular respiration

Magnesium maintains a mitochondrial respiratory coupling chain, in which phosphorylation and oxidation obtain high efficiency. Magnesium ions might be transported to the mitochondrial matrix across Mrs2p channel of the inner mitochondrial membrane, whose activity depends on both electric potential and Mg^{2+} concentration, but the electrophysiological profile of Mrs2p remains to be developed (Kolisek 2003).

The flux Mg^{2+} level in the mitochondrial matrix modulates á-ketoglutarate dehydrogenase (Chakraborti et al. 2002), pyruvate dehydrogenase and glutamate dehydrogenase (Panov, Scarpa 1996) activity. Alterations of the matrix Mg^{2+} concentration (coupled with alternatively to changes of Ca^{2+}) are reflected in the mitochondrial respiration rate.

Moreover, Lin et al. (1993) demonstrated that Mg^{2+} is an integral component of subunit IV of cytochrome c oxidase complex, the last enzyme of the respiratory chain catalyzing molecular oxygen reduction. The volume of an organelle is regulated by the matrix magnesium through direct control of the K^+ /H^+ antiporter, inhibition of mitochondrial inner membrane anion channel (IMAC) as well as through indirect modulation of the channel's permeability.

IMAC channels display selectivity among monovalent (Cl^-, HCO_3^-) as well as polyvalent (e.g. citrate) ions. These channels are probably also involved in the synchronization of oscillation in a mitochondrial membrane potential of isolated cardiomiocytes. Evidence has been provided that IMAC regulates the flow of anionic peroxidase from mitochondria during the ischaemic preconditioning (IPC) (Skalska et al. 2006). Although the IMAC control mechanism has not been completely elucidated, Beavis and Powers (2004) suggested that the matrix Mg^{2+} as well as the protons impair channel activity.

The IMAC activation precedes the opening of the mitochondrial permeability transition pore (PTP), thereby promoting cell death. The PTP opening is a direct cause of the death of neurons in a damaged brain or in cardiac myocytes during ischemia and reperfusion. PTP also plays a role in muscular dystrophy (DMD), caused by deficiency of collagen VI, as well as in hepatocytosis, inducted by cancerogenic factors (Skalska et al. 2006). The increase of the mitochondrial calcium pool facilitates the PTP opening whereas

a larger matrix Mg^{2+} concentration blocks this channel. Moreover, ZORATTI and SZABO (1995) showed that megachannels are inhibited by divalent cations, such as Mg^{2+} or Mn^{2+}, nucleotides: ADP and ATP as well as poliamines. DOLDER et al. (2003) established that magnesium plays an indirect role in modulating the PTP opening. They proved that creatine kinase can regulate the PTP size by tightly associating to the mitochondrial membrane and remaining in an active state. Impaired concentration of the extramitochondrial Mg^{2+} causes reduction of creatine kinase activity and increased pore permeability (DOLDER et al.).

Magnesium ions are also essential to glutathione synthesis, which can be confirmed by the fact that GSH level in the red blood cells of rats decreased after 2-3 weeks of a Mg^{2+}-deficient diet (WĘGLICKI et al. 1996). Glutathione depletion enforces reactive oxygen species accumulation, resulting in mitochondrial dysfunction, which is decisive in apoptotic cascade. The changes in the mitochondrial membrane's potential lead to the opening of megachannels in mitochondrial membranes, to alterations of membrane permeability, to translocation of cytochrome c and apoptosis inducing factor (AIF) from the mitochondria to the cytosol, which is the starting point for programmed cell death.

The above facts confirm the key role of Mg^{2+} in the regulation of mitochondrial function, including the control of their volume, composition of ions and ATP production.

Magnesium and calcium ion transport

Magnesium ions are important for maintaining cell homeostasis because they are essential to the stabilization of cell membranes, to the activation of sodium-potassium pump (Na-K-ATP-ase) or calcium pump (Ca-ATP-ase), and to the regulation of composition of intra- and extracellular liquid (HARTWIG 2001, COWAN 1995).

As calcium antagonist, magnesium increases the neuromuscular excitability and has an antispastic and anticonvulsive effect, impairing the contractibility of muscles.

As early as in in 1988, WHITE and HARTZELL showed that free intracellular magnesium can regulate the functioning of calcium channels. BARA and GUIET-BARA (2001) have confirmed that extracellular magnesium salts ($MgCl_2$ or, to a smaller extent, $MgSO_4$) reduce the influx of calcium through high-voltage channel Ca^{2+} type L in vascular smooth muscle cells (VSMCs) and vascular endothelial cells (VECs) of human plancenta (BARA, GUIET-BARA 2001), and consequently modulate the tonus of placental vessels. Mg^{2+} and GTP binding sites are assumed to reside in the intracellular C-terminal side of the a1 subunit of the channel. In basal conditions (i.e. the dephosphorylated channel and Mg^{2+} and GTP abundant on the intracellular side) Mg^{2+} and GTP binding to C-terminal inhibit the current conduction. A decrease in Mg^{2+} without intracellular GTP produces a current conducting state but

addition of GTP blocks the channel. Phosphorylation results in both Mg^{2+} and GTP blocks by unbinding these blocking substances through conformational change of the channel protein.

Serrano has described a similar blocking effect of extracellular magnesium on α1G T-type calcium channels, which play an important role in the mechanisms underlying thalamocortical oscillation (SERRANO et al. 2000). This is particularly essential because T channels are not blocked by classic calcium antagonists (except for mibefradil which is not used in clinical practice on account of undesirable action).

Whether or not Mg^{2+} ions modulate the action of store-operated calcium release-activated Ca^{2+} channels (CRAC), involved in regulation of inflammatory mediators production in allergic reactions as well as in differentiation and activation of T lymphocytes, is still not completely elucidated.

While the results of some experimental research have shown that intracellular magnesium modulates activity and selectivity of CRAC, others suggest that the channels regulated by intracellular Mg^{2+} are not CRAC channels but rather Mg-inhibited cation (MIC) channels that open as Mg^{2+} is washed out of the cytosol. MIC have been defined as another class of channels because they display different functional parameters from those displayed by CRAC in terms of inhibition (e.g. MIC are not blocked by SKF 96365 – the inhibitor of CRAC channels) or selectivity (unlike CRAC, MIC channels are permeable to Cs^+ ions; PCs/PNa = 0.13 vs. 1.2 for MIC) (PRAKRIYA, LEWIS 2000).

Studies carried out on rats with arterial hypertension have confirmed that extracellular Mg^{2+} imitates nifedipine in the process of reducing Ca^{2+} entry to vascular smooth muscle cells through store-operated channels (SOCs), resulting in the widening of circular vessels and a decrease in peripheral resistance as well as blood pressure (ZHANG et al. 2002).

Magnesium and potassium ion transport

Potassium channels play a crucial role in the regulation of membrane potential in smooth muscle cells and vascular tone.

As the equilibrium potential for potassium ions in vascular smooth muscle cells is more negative (-84 mV) than the cell's resting potential (-60 to -70 mV), the opening of potassium channels induces the K ion outflow from the cell. The loss of cations caused by an increase in the absolute value of membrane potential leads to the closing of L-type voltage-gated calcium channels (VGCC-L), to a decrease in intracellular calcium concentration as well as to relaxation of vessels. Blocking of potassium channels, however, lowers membrane potential, stimulates calcium ion inflow via voltage-gated ion channels (VDCC) and produces vessel contraction (BARANOWSKA et al. 2007).

TAMMARO et al. (2005) have provided evidence that intracellular Mg^{2+} ions affect voltage-dependent K channels (Kv), which regulate potassium ion dis-

tribution and cooperate with K_{Ca} channels in control of arterial vessels convolution in vascular smooth muscle cells. It was observed that an increase in the intracellular Mg^{2+} level slows down the K_V channel activation, causes inward rectification at positive membrane potentials and shifts voltage-dependent inactivation. The above results demonstrate that intracellular Mg^{2+} can act as a potent modulator of K_V channel in vascular smooth muscle cells, representing a novel mechanism for the regulation of K_V channel activity in the vasculature.

Cell magnesium also regulate the action of Ca^+-dependent K^+channels (BK_{Ca}), essential for modulating muscle contraction and neuronal activities such as synaptic transmission or hearinghttp://www.nature.com/nature/journal/v418/n6900/full/nature00941.html - B1 (SHI et al. 2002). Physiological activation of BK_{Ca} channels counteracts depolarization of cell membranes, contraction of blood vessels and increasing pressure (BARANOWSKA et al. 2007). Because of the importance of BK channels in neurotransmitter release and vascular tone, Mg^{2+} modulation of BK channels may play a substantial role in these pathophyisological processes. Mg^{2+} modulates their permeability by blocking the opening of a BK channel or by stimulation of channels independently from Ca^{2+} and voltage changes following binding to an open channel in different than Ca specific site or in no site (SHI et al. 2002). The structural separation between the binding site and the activation gate indicates that Mg^{2+} binding activates the channel by an allosteric mechanism; i.e., Mg^{2+} binding may cause a conformational change at the binding site that propagates to the activation gate for a channel opening (HUANGHE 2008).

Intracellular Mg^{2+} affects bioelectrical activity of the heart via regulation of inward rectifying potassium channels (K_{IR}), which are responsible for blocking outflow of K ions from cell and repolarization (BARANOWSKA et al. 2007).

Physiological concentrations of intracellular Mg-ADP complex regulate the sensitivity of ATP-sensitive potassium channels (K_{ATP}) to sulphonylurea derivatives. Sulphonylurea derivatives, used to treat type 2 diabetes, stimulate insulin secretion by blocking K_{ATP} channels in pancreatic β-cells. An intracellular Mg-ADP complex modulates sulphonylurea block, enhancing the inhibition of Kir6.2/SUR1 (β-cell type) and decreasing that of Kir6.2/SUR2A (cardiac-type) channels. This is important because the opening of K_{ATP} channels is regarded as an endogenous cardioprotective mechanism so the blocking effect of sulphonylurea derivatives in the cardiovascular system may have deleterious effects (REIMANN et al. 2003).

The influence of Mg^{2+} on K^+ channels is not limited to the cell membrane. BEDNARCZYK et al. (2005) have shown that matrix Mg^{2+} ions affect mitochondrial ATP-dependent potassium channel (K_{ATP}) in the heart, which plays a key role in protecting from ischemia/reperfusion. The ATP/Mg^{2+} complex inhibits K_{ATP} activity and free magnesium ions regulate both the channel conductance and open probability. Another study has suggested that mi-

toK_{ATP} channels make functional connection with mitochondrial pyruvate dehydrogenase forming a larger, multiprotein complex. A hypothesis has been formulated that enhanced activity of mitoK_{ATP} channel protects the heart muscle during myocardial ischemia as well as neurons, brain cells and skeletal muscle cells (SKALSKA et al. 2006).

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