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PHARMACOLOGICAL PROPERTIES OF CALCIUM AND MAGNESIUM: UNITY AND STRUGGLE OF OPPOSITES

In the review article, the authors, on the basis of literary data provided in Scopus, Google Scholar, and other publishers, provide information on the physicochemical, biochemical, pharmacological, and clinical properties of calcium and magnesium, emphasize their general pharmacodynamics, emphasize their differences, and reveal the stages, characteristic of hyper- and hypocalcemia and magnesiumemia. The stability of magnesium complexes with glucose and glucosamine is higher than with calcium. For coordination compounds of magnesium with glucose, the entropic contribution is greater, and for compounds of calcium with glucose – the enthalpic contribution. Calcium ions bind to proteins with greater activity than magnesium ions. The energy required for dehydrating magnesium is greater than for dehydrating calcium. Hypercalcemia and hypermagnesemia are observed less often than hypocalcemia and hypomagnesemia. The effect of calcium and magnesium drugs on the bone system, the effect on the cardiovascular and nervous systems, and the digestive tract is revealed. The peculiarity of the effect of calcium medicines. on the blood coagulation system is emphasized, they also have an anti-allergic effect. Calcium drugs affect all phases of blood coagulation. The antiallergic effect of calcium medicines is associated with stabilization of the cell membrane, inhibition of exudative reactions, influence on the hyaluronidase system with a change in vascular permeability. Magnesium-containing agents have a greater range of effects on cardiovascular and neurological drugs. Calcium drugs have a positive inotropic effect, increasing the strength of contractions of the myocardium and skeletal muscles. Calcium medicines can cause arrhythmias due to influx through calcium channels. Magnesium drugs have antiarrhythmic, antihypoxic and antiischemic effects. In the nervous system, calcium can

play the role of a neurotransmitter. Magnesium medicines have a sedative, analgesic, antihypoxic, anticonvulsant effect. Magnesium is also considered a natural anti-stress factor. Magnesium deficiency can cause depression, cognitive impairment, and neurodegenerative diseases. There are calcium and magnesium monodrugs, as well as complex means. Calcium chloride, calcium gluconate, calcium glycerophosphate, calcium lactate are known among calcium medicines. From magnesium medicins, monodrugs are used – magnesium sulfate, magnesium oxide, magnesium hydroxide, as well as complex drugs – asparcam, rhythmocor, ATP-forte, magne B_6.

Key words: *calcium, magnesium, pharmacodynamics, mechanism of action, indications.*

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ФАРМАКОЛОГІЧНІ ВЛАСТИВОСТІ КАЛЬЦІЮ ТА МАГНІЮ: ЄДНІСТЬ І БОРОТЬБА ПРОТИЛЕЖНОСТЕЙ

В оглядовій статті автори на підставі літературних даних, наведених у видавництвах Scopus, Google Scholar та ін., наводять відомості щодо фізико-хімічних, біохімічних, фармакологічних, клінічних властивостей кальцію і магнію, підкреслюють їх загальну фармакодинаміку, роблять акцент на їх відмінностях та розкривають етапи, характерні для гіпер- і гіпокальціємії і магніємії. Стійкість комплексів магнію з глюкозою і глюкозаміном вища, ніж із кальцієм. Для координаційних сполук магнію з глюкозою більшим є ентропійний внесок, а для сполук кальцію з глюкозою – ентальпійний. Іони кальцію зв'язуються з білками з більшою активністю, ніж іони магнію. Енергія, необхідна для дегідратації магнію, більша, ніж для дегітрадації кальцію. Гіперкальціємія і гіпермагніємія спостерігаються рідше, ніж гіпокальціємія та гіпомагніємія. Розкривається дія препаратів кальцію і магнію на кісткову систему, вплив на серцево-судинну та нервову системи, травний канал. Підкреслюється особливість впливу препаратів кальцію на систему згортання крові, вони також мають протиалергічний вплив. Препарати кальцію впливають на всі фази згортання крові. Протиалергічна дія препаратів кальцію пов'язана зі ста-

білізацією клітинної мембрани, пригніченням ексудативних реакцій, впливом на систему гіалуронідази зі зміною проникності судин. У магнійуміщуючих засобів більше діапазон впливу серцево-судинних та неврологічних препаратів. Препарати кальцію виявляють позитивний інотропний вплив, підвищуючи силу скорочень міокарду та скелетних м'язів. Препарати кальцію можуть викликати аритмії завдяки надходженню по кальцієвих каналах. Препарати магнію мають протиаритмічну, антифібриляторну і протиішемічну дію. У нервовій системі кальцій може грати роль нейротрансміттера. Препарати магнію мають заспокійливу, анальгетичну, антигіпоксичну, протисудомну дію. Магній також уважають природним антистресовим фактором. Дефіцит магнію може викликати депресію, когнітивні порушення пам'яті, нейродегенеративні захворювання. Наводяться монопрепарати кальцію і магнію, а також комплексні засоби. Серед препаратів кальцію відомі кальцію хлорид, кальцію глюконат, кальцію гліцерофосфат, кальцію лактат. Із препаратів магнію застосовують монопрепарати: магнію сульфат, магнію оксид, магнію гідроксид, а також комплексні препарати: аспаркам, ритмокор, АТФ-форте, магне В6.

Ключові слова: *кальцій, магній, фармакодинаміка, механізм дії, показання.*

Alkaline earth metals (calcium, magnesium) play an important role in the functioning of vital organs and systems, which is why they are called biometals.

The content of calcium in the body is 25,000 mmol/1000 g, and magnesium is 1,000 mmol/25 g. Most of the calcium is contained in bone tissue, while the distribution of magnesium is determined in all tissues and organs (Kvitka et al, 2021, pp. 40–44). Compared to calcium ions, magnesium ions are more hydrated and have a pronounced ability to form coordination bonds with elements of biomembranes with the formation of coordination ligands. As the concentration increases, the ability of magnesium to form complexes decreases. Magnesium not only competes with calcium, but also prevents sodium from entering the cells. Magnesium forms complexes with membrane polarizing groups. Magnesium and calcium interact with both glucose and glucosamine.

Stability of magnesium complexes with glucose is higher than with calcium, which is associated with electrostatic interaction. For coordination compounds of magnesium with glucose, the entropic contribution is greater, and for compounds of calcium with glucose – the enthalpic contribution. Complexes of magnesium with glucosamine are more stable than calcium with glucosamine. Both calcium and magnesium can bind to proteins, although Ca ions^{2+} bind to proteins with greater activity: the ionic radius of Ca^{2+} (0.99Å) larger than the ionic radius of Mg^{2+} (0,95Å).

The energy needed to dehydrate calcium is 0,375 cal/mol, and magnesium is 14,19 cal/mol. However, calcium and magnesium bind to proteins, ionic bonds of calcium with proteins in 10-3 and 10-4 times more than magnesium (El Beleidy et al, 2017, pp. 60–64).

Calcium and magnesium are involved in energy supply, muscle contraction, and functioning of vital organs. Calcium and magnesium enter the body with food, water, and juices. Hypercalcemia and hypermagnesemia are rare. The cause of hypercalcemia can be hyperparathyroidism, malignant neoplasms, including myeloma with or without bone metastases. Excessive intake of vitamin D rarely causes hypercalcemia, but its hydroxyl derivatives, such as calcitriol and alpha-calcidol, can cause this condition. Therefore, when taking the above-mentioned drugs, it is necessary to regularly determine the level of calcium in the blood. The course of hypercalcemia is usually asymptomatic. In severe forms of hypercalcemia, there is pain in the bones and abdomen, as well as the formation of calculi in the renal tubules (Vozianov et al, 2018, pp. 85–90).

The phenomenon of hypocalcemia in adults is rare. Its causes may be an insufficient amount or complete absence of parathyroid hormone, vitamin D deficiency, lack of sunlight, kidney pathology, or malabsorption of calcium in the intestines. Hypocalcemia is observed in renal failure, pancreatitis, low protein level in the blood, increased calcium content in bones, long-term treatment with loop diuretics, sepsis (Li et al, 2018; Garbincius & Elrod, 2022).

Calcium deficiency is observed during pregnancy and lactation, which can lead to delayed fetal development and insulin resistance (Takaya, 2021, p. 7008). Calcium and iron are necessary for the development of the fetus, so calcium and iron preparations should be included in the diet of pregnant women (Abioye et al, 2021, pp. 1084–1101). In addition, the calcium signaling system plays an important role in the development of epithelial tissue (Brodskiy & Zartman, 2018, p. 051001).

Physical and emotional stress increase the need for magnesium. Hypomagnesemia is diagnosed when the level of magnesium in the blood plasma rises above 20 mmol/l. The main causes of the development of hypermagnesemia are chronic kidney diseases and acute renal failure. It is believed that hypermagnesemia can be iatrogenic and it is diagnosed in patients taking magnesium preparations in significant quantities for the treatment of eclampsia and epilepsy. Hypermagnesemia can be detected in patients who have been taking magnesium-containing laxatives for a long time. Hypermagnesemia is noted in patients taking lithium drugs, while the level of magnesium in the blood increases in parallel with the level of calcium (Kursov et al, 2021, pp. 56–67).

Hypomagnesemia is observed in severe diseases of vital organs, with insufficient intake of magnesium with food. Some medications can lead to hypomagnesemia: such as histamine receptor blockers, sodium bicarbonate, antibiotics, antituberculosis, antiviral, antidiabetic drugs, corticosteroids, estrogen, and some others (Kursov et al.,

2021, pp. 56–67). In diseases requiring the use of loop diuretics, simultaneous detection of hypocalcemia and hypomagnesemia was observed (Filyk, 2021, pp. 36–42).

Pharmacodynamics of calcium and magnesium is related to their biochemical and biophysical properties. In micromolar concentrations, calcium activates the synthesis of cAMP in the heart by attaching calmodulin to adenylate cyclase. At higher concentrations, calcium suppresses cAMP synthesis by displacing magnesium from activated sites on the activated component of adenylate cyclase. Hydrolysis of cAMP is carried out by phosphodiesterase. Calcium contributes to the activation and release of adrenergic mediators from nerve endings, conduction of impulses, regulation of enzymes, participates in the formation of enzyme complexes. Calcium is involved in the mechanisms of muscle contractility, increases the body's resistance to infection, activates phagocytosis, and can participate in the activation of hormones. Calcium can be a cofactor of many enzymes or participate in the formation of enzyme complexes. Parathyroid hormone and vitamin D play the main role in the regulation of calcium metabolism. Violations of Ca release mechanisms $^{2+}$ from the sarcoplasmic reticulum, changes in the activity of ATPase and the formation of mRNA underlies the occurrence of atrial fibrillation (Valentim et al, 2022, p. BSR20211997).

The influx of calcium stimulates intracellular and extracellular signaling systems associated with consciousness. Changes in the reception of these signals leads to the emergence of nervous and psychiatric diseases. Neurological disorders in adults are caused both by disorders of calcium metabolism in general and by disorders of the functioning of signaling systems. It is the establishment of the mechanisms of disruption of signaling systems and calcium metabolism that leads to the search for treatment of mental diseases (Arjun McKinney et al, 2022, p. dev198853).

Magnesium is considered a universal regulator of biochemical processes, participating in energy and plastic exchanges. It is a cofactor of many enzymes, participates in more than 300 biochemical reactions. Magnesium can form complexes with ATP molecules, activate more than 300 enzymes, including ATPases. It counteracts the uncoupling of oxidation and phosphorylation. Participates in the synthesis of nucleic acids. Promotes activation of creatine kinase, Ca^{+}-Na^{+}-ATPase, Ca-ATPase, enzymes of glycolysis and others (Al Alawi et al, 2018, pp. 1–17). Most of all calcium in the body is contained in bones and teeth, when calcium preparations are administered, calcium-phosphorus exchange is stimulated. (Han et al, 2020, pp. 124–129). Lack of calcium leads to bone resorption, in turn in Ca^{2+} and phosphorus, can cause inflammation (Klein, 2018, p. 69). But we should not forget that magnesium contributes to increasing the level of calcium and keeping calcium in the cell, as well as the development of tooth enamel (Klitynska & Stishkovskyy, 2020, pp. 130–137). In addition, magnesium preparations are recommended for use in case of postoperative hypocalcemia. (Kvitka et al, 2021, pp. 40–44). Unlike magnesium, calcium preparations affect all phases of blood coagulation, increase the adhesiveness of platelets.

Calcium preparations are prescribed for edema, capillary bleeding, and the consequences of hemorrhage. These drugs also have an anti-allergic effect, stabilizing cell membranes and suppressing exudative reactions, as well as affecting the hyaluronidase system and reducing the permeability of the vessel wall. Calcium preparations are prescribed as an aid in allergic reactions.

At the same time, both calcium and magnesium have a multifaceted effect on the cardiovascular system. Calcium preparations have a positive inotropic effect, increasing the strength of contractions of the myocardium and skeletal muscles. At the same time, calcium binds to the troponin-tropomyosin complex. Troponin changes its structure and affects the structure of actin and myosin and their interaction. Drugs can stimulate adrenergic mediation, which leads to activation of beta-adrenoceptors, activation of adenylate cyclase, formation of cAMP, activation of protein kinases, phosphorylation of Ca^{2+}-channels, increasing Ca^{2+} influx into the cytoplasm during the action potential, increasing the force of heart contraction (Beghi et al., 2022; Valentim et al, 2022).

An increase in the intracellular concentration of calcium leads to the activation of calcium-dependent proteins. Calcium ions interact with cAMP, cGTP and inositol phosphate. Calcium is considered the strongest second messenger, which transmits external signals from the receptor on the membrane to other cellular structures. The introduction of calcium preparations accelerates the release of calcium from the sarcoplasmic reticulum and its entry into muscle fibers. This leads to the activation of protein kinases, phosphorylation of calcium channels of the sarcolemma, and an increase in the influx of calcium into the sarcoplasm during the action potential, which further increases the force of contractions. But calcium preparations are not part of cardiotonic drugs, nor are they hypertensive drugs, although they can stimulate smooth muscles. As a means of increasing muscle contractility, calcium derivatives were once used among drugs that increase the contractility of the myometrium during childbirth. As for the cardiovascular system, calcium-containing drugs can cause arrhythmias due to influx through L- and T-type calcium channels (van der Sande et al, 2018, pp. 230–235). In recent years, it has been established that calcium overload leads to atrial fi-

brillation (Dai et al, 2021, pp. 1177–1197). Significant accumulation of calcium in the heart muscle causes cardiomyopathy in skeletal muscles, can lead to myopathy (Frachisse et al, 2020; Valentim et al, 2022).

The occurrence of pathological processes in the cardiovascular system in the body as a whole is associated with a low magnesium content. Low magnesium content increases the oxidative activity of neutrophils, high magnesium content reduces the production of oxidative radicals in rats and polymorphonuclear cells in humans (Liu & Dudley, 2020, p. 907). Loss of magnesium by the myocardium was established in myocardial infarction and acute heart failure, especially in the area of myocardial necrosis. Low levels of magnesium led to destabilization of cardiomyocyte membranes, while high levels of magnesium stabilized the membranes. This explains the fact that magnesium preparations are effective in various forms of tachyarrhythmias, including those caused by cardiac glycosides, neuroleptics observed in the postoperative period (Pickering et al, 2020, p. 3672). The anti-ischemic effect of magnesium was proven by experiments, claiming that when its content is reduced, vasospasm occurs. There are data proving the expediency of using magnesium preparations in patients with myocardial infarction and ST segment elevation (Szapary et al, 2021, p. 608193).

Organic salts of magnesium, such as magnesium orotate, citrate, lactate, pyroglutamate are better absorbed and have greater bioavailability than inorganic calcium – sulfate, chloride, hydroxide, oxide. It is believed that treatment with magnesium is more effective when its fixatives vitamin B_1, B_6, glycine are administered in parallel. Magnesium with vitamin B_6 is prescribed for the prevention of endothelial dysfunction in arterial hypertension (Marushko et al, 2020, pp. 70–74). The drug asparcam (panangin), whose active ingredients are potassium and magnesium asparaginate, also has high bioavailability. The drug is included in complex pharmacotherapy for the treatment of heart rhythm disorders, coronary heart disease, and chronic circulatory failure. The presence of immunotropic and anti-inflammatory properties in magnesium is of great importance for the treatment of cardiovascular diseases. Thus, a decrease in interleukins in the blood, namely IL1, IL6, IL8, as well as tumor necrosis factor α – TNFα, was observed when magnesium preparations were prescribed (Ozen et al, 2019, pp. 463–471).

Both calcium and magnesium can be considered modulators of the activity of the nervous system (Yuan et al, 2022, p. 103865). In the nervous system, calcium plays a role in reproducing the connection between neurons and glia (Khaitin, 2021, p. 13344) Calcium in excessive amounts can cause neurodegenerative changes, including when the level of calcium increases, neurodegenerative disorders are detected, such as a decrease in intelligence, deterioration of mental activity (Proietti Onori & van Woerden, 2021, pp. 209–220). In Alzheimer's disease, a deficiency of calcium signals is determined against the background of astrocyte degeneration. calcium hyperreactivity, calcium oscillations are noted (Verkhratsky, 2019, p. a035188). Calcium can interfere with protein cells, which are neurotransmitters, which then enter extracellularly. This process is called exocytosis. Exocytosis in neurons and neuroendocrine cells is explained by the combination of proteins with calcium, while protein-protein protein-lipid interaction occurs. That is, calcium interferes with molecular cloning (Anantharam & Kreutzberger, 2019, pp. 417–434). Degeneration of the substance of dopaminergic neurons is responsible for the nuclear motoneuron deficit in Parkinson's disease. These neurons are autonomous pacemakers that contain a significant proportion of cytosolic Ca^{2+}, which leads to oscillation, is considered to be the result of oxidative stress. Fluctuations in calcium content play a role in mitochondrial respiration, bioenergetics, and the occurrence of oxidative stress (Zampese & Surmeier, 2020, p. 2045).

It is known that both calcium and magnesium could simulate metabolic changes in the central nervous system. It is also known that magnesium preparations have a sedative, analgesic, antihypoxic, anticonvulsant effect. To some extent, this is due to the blocking of calcium influx through potential-dependent channels. Magnesium is an agonist of type A of GABA receptors and an antagonist of angiotensin II receptors, activating neurotransmission associated with the function of protein kinase C (Chiarello et al, 2014, pp. 1–9). Magnesium is a natural anti-stress factor, inhibits the development of excitation processes in the CNS, reduces the body's sensitivity to external influences. Magnesium protects NMDA from the effects of toxins and provides a neuroprotective effect (Dikke, 2017, pp. 59–68). Symptoms of magnesium deficiency and stress are very similar and are accompanied by dizziness, restlessness, weakness, restlessness, headache. Magnesium penetrates very well through the blood-brain barrier, controls the excitability of the membrane, is contained in significant quantities in the extracellular space and cerebrospinal fluid, plays a significant role in brain homeostasis. In the cerebrospinal fluid, magnesium is found in free and protein-bound forms (Dikke, 2017, pp. 59–68).

Hypomagnesemia carries not only the risk of neurological and mental diseases, but also type 2 diabetes, metabolic syndrome, osteoarthritis, and cardiovascular diseases (de Baaij et al., 2015, pp. 1–46). Magnesium deficiency leads not only to stress, but also to depression, cognitive memory impairment, and degenerative

diseases. Manifestations of central nervous system disorders are correlated with long-term calcium deficiency, and long-term magnesium deficiency leads to impaired hippocampal function and neurodegenerative and cognitive disorders (Lo Piano et al, 2019, pp. 1–15).

Magnesium deficiency can cause bipolar disorders, magnesium ions block NMDA receptors, calcium channels, entering into non-competitive antagonism with glutamate, inhibit excitotoxicity. magnesium deficiency is observed in Parkinson's disease and Alzheimer's disease (Semenenko, 2019, pp. 108–115). Regarding the effect on the digestive tract, magnesium oxide and magnesium hydroxide are antacids, magnesium sulfate is an osmotic laxative drug. It posessis cholekinetic, cholespasmolytic propertie. In recent years, new information has appeared regarding the use of calcium and magnesium medicines. so, on one hand, the scientists believe that calcium derivatives will be useful for COVID-19 (Alemzadeh et al, 2021, pp. 1219–1228). On the other hand, influence of calcium may cause carcinogenesis (Danese et al, 2021, p. 119061). Regarding magnesium, it has been established that a lack of magnesium can disrupt the activity of almost all organs and systems.

CONCLUSIONS. Calcium drugs are calcium chloride, calcium gluconate, calcium glycerophosvate, calcium lactate. Magnesium monodrugs – magnesium sulfate, magnesium oxide, magnesium hydroxide, complex drugs – asparcam, rhytmokor, ATP-forte, Magne B_6.These drugs are used in our country and other couantries widely.

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