



The Impact of Chronic Magnesium Deficiency on Excitable Tissues—Translational Aspects

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Abstract

Neuromuscular excitability is a vital body function, and Mg^{2+} is an essential regulatory cation for the function of excitable membranes. Loss of Mg^{2+} homeostasis disturbs fluxes of other cations across cell membranes, leading to pathophysiological electrogenesis, which can eventually cause vital threat to the patient. Chronic subclinical Mg^{2+} deficiency is an increasingly prevalent condition in the general population. It is associated with an elevated risk of cardiovascular, respiratory and neurological conditions and an increased mortality. Magnesium favours bronchodilation (by antagonizing Ca^{2+} channels on airway smooth muscle and inhibiting the release of endogenous bronchoconstrictors). Magnesium exerts antihypertensive effects by reducing peripheral vascular resistance (increasing endothelial NO and PgI_2 release and inhibiting Ca^{2+} influx into vascular smooth muscle). Magnesium deficiency disturbs heart impulse generation and propagation by prolonging cell depolarization (due to Na^+/K^+ pump and K_{ir} channel dysfunction) and dysregulating cardiac gap junctions, causing arrhythmias, while prolonged diastolic Ca^{2+} release (through leaky RyRs) disturbs cardiac excitation-contraction coupling, compromising diastolic relaxation and systolic contraction. In the brain, Mg^{2+} regulates the function of ion channels and neurotransmitters (blocks voltage-gated Ca^{2+} channel-mediated transmitter release, antagonizes NMDARs, activates $GABA_A$ Rs, suppresses nAChR ion current and modulates gap junction channels) and blocks ACh release at neuromuscular junctions. Magnesium exerts multiple therapeutic neuroactive effects (antiepileptic, antimigraine, analgesic, neuroprotective, antidepressant, anxiolytic, etc.). This review focuses on the effects of Mg^{2+} on excitable tissues in health and disease. As a natural membrane stabilizer, Mg^{2+} opposes the development of many conditions of hyperexcitability. Its beneficial recompensation and supplementation help treat hyperexcitability and should therefore be considered wherever needed.

Keywords Chronic magnesium deficiency · Excitability · Smooth muscles · Skeletal muscles · Heart · Nervous system

Introduction

Magnesium is an earth-alkaline mineral bioessential for all living creatures. It is a very important structural and functional constituent of plant, animal and human organisms. Magnesium is the core element in the structure of chlorophyll, which enables plants to capture the solar energy needed for photosynthesis. Magnesium salts phosphate and

carbonate contribute to the formation of bone minerals in vertebrates, providing the skeleton with adequate bone density and strength. In mammals, Mg^{2+} is a dominantly intracellular cation and represents the most abundant divalent cation in the cell. Table 1 shows some of the most important physico-chemical properties of Mg^{2+} ion.

Being very abundant inside cells, Mg^{2+} participates in various cellular processes, including cell cycle regulation and maintenance of genome structure and stability. Magnesium also facilitates numerous biochemical reactions in many tissues [1]. The enzyme databases list a number of different enzymes having Mg^{2+} cations as enzyme activators (approximately 200) or cofactors (over 600). Adenosine triphosphate (ATP) molecules are always complexed with Mg^{2+} , and Mg^{2+} -ATP facilitates energy-dependent reactions and processes in the cell [2]. As a key cofactor for

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Table 1 Major physico-chemical characteristics of Mg^{2+} ion relevant for human cell physiology

Atomic number	12
Charge	+
Valence	2
Electron configuration	$2p^6$
Coordination number	6
Ionic radius of Mg^{2+}	72 pm
Ionic radius of $Mg^{2+}(aq)$	~ 400 times larger than the radius of dehydrated Mg^{2+} ion (two shells of waters of hydration)
Abundance in the human body	The fourth most abundant mineral
Localization in the body fluid compartments	Predominantly intracellular (mitochondria constitute a major cellular Mg^{2+} pool)

glycolytic pathway enzymes, Mg^{2+} also plays a significant role in glucose metabolism and glycoregulation [3]. Inside the cell, Mg^{2+} serves the role of integrating a number of signals reaching the cell, much like a secondary messenger, whereby an adequate concentration of free intracellular Mg^{2+} is required for cell homeostasis. Both inside and outside the cell, Mg^{2+} is generally considered to antagonize Ca^{2+} . Magnesium also helps regulate mitochondrial functions. Most of Mg^{2+} content in the cells is actually found in the mitochondria. It is required for the process of oxidative phosphorylation in the mitochondrial respiratory chain. The inner mitochondrial membrane is provided with a high conductance Mg^{2+} -selective ion channel (the Mrs2p eukaryotic Mg^{2+} influx system, which is homologous to the prokaryotic Mg^{2+} transporter CorA), enabling adequate mitochondrial Mg^{2+} uptake [4]. However, the structure and function of Mg^{2+} transporting systems in eukaryotic cell membranes have not yet been completely revealed. Several types of Mg^{2+} transport proteins move Mg^{2+} across the cell membranes of the eukaryotes: solute carrier 41 (SLC41), cyclin M (CNNM) and transient receptor potential melastatin (TRPM) 6 and 7 [5, 6]. However, specific membrane transport mechanisms for Mg^{2+} are still much less familiar than those for other major cations: Na^+ , K^+ and Ca^{2+} .

Biological effects of magnesium do not end with a list of its roles in cell and tissue structure or metabolic and immune regulation. In addition, Mg^{2+} ions are also required for the adequate function of cells, tissues and organs showing a very important electrophysiological property of excitability. In a broader sense, this makes Mg^{2+} (along with other more frequently mentioned electrolytes: Na^+ , K^+ and Ca^{2+}) necessary for the maintenance of normal neuromuscular excitability as a vital body function. More specifically, Mg^{2+} plays a fundamental role in modulating ionic homeostasis and maintaining electrical processes, as accomplished by other major cations. A deficiency of Mg^{2+} in the body can

severely disbalance or disrupt the functions of excitable cells and tissues. The research focus of this paper is to separately review and emphasize the fundamental importance of maintaining proper Mg^{2+} homeostasis for all excitable tissues and to present some of the underlying pathogenetic mechanisms by which the widespread condition of Mg^{2+} depletion can lead to a general state of hyperexcitability with systemic manifestations. The importance of nutritional Mg^{2+} balance for hyperexcitability disorders is stressed. The implications for clinical outcomes are described. The aim of this study was to elucidate the significance of preventing various clinical conditions, including urgent conditions, by compensating for the chronic Mg^{2+} deficiency that contributes to their development, with a special emphasis on excitable tissues.

Excitable Tissues

Electrical excitability and conductivity are two closely related bioelectrical phenomena of living tissues capable of generating and propagating electrical impulses. Namely, membranes of certain types of cells and tissues exert electrophysiological properties that enable them to be sensitive to certain stimuli from the environment and provide them with an endogenous ability to respond to such stimulation by transitioning from a state of electrical rest to a state of electrical activity [7]. Excitability represents one of the basic functions of life. Ever since the early works of Luigi Galvani on what he called the “living” electricity, the electrical nature of excitability has continued to fascinate scientists. This eighteenth-century Italian physician and physicist experimentally established that it is the electricity that serves as the medium through which the nerves send signals and the muscles contract. Until today, electrophysiology continues to study intensively the mechanisms underlying electrical phenomena in excitable tissues in health and disease.

Excitable tissues comprise primarily the nervous tissue of the central and peripheral nervous system and muscle tissues (smooth muscles, skeletal muscles and heart muscle—myocardium) but also include other types of cells, such as some endocrine gland cells. There is growing knowledge on astrocytic excitability and gliotransmission as well. An excitable cell in general has the ability to generate electrical signals in response to various stimuli (electrical, chemical, mechanical, light and others). The response to stimulation is mediated by rapid changes in the cell membrane electrical potential, generated by ion fluxes across the membrane [8]. Thus, excitation is a specific sum of changes in ion conductance, providing an excitable membrane with the inner ability to become electrically activated. Tissues differ in their intrinsic degree of excitability. Nerve cells and fibres show the highest excitability; skeletal muscles have lower excitability than nerves; the myocardium has even lower excitability, and smooth muscles have the lowest degree of

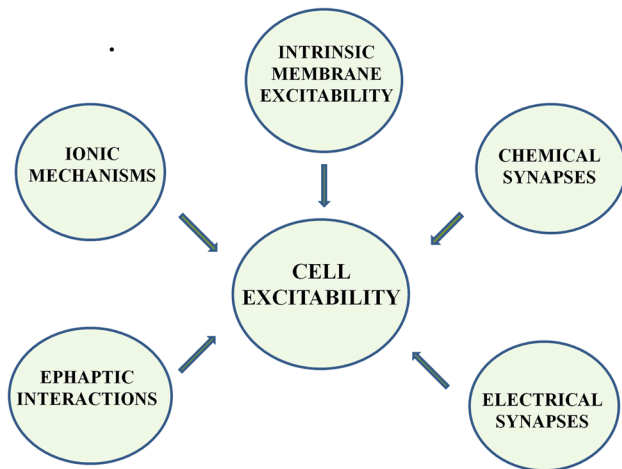


Fig. 1 Major components of nonsynaptic and synaptic cell excitability. Intrinsic membrane excitability refers to ion channels, transporters, pumps and neurotransmitter receptors expressed in the cell membrane

excitability. Excitable cells process and transmit information in the form of electrical signals. Stimuli of sufficient intensity depolarize the excitable membrane to the threshold potential level, thereby initiating an active all-or-none electrical response, i.e. an action potential (AP), typically in the form of a spike. The transient reversal in the membrane potential that emerges can then be transmitted along the membrane without a decrease in amplitude (nerve impulse propagation). Excitability includes various mechanisms of reaction to stimuli: synaptic and nonsynaptic ones, the latter including those intrinsic (endogenous) for the excitable membrane itself, the ionic mechanisms and the fast electric cell-to-cell communication via electrical field effects of the extracellular space and the electrotonic coupling. Figure 1 illustrates mechanisms contributing to overall cell excitability.

Disorders of cell excitability accompany numerous congenital and acquired diseases. For example, channelopathies can result from mutations in genes encoding for the synthesis of subunits of individual ion channels and receptors, or from many acquired pathophysiological conditions (neurological, neuromuscular, cardiovascular, etc.). Excitability disorders can also arise due to alterations in general homeostasis, such as in various water-salt and acid-base imbalances. Altered excitability underlies numerous states of hyperexcitability (e.g. epilepsy and seizures, migraine headache attacks, paroxysmal neuralgic pain, cardiac tachyarrhythmias) on one side and hypoexcitability on the other (e.g. loss of consciousness, respiratory centre depression, blockage of heart impulse conduction) [9]. Disorders of Mg^{2+} homeostasis inevitably alter cell excitability. This review discusses the importance of Mg^{2+} homeostasis and

chronic Mg^{2+} deficiency from an electrophysiological point of view, including the clinical implications.

Magnesium as a Bioessential Element

Magnesium is much more abundant in the intracellular fluid (Mg^{2+} second to K^+) than in the extracellular fluid. The regulation of Mg^{2+} homeostasis in the body is maintained primarily by kidney function through the process of tubular reabsorption of filtered Mg^{2+} . Intestinal Mg^{2+} absorption and exchange with Mg^{2+} depots from the bone matrix contribute to the maintenance of the Mg^{2+} balance [10]. To plan a nutritionally adequate individual diet, the recommended dietary allowance (RDA) is often used as a measure of the currently recommended average daily intake. The value represents the amount of a given nutrient sufficient to meet body needs in most healthy individuals of a given age and sex. Magnesium is a nutrient fundamental for overall health. The magnesium RDA for adults is 400–420 mg for men and 310–320 mg for women (more if pregnant or breastfeeding) [11]. The most abundant source of highly bioavailable Mg^{2+} are magnesium-rich naturally occurring mineral waters, as Mg^{2+} is more easily absorbed from water intake than from food. Mineral water is considered a source of magnesium only if it has a Mg^{2+} content of at least 50 mg Mg^{2+} /L.

The total body magnesium content equals approximately 21–28 g (~ 1 mol), with 99% of the amount being distributed inside the cells (mostly in bones, muscles and other soft tissues), while only approximately 1% of the total body magnesium is present extracellularly. Consequently, blood Mg^{2+} levels determined by routine laboratory tests cannot precisely reflect the actual magnesium body reserves [12]. Therefore, a state of severe magnesium deficiency in the body can be present even with total serum Mg^{2+} level within the normal range [3]. In clinical practice, measuring the total Mg^{2+} concentration (tMg^{2+}) in the serum is the most commonly used test to assess magnesium status in the body. The magnesium concentration should be measured from blood serum samples and not blood plasma (as many anticoagulants added to plasma samples also bind Mg^{2+} in addition to Ca^{2+} , thus resulting in a falsely lower level of free Mg^{2+}) [10]. The normal range of reference values for the stable concentration of tMg^{2+} is usually 0.70–1.15 mmol/L. A minor portion of the measured tMg^{2+} in the blood is complexed with anions (~ 10%) or protein bound (30–40%), while the free, ionized Mg^{2+} fraction constitutes approximately 50% of the total magnesemia. Ionized Mg^{2+} (iMg^{2+}) represents the biologically and electrophysiologically active Mg^{2+} form. Although the serum iMg^{2+} concentration ($[iMg^{2+}]$) is influenced by the plasma protein concentration and the acid-base status, it is considered by some authors to be a more specific marker of Mg^{2+} status

compared to tMg^{2+} concentration that correlates better with some physiological and clinical parameters [13].

In regard to the negative balance of Mg^{2+} metabolism in the body, different conditions are possible, implying a dominant depletion of extracellular (or outer) Mg^{2+} (Mg^{2+}_o) and/or intracellular (inner) Mg^{2+} (Mg^{2+}_i) in body fluids, including normomagnesemic or hypomagnesemic, asymptomatic or symptomatic and acute or chronic Mg^{2+} deficiency. Biologically active Mg^{2+} is always the free, ionized, unbound Mg^{2+} fraction, with the concentration of ionized intracellular Mg^{2+} ($[iMg^{2+}_i]$) being approximately the same as the concentration of the ionized fraction of extracellular Mg^{2+} ($[iMg^{2+}_o]$) [12]. Disturbances in Mg^{2+} homeostasis can be reflected in alterations in serum Mg^{2+} concentrations. Dymagnesemia is associated with severe diseases and conditions. Hypomagnesemia, a decreased serum Mg^{2+} concentration, has an estimated prevalence of 2.5–15% in the general population, which rises with increasing age [14]. Hypomagnesemia is typically asymptomatic until tMg^{2+} level decreases to < 0.5 mmol/L. The aforementioned lower limit of the reference interval for the serum tMg^{2+} level derived from earlier studies is now considered to be too low. Recent research has suggested the use of Mg^{2+} concentration of ≥ 0.85 mmol/L in order to reduce the risk of cardiovascular disease, type 2 diabetes mellitus (DM) and other conditions frequently associated with magnesium deficiency in the body [15].

The condition of Mg^{2+} deficiency in the body (with or without hypomagnesemia) represents probably the most common unrecognized electrolyte disbalance, concerning several unfavourable facts like the endemic of chronic dietary magnesium deficiency especially in developed countries, its frequent subclinical forms and a frequent failure to measure Mg^{2+} in patients [14]. Practical difficulties exist in measuring the level of serum iMg^{2+} , the red blood cell (RBC) Mg^{2+} content and the urinary Mg^{2+} excretion.

Magnesium Deficiency

Growing Prevalence of Mg^{2+} Deficiency in the General Population

Magnesium deficiency is a condition in which the total magnesium content in the body is reduced [16]. In humans, it can occur for several reasons: insufficient magnesium intake (due to a lack of magnesium in the soil and consequently in the foodstuff of plant and animal origin, a high prevalence of processed food and magnesium-poor water in the diet, malabsorption, maldigestion, etc.), increased loss of Mg^{2+} from the body (especially via urine or digestive tract) or due to a redistribution of Mg^{2+} from the extracellular to intracellular compartment, etc. [17]. Modern daytime is characterized

by reduced magnesium dietary intake. The degree of magnesium depletion from soil and water is more pronounced in urban and industrial areas, as biogeochemical monitoring in many countries continuously reports. The reduced availability of Mg^{2+} for the plants from the soil probably results from a combined action of a number of unfavourable factors, such as increasing use of artificial fertilizers (whereby other minerals compete with Mg^{2+} in the absorption process through the roots and inhibit Mg^{2+} uptake into plant cultures), as well as bleaching Mg^{2+} salts out of soil surface layers due to the effect of acid rains [18]. Magnesium deficiency in plants reflects onto magnesium deficiency in both animals and humans. The modern diet is usually poor in foods high in magnesium (green leafy vegetables, legumes, nuts, seeds and whole grains) and unfortunately frequently saturated with magnesium-depleted processed and refined foodstuffs [2]. These historical changes in food mineral content and human nutrition habits in the last century have led to a significant and progressive decline in the average dietary intake of magnesium worldwide, which is a great concern for human health [19, 20]. Furthermore, alcohol intake induces loss of Mg^{2+} body stores [21]. Additionally, certain drugs can also affect total magnesium body content (loop diuretics, proton pump inhibitors, tetracycline and quinolone antibiotics, cytostatics, etc.), resulting in a negative Mg^{2+} balance [22]. Major factors contributing to the development of acquired Mg^{2+} deficiency are listed in Fig. 2.

Difficulties in Diagnosing Mg^{2+} Deficiency

Early stages of chronic Mg^{2+} deficiency are clinically asymptomatic and can only be discovered through laboratory tests if Mg^{2+} content in specific samples is found to be below the normal range. The first choice for a single test to be performed is usually to measure the serum Mg^{2+} concentration. However, since total serum Mg^{2+} accounts for only a minor portion ($< 1\%$) of the total Mg^{2+} content in the body, to measure serum Mg^{2+} alone is of little diagnostic value in order to diagnose Mg^{2+} deficiency. Therefore, testing for Mg^{2+} loss from the intracellular Mg^{2+} stores is equally important. It is usually performed from a sample of isolated RBCs. The reference value for intracellular Mg^{2+} concentration of RBCs is 2.40–2.57 mmol/L [16]. Nevertheless, inside the cell, the compartment of the intracellular fluid which is the most abundant with Mg^{2+} are the mitochondria. Since RBCs have no mitochondria, measuring the concentration of intracellular Mg^{2+} from a RBC sample is a method with obvious practical limitations. Hence, the initial stage of whole-body Mg^{2+} deficiency has (apparently paradoxically) normal findings of both total serum Mg^{2+} and RBC Mg^{2+} , but it can be discovered by a third test of measuring Mg^{2+} content in the 24-h urine. Normal average 24-h urinary Mg^{2+} excretion is approximately 100 mg.

Fig. 2 Major factors causing the development of acquired Mg^{2+} deficiency

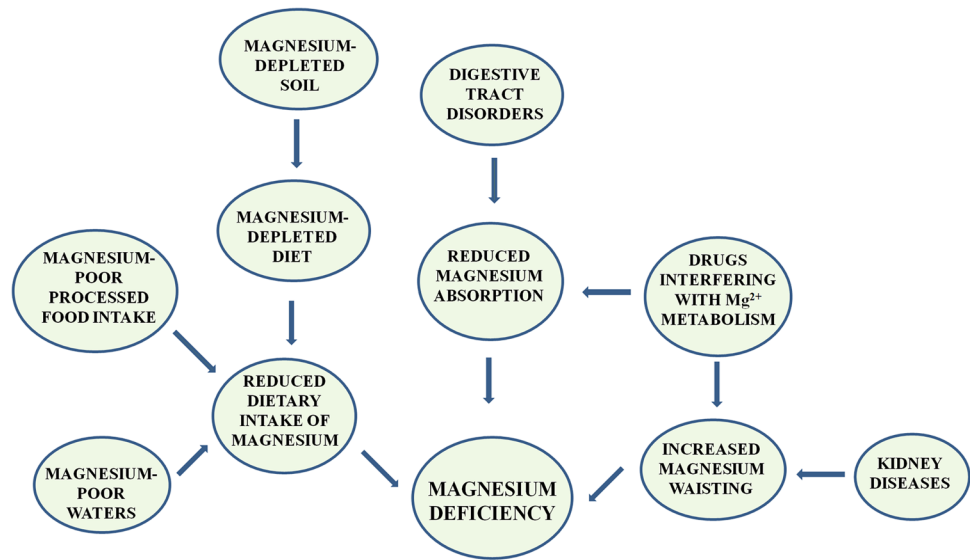


Table 2 The staging of Mg^{2+} deficiency according to clinical laboratory test results

Type and stage of Mg^{2+} deficiency	Total serum Mg^{2+} concentration	RBC intracellular Mg^{2+} concentration
Type I, stage 1 Mg^{2+} deficiency	Normal	Normal
Type I, stage 2 Mg^{2+} deficiency	Normal	Decreased
Type II, stage 3 Mg^{2+} deficiency	Decreased	Normal
Type II, stage 4 Mg^{2+} deficiency	Decreased	Decreased

Decreased urinary Mg^{2+} in an individual with healthy kidneys is indicative of Mg^{2+} depletion. An increased urinary Mg^{2+} excretion (> 150 mg/24 h) in a patient with kidney disease is called the urinary Mg^{2+} wasting, and it leads to Mg^{2+} depletion from the body [16, 23]. Types and stages of Mg^{2+} deficiency according to clinical laboratory test results [16] are presented in Table 2.

Since performing all these tests and some additional tests (like the magnesium loading test) is a demanding and not a routine procedure, many patients with Mg^{2+} deficiency, especially the normomagnesemic ones, remain undiagnosed and untreated. If untreated, Mg^{2+} deficiency progresses in a continuum from subclinical normomagnesemic (type I) Mg^{2+} deficiency in the first two more subtle stages, to overt, clinically manifested, acute or chronic hypomagnesemic (type II) Mg^{2+} deficiency. The described laboratory tests can be used to diagnose Mg^{2+} deficiency and to differ among its stages. Among these, the condition of chronic subclinical Mg^{2+} deficiency is currently particularly common in the general population. It refers to a clinically silent reduction in certain Mg^{2+} -dependent physiological functions that is difficult to diagnose because it is still unmanifested and because it results from Mg^{2+} depletion from the intracellular compartment of body fluids, where Mg^{2+} level is not routinely measured (stages 1

and 2 according to Mansmann) [23]. However, it does represent a risk factor that depletes some functional reserves, thus predisposing individuals to the occurrence of numerous chronic diseases of different body organs. For example, there is a rising awareness that Mg^{2+} deficiency is in fact one of the major, albeit yet underrecognized drivers of cardiovascular diseases [24]. Additionally, protracted Mg^{2+} depletion and hypomagnesemia are often accompanied by imbalances of other electrolytes, particularly refractory hypokalaemia and hypocalcaemia.

The condition of magnesium deficiency is in fact a type of malnutrition. Frequent subclinical form of the condition, absence of clinical interest for it and difficulties in the procedure of laboratory diagnostics make it usually go unnoticed for long. Chronic latent Mg^{2+} deficiency is nowadays very common; for example, it is present in $> 25\%$ of the US population [15]. Magnesium deficiency is a factor contributing to the pathogenesis of numerous chronic illnesses and can also be associated with a number of acute clinical conditions. Emerging evidence also stresses the importance of maintaining adequate Mg^{2+} homeostasis in critically ill patients in intensive care and coronary units, where a strong association is established between Mg^{2+} depletion and increased mortality [25, 26]. However, despite its considerable clinical importance,

Mg^{2+} is usually still not included in routine laboratory assessments and must be specifically ordered based on clinical suspicion.

Importance of Magnesium for Excitable Tissues

Besides the many metabolic and structural functions of magnesium, this electrolyte possesses a true abundance of electrophysiological roles which are not yet completely appreciated enough. When determining serum electrolyte concentrations, Mg^{2+} is frequently clinically neglected (since Na^+ , K^+ and Ca^{2+} are considered the major cations, and Mg^{2+} is not included in the routine serum ionogram). Since health care systems between the countries can vary, as well as the practices between different clinical laboratories and departments, the need to standardize the procedure by uniformly including Mg^{2+} measurements whenever checking for serum electrolytes is even more justified.

In our body fluids, dissolved Mg^{2+} ion is hydrated with a large ionic radius of $Mg^{2+}(aq)$, due to its double shell of waters of hydration, making most of the ion channels in biological membranes impermeable to it [1]. Magnesium ion has the same total number of electrons as Na^+ but is predominantly found intracellularly—much like K^+ , only Mg^{2+} is divalent; Mg^{2+} has a chemical reactivity similar to that of Ca^{2+} but is usually a biological antagonist of Ca^{2+} . These and some other features help Mg^{2+} serve as one of the regulatory cations for the activity of excitable tissues. Magnesium mediates a number of complex effects that help to control membrane excitability in many cell types. This regulatory role comprises the effects of Mg^{2+} on excitable membranes via nonsynaptic and synaptic mechanisms that determine the excitability and firing pattern of individual excitable cells. Magnesium contributes to their functions by modulating the activity of a number of membrane ion transport systems (ion channels, transporters and pumps and receptors for certain neurotransmitters) in excitable cells. Both the extracellular (outer) Mg^{2+} concentration ($[Mg^{2+}]_o$) and the Mg^{2+} concentration ($[Mg^{2+}]_i$) significantly influence cellular and synaptic processes in nervous and muscular tissues.

Magnesium is required for the proper function of nerve and muscle cells, as Mg^{2+} primarily modulates intrinsic membrane processes, intercellular communication as well as muscle contraction and helps regulate tissue metabolism. Namely, Mg^{2+} exerts direct effects on the excitability and conductivity of excitable membranes at the cellular, subcellular and molecular levels. Magnesium is known to act as a voltage regulator of multiple membrane ion conductances (through several types of Na^+ , K^+ and Ca^{2+} ion channels) and as an essential cofactor for the Na^+/K^+

pump activation. Magnesium is considered to be an important physiological Ca^{2+} antagonist, as extracellular Mg^{2+} ions inhibit the inward Ca^{2+} current through voltage-gated Ca^{2+} channels in excitable cells. In addition to influencing the passive and active properties of excitable membranes, Mg^{2+} also helps regulate the processes of synaptic neurotransmission by modulating the functions of chemical and electrical synapses. Magnesium exerts numerous effects on smooth muscles, skeletal muscles, the heart, the brain and peripheral nerves, thus accomplishing its important role in the physiology and pathophysiology of excitable tissues and organs. A number of their functional abnormalities are induced by Mg^{2+} deficiency. Indeed, when symptomatic, Mg^{2+} deficiency usually does present as involvement of the cardiovascular system and the central and peripheral nervous systems, while other structures are less affected. Here, a joint search of the literature was performed to unite the preclinical and clinical findings on the regulatory role of Mg^{2+} on cell and tissue excitability. This review also describes a general pathophysiological condition of low-grade or more severe hyperexcitability which can arise from a chronic Mg^{2+} deficiency. The functional disorders of excitable tissues associated with Mg^{2+} deficiency, known underlying mechanisms and the resulting clinical conditions are described.

Mg^{2+} and Smooth Muscles

Magnesium is necessary for the proper function of smooth muscle cells (SMCs) in blood vessel walls, airways and structures of the digestive and urogenital tract. Having antagonistic properties to Ca^{2+} , Mg^{2+} generally exerts a relaxing effect on SMCs.

Mg^{2+} and Vascular Smooth Muscle

Subclinical magnesium deficiency is a significant factor contributing to the mechanisms of pathogenesis of certain cardiovascular diseases, however, still insufficiently recognized. It is clinically known that magnesium physiologically helps regulate arterial blood pressure (BP), while magnesium deficiency is associated with high BP. This is confirmed by the findings that in experimental animals and humans, a magnesium-poor diet increases BP values, while magnesium supplementation achieves a moderate BP-lowering effect among the hypertensive [27]. In these individuals, magnesium supplementation provides an efficient protective vasodilatory and hypotensive effect, with an inverse relationship established between the Mg^{2+} concentration on the one hand and the BP value, on the other hand, in hypertensive patients [28]. Furthermore, magnesium supplementation was found to significantly lower BP in individuals with preclinical metabolic conditions (insulin resistance, prediabetes) or

an overt noncommunicable chronic disease (DM, cardiovascular diseases) [29].

Since Mg^{2+} deficiency has a certain role in the development of arterial hypertension, while its supplementation has a beneficial BP-lowering effect, Mg^{2+} action in arterial hypertension was examined. Several mechanisms were found to underlie the antihypertensive effect of Mg^{2+} . In addition to affecting endothelial function by increasing endothelial nitric oxide (NO) and prostacyclin (prostaglandin I_2) release [30], Mg^{2+} participates in the control of vascular smooth muscle tone, reactivity and contraction by reducing peripheral vascular resistance and thereby indirectly regulates BP. As a natural antagonist of Ca^{2+} , Mg^{2+}_o ions inhibit Ca^{2+} influx into vascular SMCs via L-type voltage-gated Ca^{2+} channels (VGCCs), thereby reducing the tone and resistance of peripheral arterioles. Alternatively, Mg^{2+}_i can act as a Ca^{2+} antagonist, which causes Mg^{2+}_i depletion to also mediate the vasoconstrictor effect of the increased intracellular concentration of Ca^{2+} ($[Ca^{2+}]_i$) in the vascular smooth muscle [28, 31].

In SMCs, Mg^{2+} ion helps regulate not only Ca^{2+} but also K^+ fluxes through the SMC membrane. Potassium ion channels are key to attenuating excitation in SMCs. Calcium-activated K^+ channels (K_{Ca}) are important for controlling various physiological processes, including SMC contraction. In particular, K_{Ca} with a large single-channel conductance (BK channel) is widely expressed in several SMC types and maintains smooth muscle relaxation by buffering Ca^{2+} -mediated cell depolarization. In the vascular system, BK channels help regulate the SMC contractile state; BK channels expressed in SMCs of the vascular wall of muscular arteries and arterioles play a critical role in regulating their tone and diameter. Their activation integrates both membrane depolarization and increases in the concentration of Ca^{2+}_i [32]. Magnesium participates in vascular regulation by BK channels, whereby Mg^{2+} ion binds to a low-affinity regulator of the conductance domain and exerts complex effects on BK channel activity. Namely, Mg^{2+}_i decreases the BK current amplitude, but the affinity and voltage-sensitivity of the Mg^{2+}_i block depend on the concentration of free, ionized intracellular Ca^{2+} ion ($[iCa^{2+}]_i$). In the presence of micromolar ($1 \mu M$) iCa^{2+}_i , physiological iMg^{2+}_i levels tonically facilitate BK channel activation by Ca^{2+} in vascular SMCs. This effect of the Mg^{2+}_i -enhanced outward K^+ current through BK channels together with the Mg^{2+}_o -mediated suppression of Ca^{2+} entry through VGCCs both contribute to the vasodilatory effect of elevated Mg^{2+} concentrations. However, under the pathophysiological conditions of Mg^{2+}_i depletion in SMCs, a decrease in BK channel activity favours cell depolarization, and the resulting increase in vascular tone may even induce vasospastic responses. Therefore, both intra- and extracellular Mg^{2+} depletion contribute to arteriolar constriction and

the development and maintenance of arterial hypertension [33].

An underlying cellular ionic imbalance develops in vascular SMCs in arterial hypertension, affecting the intracellular ratio between the levels of biologically active ionized fractions of the two divalent cations, $[iCa^{2+}]_i$ and $[iMg^{2+}]_i$. The $[iCa^{2+}]_i:[iMg^{2+}]_i$ ratio in vascular SMCs determines the degree of vasoconstriction (ratio increase) or vasodilation (ratio decrease). When vasoconstriction predominates—hypertension develops, but at an early stage of the disease, a high magnesium intake diet can reduce tissue calcium accumulation and favour the opposite. Furthermore, these $iCa^{2+}_i:iMg^{2+}_i$ dynamics are also subject to shifts depending on blood sugar levels even in normal subjects, as oral glucose loading itself increases iCa^{2+}_i and decreases iMg^{2+}_i , as does hyperglycemia *in vitro* [34]. According to the ionic hypothesis of Resnick, a generalized cardiovascular-metabolic disease results from common ionic and the associated abnormalities at the cellular level, with the same basic pathophysiological conditions of elevated level of $[iCa^{2+}]_i$, and suppressed levels of $[iMg^{2+}]_i$ and intracellular pH value (pH_i), occurring in a number of tissues. This leads to the development of essential hypertension, left ventricular hypertrophy, obesity, hyperinsulinemia, insulin resistance and non-insulin-dependent DM, which often coexist clinically [35, 36].

Mg^{2+} and Bronchial Smooth Muscle

Regarding the role of magnesium in respiratory system function, clinically known the best is that Mg^{2+} deficiency is highly prevalent in patients with bronchial asthma who can significantly benefit from the bronchodilatory effect of magnesium. Pulmonary function test parameters are significantly decreased in asthmatic patients with hypomagnesemia as compared to those with normomagnesemia. Adequate Mg^{2+} status can help control asthma and other chronic obstructive pulmonary diseases (COPDs) [37]. Magnesium is given to rapidly improve expiratory airflow through the narrowed airway lumen in asthmatic patient's respiratory tract. Inhaled Mg^{2+} improves oxygen saturation and reduces morbidity in patients with paediatric refractory acute asthma [38]. Clinical studies have shown that hypomagnesemia is generally common in patients with asthma, and that serum Mg^{2+} levels are particularly low in asthmatic patients with frequent asthmatic attacks, severe exacerbations and uncontrolled disease. The serum Mg^{2+} concentration is positively correlated with the level of symptom control in patients with asthma and may even serve as an important marker of asthma severity. Low serum Mg^{2+} is very common in patients with asthmatic status, the most severe and directly life-threatening form of acute exacerbation of the disease [39]. However, all the relevant

mechanisms of action of Mg^{2+} as a bronchodilator remain insufficiently understood [40].

Alterations in the dynamic $[iCa^{2+}_i]:[iMg^{2+}_i]$ ratio in airway SMCs can play a role in respiratory function performance. Similarly to vascular smooth muscle, $Ca^{2+}:Mg^{2+}$ interplay can affect bronchial smooth muscle and the airway resistance to airflow. When Mg^{2+} is deficient, the action of Ca^{2+} is enhanced, favouring bronchial obstruction [41]. Since $Ca^{2+}:Mg^{2+}$ ratio imbalance can contribute to COPD worsening, Mg^{2+} status should be monitored in COPD patients, and its deficiency should be corrected. In bronchial asthma, airway hyperresponsiveness, hypercontractility and inflammation are the key pathophysiological features. Magnesium favours bronchodilation by suppressing bronchoconstriction through multiple effects. By interacting with Ca^{2+} in airway SMCs and stabilizing their membranes, Mg^{2+} antagonizes Ca^{2+} -mediated bronchoconstriction, but Mg^{2+} also inhibits the release of endogenous bronchoconstrictors: histamine from mast cells and NO, acetylcholine (ACh) and substance P (SP) from nerve endings. Additionally, findings from studies on the role of Mg^{2+} in the inflammatory reaction show an increased release of certain proinflammatory cytokines and positive acute-phase reactants in Mg^{2+} deficiency, supporting the actions of Mg^{2+} as an auxiliary anti-inflammatory agent. Since magnesium supplementation acts to suppress the chronic inflammatory process, Mg^{2+} -induced bronchodilation is at least partially mediated by a reduced degree of bronchial inflammation in asthmatic patients and other COPD patients. The use of intravenous (*i.v.*) and nebulized or aerosolized $MgSO_4$ in the treatment of acute asthma produces significant improvement of respiratory function, due to the beneficial combination of an immediate moderate bronchodilatory effect that persists owing to the prolonged anti-inflammatory action of magnesium. Patients with extremely severe asthma exacerbations receive the greatest benefit from parenteral Mg^{2+} administration in the acute phase and additional Mg^{2+} inhalations in the calm phase of the disease [3]. Animal studies have confirmed that $MgSO_4$ inhalations exert bronchodilatory and bronchoprotective effects, as inhaled Mg^{2+} relieves airway obstruction and attenuates airway inflammation [42].

Mg^{2+} and Urogenital Tract Smooth Muscle

With respect to the relevance of Mg^{2+} for the function of the urogenital tract smooth muscles, it is in obstetrics that Mg^{2+} has its greatest clinical application. Magnesium deficiency is common even in healthy pregnant women, considering their increased physiological needs for this mineral, which are frequently unmet. The serum levels of tMg^{2+} and iMg^{2+} often decrease significantly even during otherwise normal pregnancy with increasing gestational age, as the growing foetus takes up Mg^{2+} from the mother's blood

and consumes it to build up its own tissues during development. A significant correlation exists between maternal hypomagnesemia and preterm delivery [43]. Magnesium is used not only to relieve muscle spasms during pregnancy and prevent premature labour but also to prevent and stop convulsive attacks in gestational hypertensive encephalopathy. Magnesium sulphate efficiently achieves tocolysis through the selective inhibition of myometrial contractions during pregnancy, showing a prolonged tocolytic effect. Magnesium tocolytic therapy is generally limited to the second line of tocolysis when β_2 adrenergic tocolytic agents do not manage to reduce uterine contractions sufficiently. By acting as a Ca^{2+} antagonist, Mg^{2+} achieves its tocolytic effect on the pregnant uterus by competitively blocking Ca^{2+} influx through voltage-gated Ca^{2+} channels and potentially by inhibiting myosin light chain kinase, which is necessary for the contraction of myometrial cells [43]. In addition to inhibiting uterine contractility, Mg^{2+} helps reduce high BP during pregnancy and suppresses brain hyperexcitability in hypertensive encephalopathy of preeclampsia/eclampsia. Magnesium sulphate treatment can protect the integrity and function of the blood-brain barrier (BBB) and prevent brain edema formation, by decreasing BBB permeability during acute hypertension in late pregnancy, as shown in experimental animals [44]. Antenatal $MgSO_4$ is also used for foetal neuroprotection in preterm infants, to reduce the incidence and severity of cerebral palsy, but the mechanism of action is not fully understood yet [45].

Mg^{2+} and Digestive Tract Smooth Muscle

In the context of the effects of Mg^{2+} on digestive tract smooth muscle, besides the already known effect of Mg^{2+} on antagonizing Ca^{2+} , an additional possible mechanism of the laxative effect of Mg^{2+} can be observed. Relaxation of the intestinal muscle wall occurs by means of Mg^{2+} binding to adrenergic β receptors, similar to the effect of propranolol [46].

Mg^{2+} and Skeletal Muscles

Skeletal musculature with its tone, strength and reflex activity enables the maintenance of body posture and locomotion, while contractions of respiratory muscles ensure adequate mechanics of lung ventilation and the vitally important breathing function. Magnesium contributes to the normal electrical and mechanical activity of skeletal muscles, producing an overall membrane stabilizing and relaxing effect, while in Mg^{2+} deficiency, skeletal muscle fibres become hyperexcitable and hypercontractile.

As a divalent cation, Mg^{2+}_o binds to the surface of the cell membrane, providing surface potential that adds to the transmembrane potential in generating the electrical field that voltage-gated sodium channels (VGSCs) are sensing,

thereby affecting the level of the threshold potential of the skeletal muscle cell membrane. Therefore, the effects of Mg^{2+} deficiency on the electrical excitability of skeletal muscle cells are direct and mediated by a shift in the voltage dependence of VGSC activation. In low Mg^{2+} solution, a smaller depolarization is sufficient for the cell to fire an AP [47].

The contraction of skeletal muscle cells is a Ca^{2+} -dependent process initiated by the depolarization of the sarcolemma. Contact and functional coupling between t-tubules and the sarcoplasmic reticulum (SR) enable the opening of the ryanodine receptor (RyR) Ca^{2+} channel. The binding of released Ca^{2+} ions to troponin and myosin fibres results in conformational changes that ensure myofibril contraction. Due to its nature of a Ca^{2+} antagonist, Mg^{2+} competes for Ca^{2+} -binding sites on these proteins [3]. Under normal conditions, $[Mg^{2+}_i]$ is approximately 10,000 times greater than $[Ca^{2+}_i]$ in skeletal muscle cells [48]. Therefore, in the resting state, Mg^{2+} occupies almost all of the Ca^{2+} -binding sites. Magnesium gets to be replaced by Ca^{2+} only when $[Ca^{2+}_i]$ increases after cell depolarization, through Ca^{2+} influx and Ca^{2+} release from the SR. In the case of subclinical Mg^{2+} deficiency, however, the resulting Mg^{2+}_i depletion leaves more free Ca^{2+} -binding sites on contractile protein fibres, permitting excess Ca^{2+} to bind, which results in muscle hypercontractility [3]. The condition clinically manifests as muscle cramps. Recurrent muscle cramps are an important symptom of severe chronic Mg^{2+} deficiency. Although the role of Mg^{2+} in the pathogenesis of muscle cramping has not been fully elucidated, it is assumed to originate largely from the direct effect of Mg^{2+} on muscle contractions, since Mg^{2+} physiologically antagonizes Ca^{2+} binding to the contractile proteins of the sarcomere. In addition, neuronal hyperexcitability in Mg^{2+} -deficient individuals may contribute to the skeletal muscle tone increase that they suffer from [49].

Both professional and recreational athletes have physiologically increased nutritional needs for magnesium, making them particularly sensitive to disorders of Mg^{2+} status in the body. Adequate magnesium intake is very important for athletes to improve muscle strength and endurance, provide for muscle recovery after physical activity, and for the general condition of good psycho-physical fitness. Insufficient average dietary magnesium intake in athletes (less than 260 mg/day in men and 220 mg/day in women) does not provide adequate replenishment of depleted Mg^{2+} stores and easily leads to Mg^{2+} deficiency. Therefore, it is recommended that athletes supplement their diet with an adequate amount of magnesium [50]. Magnesium is one of the most frequently supplemented minerals. Its supplementation should be considered wherever possible, as it is proven to be safe in individuals with preserved kidney function. Magnesium supplementation is also recommended for the elderly, since Mg^{2+}

deficiency and sarcopenia (increased loss of muscle mass and strength during aging) are both common. Poor Mg^{2+} status is thought to actually contribute to the development of sarcopenia in elderly people. The serum Mg^{2+} concentration is significantly associated with muscle performance indices, as shown by recent clinical studies investigating the relationship between Mg^{2+} status and muscle performance in this age group. These findings suggest that elderly individuals may benefit from compensation of the existing Mg^{2+} deficiency to support their muscle performance [51]. Magnesium has several other beneficial effects on skeletal muscles, as its supplementation improves muscle strength in untrained individuals and prevents muscle atrophy during corticosteroid treatment [52].

Mg^{2+} and the Heart

Magnesium depletion is considered to play an important role in the development of a number of conditions affecting the heart and arterial blood vessels: atherosclerosis, arterial hypertension, coronary artery disease (CAD) and congestive heart failure [53]. Hypomagnesemia itself causes changes in the electrocardiogram (ECG), such as depressed ST segment, low-amplitude T wave and prolonged QT interval [49]. The arrhythmogenic effect of Mg^{2+} deficiency is also clinically well known [30, 54].

Mg^{2+} and Electrical and Mechanical Activity of the Heart

The action of the heart as the central pump of the cardiovascular system is a vital body function. Adequate Mg^{2+} homeostasis contributes to its proper electrical and mechanical activity, including parts of the conduction system of the heart and the atrial and ventricular working myocardium. *In vitro* studies have shown that Mg^{2+} is largely involved in the molecular mechanisms of cardiac excitation and contraction [55, 56]. Excitable membranes, including those of the structures of the heart, all require adequate both $[Mg^{2+}_i]$ and $[Mg^{2+}_o]$, in order to maintain their normal resting membrane potential (RMP) level and oppose the development of hyperexcitability. Magnesium ion plays an indirect role in establishing the RMP in excitable cells, through the regulation of Na^+/K^+ ion pump activity and inwardly rectifying K^+ channel (K_{ir}) function. As an essential cofactor for all enzymatic reactions involving ATP, Mg^{2+} is also critical for the biological activity of the Na^+/K^+ pump, which enables the primary active transport of Na^+ and K^+ across the membranes. Following AP repolarization, pump activity generates subsequent afterhyperpolarization which contributes to maintaining the normal duration of the overall refractoriness of an excitable membrane. This protects the cell from the appearance of subsequent secondary depolarizations and the heart from the development of ectopic foci. When Na^+/K^+

pump activity is pathophysiologically suppressed (e.g. in cell Mg^{2+} depletion) or metabolically inhibited (e.g. in tissue hypoxia and ischemia), the excitable membrane is no longer able to maintain its normal Na^+ and K^+ concentration gradients and normal RMP level. The resulting local membrane depolarization brings the membrane closer to the threshold level, thus promoting hyperexcitability.

In the heart, Mg^{2+} provides proper regulation of yet another ion transport mechanism involved in RMP maintenance in cardiac muscle cells. The potassium inward rectifier channel is physiologically very important for the stability of the heart muscle cell RMP. Namely, cardiac K_{ir} channels prevent excess loss of K^+ from the cell during strong membrane depolarization and prolonged electrical discharge. This results from the ability of K_{ir} channel to pass the inward K^+ current rather than the outward one. Intracellular Mg^{2+} directly modulates ion permeation through the cardiac K_{ir} under physiological conditions, as Mg^{2+}_i has a pore-blocking effect. It is Mg^{2+}_i ion that is responsible for this so-called rectifying property of K_{ir} channel function, as Mg^{2+}_i blocks the channel pore. The outward K^+ current would actually be in accordance with the potential chemical energy for K^+ (according to its concentration gradient), but it gets blocked by Mg^{2+}_i . An inward K^+ current, however, easily extrudes Mg^{2+} out of the channel pore. However, in cellular Mg^{2+} deficiency, the channel is dysregulated since its key feature of inward rectification is lost. Loss of Mg^{2+}_i -mediated K_{ir} channel pore block prevents the necessary restoration of intracellular K^+ content and the necessary relief of the local interstitial extracellular K^+ accumulation in heart tissue after a series of repetitive APs. Therefore, intracellular Mg^{2+} depletion pathophysiologically maintains excessive membrane depolarization and favours hyperexcitability [57]. In the heart, Mg^{2+} also helps regulate several other ion currents through K^+ channels, which are essential for the control of cell excitability, such as the M type K^+ current (K_{V7}) [58], and for coupling energy metabolism to electrical activity of the cell, such as ATP-sensitive K^+ channels (K_{ATP}). Furthermore, cardiac gap junction (GJ) channel gating is also regulated by Mg^{2+} , with connexin (Cx) 40 being the dominant ventricular isoform in humans. In guinea pig ventricular muscle, cardiac GJ channel conductance is modulated by Mg^{2+}_i in a bimodal fashion, whereby low Mg^{2+}_i (< 0.6 mmol/L) increases it, while high Mg^{2+}_i (> 1.0 mmol/L) attenuates it. Its dysregulation can clearly contribute to the arrhythmogenic effects of a disordered Mg^{2+} status [59].

The mechanical activity of the heart is continuous throughout life, and as such requires that the cycles of electrical activity (membrane depolarization and repolarization) can alternate in an appropriate manner in excitable cells of the heart. Pattern change with a prolonged depolarization and a delay of repolarization significantly disrupts the processes of electrical impulse generation and conduction in

the heart. Therefore, the loss of intracellular K^+ caused by previous electrical activity, but pathophysiologically not restored due to Na^+/K^+ pump and K_{ir} channel dysfunction in Mg^{2+}_i deficiency—results in hyperexcitability of the heart. The described mechanisms explain the effect of Mg^{2+} deficiency on increasing the risk of developing various heart rhythm disorders. Magnesium deficiency in the heart disturbs cardiac AP generation and conduction, resulting in an arrhythmogenic effect, additionally due to a dysregulated Ca^{2+}_i homeostasis. Namely, a physiological rise of Ca^{2+} concentration in the cytoplasm during the AP plateau phase triggers Ca^{2+} release from the SR stores via RyRs (Ca^{2+} -induced Ca^{2+} release). In the absence of high cytosolic Ca^{2+} in the resting muscle, the activation of sarcoplasmic RyRs is normally inhibited by Mg^{2+}_i . Since Mg^{2+} also blocks the L-type Ca^{2+} channel function responsible for the AP plateau phase in myocytes, it also affects the duration of the ST segment and the entire QT interval in an ECG trace. Therefore, Mg^{2+} depletion and hypomagnesemia represent risk factors for the development of the prolonged QT interval clinical syndrome. This effect contributes to the previously described arrhythmogenic molecular mechanisms induced by Mg^{2+} deficiency [28].

A number of cardiac arrhythmias, including sinus tachycardia, premature supraventricular and ventricular beats, atrial fibrillation, ventricular tachycardia, torsade de pointes and ventricular fibrillation, can be seen in patients with hypomagnesemia. For many years, cardiology practice has confirmed the benefit of magnesium supplementation for the prophylaxis and/or treatment of heart rhythm disorders. Intravenous $MgSO_4$ administration in patients with acute myocardial infarction (AMI) leads to a significant reduction in the frequency of supraventricular and ventricular tachycardias and cardiac arrest and mortality from sudden cardiac death. Magnesium supplements are given to prevent arrhythmias after cardiosurgical interventions. Taken all together, Mg^{2+} does achieve multiple beneficial effects on the heart and blood vessels, including vasodilatory, anti-hypertensive, anti-ischaemic, anti-inflammatory and antiarrhythmic effects, which provide a significant Mg^{2+} -mediated cardioprotection [60–62].

Magnesium homeostasis is also necessary for proper mechanical activity of the heart since Mg^{2+} plays an important role in modulating myocardial contraction. Magnesium exerts a regulatory role on Ca^{2+} homeostasis in heart muscle cells in the process of cardiac excitation-contraction coupling. Cardiac muscle cell contraction is induced by an increase in $[Ca^{2+}_i]$ due to RyR activation and Ca^{2+} binding to contractile fibres, enabling cross-bridge cycling. For the formation of cross bridges between myofilaments in sarcomeres, Mg^{2+} ions and the energy source ATP are required. Magnesium also directly affects myocardial cell contraction by antagonizing Ca^{2+} binding to the key myocardial

contractile proteins troponin C, myosin and actin. The opposing effects of Mg^{2+} and Ca^{2+} on myocardial contractility may be due to the competition between Mg^{2+} and Ca^{2+} for the same binding sites on these filaments. With Mg^{2+} depletion, physiological RyR inhibition by Mg^{2+} is abolished, so that even with high cytosolic Ca^{2+} present—an additional excessive Ca^{2+} surge occurs. These mechanisms underlie the excessive RyR-mediated SR Ca^{2+} release during diastole present in Mg^{2+} deficiency. This can in turn inappropriately stimulate myocardial contraction in diastole and increase end-diastolic pressure in the ventricular cavity, contributing to the development of diastolic heart failure [30]. However, an animal study showed that long-term intake of a MgO-supplemented diet can ameliorate hypertension-induced changes: a decreased iMg^{2+}_i level and contractile dysfunction of left ventricular myocytes in hypertensive rats [63].

Mg^{2+} and Heart Diseases

Low serum Mg^{2+} levels are correlated with poor outcomes in most patients admitted with AMI, due to a greater incidence of cardiac complications (such as atrial fibrillation, cardiogenic shock and sudden cardiac death) [64]. In a Mg^{2+} -deprived heart, not only can alterations in excitation, impulse conduction and contraction develop, but even alterations of heart blood supply. Specifically, Mg^{2+} status has implications for lipoprotein metabolism, as well as the process of haemostasis. Magnesium deficiency has even been found to promote coronary artery vasospasm, which, together with arrhythmias due to Mg^{2+} depletion, significantly elevates the risk of sudden cardiac death [65]. Magnesium deficiency can impair endothelial function due to an increase in free radicals and oxidation and can evoke hyperlipidaemia, which subsequently accelerates atherosclerosis. The proinflammatory, proatherogenic and prothrombotic effects of low Mg^{2+} promote endothelial dysfunction [66]. Magnesium has a statin-like effect of inhibiting the key enzyme in cholesterol (Ch) biosynthesis, β -hydroxy β -methylglutaryl-CoA (HMG-CoA) reductase, and also decreases low-density lipoprotein (LDL) Ch and triglyceride levels and increases high-density lipoprotein (HDL) Ch by activating the enzyme lecithin cholesterol acyl transferase (LCAT). A high magnesium intake diet can help regulate the lipid profile in the blood [67]. Additionally, Mg^{2+} shows certain blood-thinning properties due to its slight anticoagulation and antiaggregation effects. Parenteral Mg^{2+} treatment acts to reduce AMI in-hospital mortality not only by decreasing the incidence of serious arrhythmias and left ventricular heart failure but also as an antithrombotic therapy for CAD patients by inhibiting platelet aggregation and thrombus formation [68]. Treatment with *i.v.* $MgSO_4$ may also be effective in the prevention of acute stent thrombosis [69].

Antiatherothrombotic and anti-inflammatory Mg^{2+} actions improve the functions of excitable tissues indirectly, as they have a beneficial effect on general and local blood circulation. Although these are metabolic and not direct electrophysiological actions of Mg^{2+} , it is virtually impossible to separate them, as they both affect the general level of excitability, particularly the long-term level of excitability, both in health and disease.

Taken together, chronic subclinical Mg^{2+} deficiency can be considered an independent cardiovascular risk factor. Many patients with heart diseases can significantly benefit from supplementing this important cardioprotectant mineral and maintaining total serum Mg^{2+} level at a revised reference level of > 0.85 mmol/L [15]. Drinking Mg^{2+} -rich waters can also act as a simple yet efficient cardioprotective measure. For example, the cardiovascular disease mortality rate correlates positively with drinking water hardness and high Ca^{2+} content but correlates negatively with Mg^{2+} content and a low $Ca^{2+}:Mg^{2+}$ ratio in drinking municipal waters in many communities in Serbia. The hydrogeological region of Western Serbia Dinarids, with drinking and natural mineral waters rich in Mg^{2+} and poor in Ca^{2+} , has a very low cardiovascular disease mortality rate [70].

Mg^{2+} and the Nervous System

Ions in the brain are closely regulated to preserve the stability of electrical activity of the brain and prevent its depression or excessive excitation. Magnesium is an essential mineral for brain function, as Mg^{2+} helps maintain ionic homeostasis through multifaceted regulation of Na^+ , K^+ and Ca^{2+} ion fluxes across nerve cell membranes. Magnesium shows a number of neuroactive effects. In the neurons of the central nervous system (CNS), Mg^{2+} ions modify the conductance properties of different types of voltage-gated and ligand-gated ion channels (ionotropic receptors) and help regulate the processes of synaptic neurotransmission in the brain, whereby Mg^{2+} has an overall stabilizing effect on the electrophysiological properties and electrical activity of central neurons. Under pathophysiological conditions, this is important for the suppression of neuronal hyperexcitability. Overt hypomagnesemia is clearly characterized by motor and sensory signs of disorders of the central and peripheral nervous system (tetany, paresthesia, seizures, etc.). Chronic latent Mg^{2+} deficiency plays a role in the development of a number of neurological, neuropsychiatric and neuromuscular disorders, such as anxiety, depression, migraine and tension headaches, chronic pain, Alzheimer's disease, Parkinson's disease, stroke and epilepsy [71].

Compared with that in blood serum, Mg^{2+} is relatively more abundant in brain tissue and cerebrospinal fluid (CSF), than are the other major cations (Na^+ , K^+ and Ca^{2+}). The mean CSF:serum ratio for Mg^{2+} is 1.2–1.3, whereas

for all other major cations, the ratios are less than 1 [72]. The Mg^{2+} concentration in the CNS extracellular fluid is even greater than that in the CSF [73]. Although Mg^{2+} requirements in all nerve cells are high, its importance for neuronal functions is not fully understood yet. Regarding electrical activity, neuronal synaptic and nonsynaptic excitability closely depend on ion exchange between the intra- and extracellular compartments. Magnesium homeostasis in the brain helps regulate neuronal excitability by modulating ion channel and neurotransmitter receptor function. The levels of Mg^{2+} in the serum, CSF and brain tissue (interstitial fluid) are highly important for normal central neuronal functions. Indicative of this is the fact that Mg^{2+} is the only cation (apart from H^+) present in higher concentration in CSF than in the blood. It is being actively secreted by the choroid plexus, as Mg^{2+} does not cross the BBB. The level of Mg^{2+} in CSF normally ranges between 0.77 and 1.17 mmol/L and reflects Mg^{2+} level in the brain parenchyma (the immediate neuronal ionic milieu). The exact relationships between serum Mg^{2+} and CSF Mg^{2+} levels and Mg^{2+} levels inside brain cells have not yet been fully elucidated, as intracerebral extra- and intracellular Mg^{2+} distribution is clinically inaccessible. However, any derangement of Mg^{2+} homeostasis in the brain due to low serum Mg^{2+} and low CSF Mg^{2+} can be an important factor in the pathogenesis of neuronal dysfunction and damage in a number of neurological conditions [74]. Therefore, supplying the brain (and whole body) with magnesium through the diet is very beneficial.

Concerning neuronal Mg^{2+}_i , it is possible to experimentally detect the dynamics of $[Mg^{2+}_i]$ during neuronal activity at the cellular level using a highly selective fluorescent Mg^{2+} probe [75]. This approach shows that neuronal depolarization triggers Mg^{2+} influx into the cell. The literature reports that a number of ion channels are physiologically inhibited by Mg^{2+}_i . These findings confirm that Mg^{2+}_i is a key modulator of nerve cell activity, making it an important biological setting for cell homeostasis. The transmembrane Mg^{2+} gradient is not as large as that of Ca^{2+} , but the ionized fraction of Mg^{2+}_i (iMg^{2+}_i) seems to be responsible for the fine-tuning of cell excitability. Therefore, $[iMg^{2+}_i]$ must be well buffered to maintain its normal range. When too much Mg^{2+} is loaded into the cells during excess neuronal activity, high $[iMg^{2+}_i]$ stimulates Mg^{2+} efflux through the Na^+/Mg^{2+} exchanger, the main cellular Mg^{2+} efflux system [75]. Fine cellular ionic homeostasis in brain cells (central neurons and glial cells) depends on a controlled ionic microenvironment provided and maintained by brain barriers (blood-brain and blood-CSF). The effects of Mg^{2+} on BBB permeability are not yet completely understood. Its interaction with neuron to astrocyte omnidirectional signaling could also be implicated [76]. Table 3 summarizes major points concerning Mg^{2+} homeostasis in the brain [73, 77, 78].

Table 3 The distribution of Mg^{2+} in different compartments of the extracellular and intracellular fluid in the brain

Blood	Total, 0.65–1.05 mmol/L; ionized, 0.55–0.75 mmol/L
CSF	Total, 0.77–1.17 mmol/L; ionized, 0.59–0.90 mmol/L
Brain ISF	Total, higher than in the CSF (difficult to measure directly); ionized, 0.4–1.4 mmol/L
Cell cytosol	Total, 14–18 mmol/L; ionized, 0.5–1.2 mmol/L
Mitochondria	Total, 15–18 mmol/L; ionized, 0.8–1.2 mmol/L

CSF cerebrospinal fluid, ISF interstitial fluid

Mg^{2+} and Nonsynaptic and Synaptic Nerve Cell Excitability

The physiological functions of many ion channels and receptors are modulated by Mg^{2+} in neurons even more than in other types of excitable cells. Magnesium reversibly increases the membrane threshold potential level and decreases cell excitability in invertebrate and mammalian nerve cells [79, 80]. This effect is partially attributable to the screening of the membrane surface charge, as extracellular Mg^{2+} binds to a variety of negatively charged lipid moieties. In central neurons, Mg^{2+}_i reduces VGSC conductance in a voltage- and concentration-dependent manner [81]. Therefore, Mg^{2+}_i deficiency pathophysiologically increases the intrinsic, endogenous excitability of neuronal membranes. Upon exposure of hippocampal neurons in culture to low- Mg^{2+} medium, spontaneous induction of continuous epileptiform activity occurs, together with upregulated VGSC expression that coincides with an increase in the persistent Na^+ current (I_{NaP}). This is a small, noninactivating fraction of the total Na^+ current through the VGSCs with sub-threshold activation [82]. Enhanced I_{NaP} promotes abnormal membrane hyperexcitability and is often epileptogenic, as it provides a major depolarizing drive for the electrogenesis of large spike afterdepolarizations (ADPs) and burst firing from the soma of principal cortical neurons, such as hippocampal pyramidal cells [83]. Magnesium also reversibly and dose-dependently suppresses nonsynaptic Na^+ -dependent epileptiform activity induced in invertebrate neurons [84]. These complex mechanisms of the regulation of Na^+ currents by intra- and extracellular Mg^{2+} add to other Mg^{2+} actions that make Mg^{2+} essential for the maintenance of overall neuronal electrical excitability.

As for K^+ ion channels, Mg^{2+} is known to block the majority [85]. Among the Mg^{2+} -sensitive K^+ channels in central neurons, widely expressed are the BK channels whose functional role is to regulate neuronal firing pattern, prevent afterdepolarizations and enable regular tonic firing. Neuronal BK channels play a critical role in the control of cell excitation by allowing the outward K^+ current in response to a depolarization or increase in Ca^{2+} levels, to repolarize the cell membrane potential. Their main function is to lessen neuronal hyperexcitability. Their voltage- and

Ca^{2+} -dependent activation with complex channel kinetics is also sensitive to Mg^{2+}_i . However, how voltage, Ca^{2+}_i and Mg^{2+}_i interact during channel activation has not yet been completely elucidated. Under physiological conditions, the overall effect of neuronal BK channel modulation by Mg^{2+}_i is to enhance channel function by facilitating BK channel opening through an electrostatic interaction with the voltage sensor [86]. Hence, the loss of Mg^{2+} -dependent BK channel activation in Mg^{2+} -depleted neurons renders them prone to overexcitation. Intracellular Mg^{2+} is reported to regulate the gating of many other channels, mostly by reducing their ion currents. Several types of transient receptor potential (TRP) ion channels from several different subfamilies, TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin) and TRPC (canonical), are also subject to inhibition by Mg^{2+}_i [87]. The Mg^{2+} -permeable channel TRPM7 is ubiquitously expressed and regulated by cytosolic Mg^{2+} -ATP levels and is considered to be a key regulator of whole-body Mg^{2+} homeostasis in mammals, which is required for cell viability [88]. Finally, Mg^{2+}_i regulates Ca^{2+}_i homeostasis by inhibiting Ca^{2+} release from cytosolic stores through inositol 1,4,5-triphosphate (IP_3) receptors and RyRs.

Cellular neuroactive effects of Mg^{2+} also include Mg^{2+} -dependent synaptic plasticity. Magnesium affects major excitatory and inhibitory neurotransmission pathways in the brain. Low extracellular Mg^{2+} in brain tissue disrupts the processes of chemical synaptic neurotransmission via different mechanisms at the presynaptic and postsynaptic level. The most important are the effects of Mg^{2+} dyshomeostasis on central neurotransmission by glutamate and γ -aminobutyric acid (GABA). On a postsynaptic level, Mg^{2+} acts as a physiological regulator of the function of central chemical synapses for glutamate, the most important excitatory neurotransmitter, and GABA, the most important inhibitory neurotransmitter in the brain. In the CNS, Mg^{2+} affects the membrane potential of postsynaptic neurons in excitatory glutamatergic and inhibitory GABAergic central synapses by modulating the activity of the N-methyl-D-aspartate (NMDA) glutamate receptor (R) and the A-type GABA receptor (GABA_AR). In central neurons at normal RMP levels and all membrane potentials below -60 mV, Mg^{2+} ions in physiological concentrations in the extracellular fluid block NMDARs in a voltage-dependent manner so that glutamate can act only on the α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) Rs. Initial membrane depolarization releases the Mg^{2+} NMDA block so that after glutamate binding, NMDARs can open already at membrane potentials above -60 mV. An inward cation current through open channels depolarizes the neuron. This discovery of NMDAR block by Mg^{2+} several decades ago actually led to a resurging interest in the neurological implications of CNS deficiency in Mg^{2+} , a previously forgotten electrolyte [89]. Glial

NMDARs are not sensitive to extracellular Mg^{2+} block [90]. In central neurons, in addition to serving as a non-competitive NMDAR blocker, Mg^{2+}_o also physiologically activates the ionotropic GABA_AR . As a GABA_A agonist, Mg^{2+} causes cell hyperpolarization, i.e. moving the membrane away from the AP threshold. This also represents a form of Mg^{2+} neuronal protection from excessive synaptic excitation. Moreover, Mg^{2+} exerts presynaptic effects on central chemical synapses, as it inhibits the release of neurotransmitters by blocking voltage-gated Ca^{2+} channels on presynaptic nerve endings.

Intracellular Mg^{2+} regulates the plasticity of electrical synapses between neurons, which are widely expressed in the mammalian brain. Magnesium ions permeate GJ channels forming electrical synapses, composed of several types of connexins (Cx36 is the main isoform in the adult brain), and modulate Cx GJ channel function. Lowering $[\text{Mg}^{2+}_i]$ augments, while increasing $[\text{Mg}^{2+}_i]$ reduces junctional conductance, affecting both the open probability and the number of functional channels in the synapse [91]. Preserving adequate Mg^{2+}_i in the brain can have a neuroprotective effect by limiting the extent of tissue dying off (by apoptotic and/or necrotic cell death) during brain ischemia and hypoxia in stroke, aneurysmal subarachnoid haemorrhage (aSAH), traumatic brain injury, etc. through the proposed mechanism of closing GJ channels by Mg^{2+}_i [92]. Dysfunction of electrical synapses can lead to obstacles in shifting between sleep and wake states, impaired learning and memory and epileptic discharge propagation. Therefore, Mg^{2+} modulation of GJs (composed of Cx36 and several other connexin types) between neurons and other cells in different brain regions can at least in part mediate the clinically beneficial neuroactive effects of Mg^{2+} in alleviating insomnia, preserving cognitive functions and suppressing seizures [92]. As a neuroprotectant, Mg^{2+} is even a good therapeutic option for the stabilization of neurocritical patients. Intravenous administration of MgSO_4 can reduce hematoma size in intracranial haemorrhage and ischemia due to cerebral vasospasm secondary to aSAH [93].

The changes in Mg^{2+} concentration physiologically significantly affect not only both chemical and electrical central synaptic neurotransmission but also the functions of the peripheral nervous system (PNS) as well. By interacting with several types of nicotinic ACh receptors (nAChRs) as a modulator of cation fluxes (Na^+ , K^+ and Ca^{2+}) through nAChRs, Mg^{2+} also helps regulate central and peripheral cholinergic neurotransmission. Centrally, Mg^{2+} reduces the ion channel conductance of neuronal nAChRs at physiological Mg^{2+} concentrations [94]. Peripherally, Mg^{2+} produces a block of the neuromuscular junction, i.e. the motor end plate (by inhibiting Ca^{2+} -dependent ACh release from presynaptic terminals), and clinically enhances the effect of nondepolarizing muscle relaxants due to their synergism on muscle-type nicotinic Rs

Table 4 Major Mg^{2+} -regulated neuronal ion channels and receptors

Voltage-gated ion channels	VGSC, K_{ir} , K_{Ca} , K_{ATP} , K_{V7} , VGCC
Transient receptor potential channels	TRPM(3, 6, 7), TRPV(1, 3, 5, 6), TRPA1, TRPC5
Gap junction channels	Cx(26, 32, 36, 43, 45, 47)
Intracellular ion channels	IP_3R , RyR
Neurotransmitter receptors	NMDAR, $GABA_A$ R, nAChR

VGSC voltage-gated sodium channel, K_{ir} inwardly rectifying K^+ channel, K_{Ca} Ca^{2+} -activated K^+ channel, K_{ATP} ATP-sensitive K^+ channel, K_{V7} voltage-gated K^+ M channel, VGCC voltage-gated calcium channel, TRPM transient receptor potential melastatin, TRPV transient receptor potential vanilloid, TRPA transient receptor potential ankyrin, TRPC transient receptor potential canonical, Cx connexin, IP_3R inositol 1,4,5-triphosphate receptor, RyR ryanodine receptor, NMDAR N-methyl-D-aspartate receptor, $GABA_A$ R γ -aminobutyric acid type A receptor, nAChR nicotinic acetylcholine receptor

[95]. Hence, the sensitivity of neuronal electrical activity to Mg^{2+} is manifold, widespread and very complex. Table 4 encompasses our attempts to enhance the present understanding of how Mg^{2+} ions function to help regulate nerve cell excitability, by summarizing a list of the most relevant ion channels and receptors known to be regulated by Mg^{2+} .

Thus, Mg^{2+} physiologically participates in the establishment and maintenance of several lines of neuronal defence against overexcitation. Previously described alterations in synaptic and intrinsic neuronal functions induced by low Mg^{2+} concentrations conjointly disrupt the delicate excitation/inhibition balance that normally prevents any episodes of hyperexcitability. Magnesium mediates a significant protective effect on central neurons by controlling powerful excitatory glutamatergic neurotransmission (antagonizing glutamate release and excessive NMDAR activation). When pathophysiologically enhanced and sustained neuronal depolarization overcomes Mg^{2+} blockade so that NMDAR overactivation prevails, mechanisms of excitotoxicity are initiated, leading to excessive accumulation of intracellular Ca^{2+} and eventual neuronal death [3]. Therefore, in the state of Mg^{2+} depletion in the body and/or in the brain, the synaptic excitability of central neurons significantly changes. These changes in central synaptic transmission (an increase in glutamatergic excitation simultaneous with insufficient GABAergic inhibition), together with previously described intrinsic membrane alterations—all drive the condition of Mg^{2+} deficiency into some form of brain hyperexcitability. The resulting hyperexcitation contributes to the mechanisms of pathogenesis of a number of neurological conditions and diseases, such as the development of seizures and epilepsy [88].

Mg^{2+} and Epilepsy and Migraine

Magnesium deficiency has an epileptogenic effect both in experimental animals *in vivo* and in various nerve tissue

preparations *in vitro*. A decreased Mg^{2+} concentration creates a hyperexcitable environment for the brain tissue [96]. Low Mg^{2+} and zero- Mg^{2+} artificial CSF is a known ictogenic medium, as it induces spontaneous epileptiform activity in hippocampal and cortical pyramidal neurons [97]. Clinical findings also confirm that the Mg^{2+} -deprived brain is hyperexcitable and can easily develop epileptic bursts. Severe hypomagnesemia provokes epileptic seizures in humans. Similarly, hypomagnesemia as a finding is more common in children with febrile seizures [98] and adults with generalized convulsive seizures [99] than in healthy individuals of the same age. Among epilepsy patients, the greatest Mg^{2+} deficiency was established in status epilepticus and severe forms of epilepsy [100]. Therefore, Mg^{2+} levels should always be measured when trying to determine seizure aetiology [101].

Approximately 1/3 of epilepsy patients respond poorly to antiepileptic drug therapy (the drug-resistant form of the disease), in whom hypomagnesemia increases seizure frequency and the risk of sudden unexpected death in epilepsy [102]. The majority of pharmacoresistant epilepsy patients also have a low serum iMg^{2+}/tMg^{2+} ratio interictally [103]. Therefore, magnesium supplementation can generally help patients with epilepsy establish and maintain good control of the disease and especially those diagnosed with a deficiency of this mineral. For example, daily administration of 450 mg of magnesium in patients with convulsions reduces the need for antiepileptic drugs, which is also beneficial for improving the overall tolerability of the applied therapy and patient compliance [71]. Parenteral Mg^{2+} administration to stop acute epileptic seizures is most commonly used to control convulsive seizures in epileptic encephalopathies. In obstetrics, $MgSO_4$ injections and infusions have long been used for the treatment of eclampsia and severe preeclampsia, a severe form of hypertensive encephalopathy during pregnancy, childbirth and midwifery that vitally endangers both mother and child. Parenteral $MgSO_4$ is given as the first choice anticonvulsant to emergently manage eclamptic convulsions, as it has the best foetal and neonatal safety profile among the antiepileptics. The antihypertensive effect of Mg^{2+} contributes to a reduction in brain edema, and the antiepileptic effect of Mg^{2+} lowers the convulsive brain threshold, both of which are therapeutically beneficial for patients with preeclampsia/eclampsia syndrome [80, 104]. Additionally, $MgSO_4$ can be used as a contributory drug in hypertensive crisis caused by pheochromocytoma to reduce severe hypertension, provide hemodynamic control and improve hypertensive encephalopathy, as Mg^{2+} acts as an adrenergic antagonist to attenuate the release of catecholamines from the adrenal medulla and antagonize catecholamine receptors [105]. Magnesium can be an effective adjunct in the treatment regimen for refractory epilepsy [106] and refractory status epilepticus [107].

The overall level of brain excitability is also increased in other types of episodic brain dysfunctions, except for epileptic seizures. Likewise, in addition to patients with epilepsy, patients with migraine exhibit reduced levels of Mg^{2+} in the serum and CSF [108]. Migraine headache attacks are considered to result from the pathophysiological phenomenon of cortical spreading depolarization (CSD). It is based on a wave front of intense and long-lasting depolarization of neuronal and glial cells, slowly propagating through the cerebral cortex, followed by hyperpolarization, i.e. cortical spreading depression. The etiological factors and pathogenetic mechanisms that initiate CSD have not yet been fully elucidated. However, it is known to be driven by a loss of cortical ion homeostasis resulting in an increase in the extracellular K^+ concentration, which depolarizes nociceptive central neurons and leads to pain. Patients with low serum Mg^{2+} and low CSF Mg^{2+} are more susceptible to migraine headache attacks. There are multiple mechanisms by which Mg^{2+} deficiency in interstitial brain tissue fluid and CSF can promote neuronal network overexcitation and cortical spread of depolarization, thus contributing to the development of a migraine attack. Increasing the voltage-dependent block of NMDARs by Mg^{2+} may serve to inhibit CSD initiation and/or propagation. Therefore, the administration of magnesium to prevent and treat migraine headache attacks has its background in migraine pathogenesis, in addition to its affirmation in clinical effectiveness [109].

Mg^{2+} and Neurodegeneration and Neuroinflammation

Changes in Mg^{2+} status can also be implicated in the processes of neuroplasticity, neuroinflammation and neurodegeneration, which are often followed by indirect changes in the level of excitability of the nervous tissue. Maintaining Mg^{2+} homeostasis in the body in general and especially in the brain also helps to preserve cognitive psychological functions, as they are found to correlate positively with Mg^{2+} concentrations in CSF and the brain [73]. Magnesium increases the release of brain-derived neurotrophic factor (BDNF), which contributes to neuronal plasticity, learning and memory [110]. A significant positive correlation is found between the levels of Mg^{2+} in brain interstitial fluid and endogenous cellular Mg^{2+} , which can be easily assessed by measuring from the RBC sample [111]. RBC $[Mg^{2+}]$, a measurable indicator of whole-body Mg^{2+} status, is found to linearly correlate with the dentate gyrus synaptic density in rat hippocampal brain slices, which is relevant for spatial and recognition memory. Long-term magnesium administration for the correction of Mg^{2+} deficiency in the brain simultaneously increases both the endogenous Mg^{2+} level and the density of hippocampal synapses and improves impaired memory function, including short-term facilitation and long-term synaptic potentiation, in older animals [111, 112].

Magnesium inhibits the release of proinflammatory SP [91]. Magnesium deficiency contributes to systemic low-grade inflammation and is also linked to neuroinflammation [110]. In mice deficient in Mg^{2+} due to a magnesium-deprived diet, the expression of neuroinflammation-related genes is induced in the hippocampus and cortex. Neuroinflammation in these brain regions can also trigger learning and memory impairments [113]. Furthermore, marked substantia nigra (SN) atrophy and selective loss of dopaminergic neurons are found in rats fed a very low magnesium diet, suggesting that low magnesium intake may be involved in the pathogenesis of SN degeneration [114]. This is probably mostly due to the loss of the remarkable anti-excitotoxic effect of Mg^{2+} , but also the loss of other beneficial effects of Mg^{2+} in the CNS. Numerous clinical studies also emphasize the potential role of Mg^{2+} deficiency in the pathogenesis of primary (Alzheimer's disease and Parkinson's disease) and secondary neurodegenerative conditions (multiple sclerosis, stroke, etc.), as well as the possibility of its therapeutic application in the early stages of the disease in order to reduce the risk of further decline of cognitive functions [104]. Magnesium L-threonate, a Mg^{2+} salt of a vitamin C metabolite and a supplement with high bioavailability, improves memory and cognition [115], enhances the clearance of amyloid β plaques, slows the progression of Alzheimer's disease [116] and attenuates the loss of dopaminergic neurons in an experimental model of Parkinson's disease [117]. Magnesium is also protective against anoxic injury in mammalian cortical neurons, as it significantly decreases anoxic neuronal death *in vitro* [118].

Mg^{2+} and Pain

Furthermore, Mg^{2+} plays a role in nociception. Animals fed a magnesium-depleted diet develop low levels of Mg^{2+} in the plasma, CSF and spinal cord, as well as a lower pain threshold. Heightened sensitivity to pain, i.e. hyperalgesia induced by Mg^{2+} deficiency, is yet another form of pathophysiologically enhanced excitability, affecting the somatosensory system. The increase in pain sensitivity in magnesium-deprived animals is partially mediated by the proinflammatory effect of low Mg^{2+} , which causes C fibre peripheral nerve endings to release more SP, a proinflammatory neuropeptide. Thereby, the increased plasma level of SP in Mg^{2+} deficiency mediates the development of neurogenic inflammation and pain. Thus, Mg^{2+} deficiency hyperalgesia can only partially be reversed by NMDAR blockade [119]. After Mg^{2+} reloading, all Mg^{2+} concentrations rapidly normalize, but the reversal of hyperalgesia (recovery of a normal pain threshold) is time delayed. This finding suggests possible long-term changes in the nociceptive pathways and/or central mechanisms involved in Mg^{2+} deficiency hyperalgesia [120]. Magnesium salts show both significant analgesic

properties and adjuvant nonsteroidal anti-inflammatory drug effects. The antinociceptive effect of Mg^{2+} was recognized in anaesthesiology several decades ago. It is considered to be achieved primarily by blocking NMDARs and central sensitization. Magnesium efficiently suppresses postoperative pain, neuropathic pain, menstrual pain, etc. As an adjuvant agent for analgesia, sedation and neuromuscular relaxation with a high therapeutic index, magnesium represents a versatile medication in the anaesthetic pharmacopoeia [121].

Mg^{2+} and Psychiatric Disorders

Since magnesium exerts an overall membrane stabilizing effect on neurons and calming effect on the brain, it can also help with insomnia [122], mood disorders [123], anxiety, inquietude, stress and attention deficit hyperactivity disorder (ADHD). A sleep-deprived brain is hyperexcitable. Poor Mg^{2+} status is associated with increased levels of circulating catecholamines and cortisol [124], low melatonin levels [125] and poor sleep quality [126], while magnesium supplementation shows a sleep-stabilizing effect [122]. An inverse association is found between dietary magnesium intake and the risk of depression [127]. Both preclinical and clinical evidences from studies on laboratory animals and human subjects show that chronic Mg^{2+} deficiency increases susceptibility to stress [124]. The scientific literature on the impact of magnesium on mental health shows that Mg^{2+} levels are often lowered in the course of several mental disorders, especially depression, anxiety, psychological stress and insomnia, and that magnesium supplementation can help alleviate symptoms [124]. In recent years, magnesium has appeared to be a novel potential adjunct therapy for psychiatric disorders [128]. Since Mg^{2+} is involved in the regulation of serotonergic, dopaminergic and cholinergic neurotransmission [129], the field of nutritional psychiatry is considering therapeutic supplementation of magnesium in different mental illnesses, with positive results confirmed in depression and anxiety. In children with ADHD, Mg^{2+} deficiency occurs more frequently than in healthy children, and Mg^{2+} supplementation proves valuable and safe as a supportive treatment for ADHD [130].

Regarding Mg^{2+} and special senses, magnesium deficiency increases the risk of retinopathy as a complication of DM, while cochlear Mg^{2+} content is negatively correlated with hearing loss in patients with cochlear damage from acoustic trauma [131]. Magnesium shows a beneficial effect of reducing the severity of tinnitus in noise-induced and idiopathic sensorineural hearing loss [132].

Mg^{2+} and Peripheral Nerves

Furthermore, Mg^{2+} participates in the functioning of PNS structures. There is evidence of the beneficial action of Mg^{2+}

on peripheral nerve regeneration after injury. Postoperative axonal regeneration and functional recovery of the injured nerve can be promoted by sewing a biodegradable magnesium wire under the epineurium during nerve surgery, due to the ability of Mg^{2+} to suppress inflammation and stimulate Schwann cell secretion of BDNF [133]. To improve Mg^{2+} status and help provide symptom relief in peripheral neuropathy [134] and several other chronic clinical conditions, transdermal magnesium treatment can also be advised. Although peroral magnesium supplementation is commonly used in individuals with Mg^{2+} deficiency to support a low-magnesium diet, transdermal magnesium delivery can be another option. Transdermal utilization of magnesium is an easy, comfortable, affordable and well-tolerated way to replenish the body with Mg^{2+} and increase the cellular Mg^{2+} content. The beneficial outcome is achieved faster than that achieved by oral means, with almost complete absorption and few side effects. Preparations for transdermal application (magnesium-containing sprays, creams, etc.) are beneficial for the prevention and treatment of migraine headaches [108], muscle cramps and some other conditions.

Clinical Implications of Magnesium Deficiency-Related Hyperexcitability

This review explains how a Mg^{2+} -deprived organism is prone to the development of different forms of tissue hyperexcitability. The primary intention of the authors of this review was to stress and summarize the most relevant effects of Mg^{2+} on the excitability of vital organs. However, for an ion as ubiquitous as Mg^{2+} in all our cells, it is almost impossible to end the list of its effects being more or less relevant to the function of excitable tissues in general. The same is true for the list of functional abnormalities of excitable tissues induced by Mg^{2+} deficiency and the manifold associated clinical indications for its supplementation. Finally, individuals with a suboptimal Mg^{2+} status are also at risk of a number of other disorders (of nonexcitable organs). Chronic latent Mg^{2+} deficiency predisposes individuals to dyslipidemia, due to a loss of the regulatory effect of Mg^{2+} on the blood lipid profile, and has been shown to be associated with atherosclerosis, metabolic syndrome, type 2 DM, osteoporosis, progressive decline in renal function in chronic kidney disease and other inflammation-related disorders [135]. All these conditions can indirectly contribute to the development of diseases of the heart, lungs and brain, making pronounced Mg^{2+} deficiency a considerable systemic disorder. Re-establishing Mg^{2+} homeostasis by recompensing or supplementing this *panacea* for the clinical conditions of hyperexcitability results in a plethora of health benefits, the majority of which are presented in Table 5.

Table 5 Major beneficial effects for excitable tissues of Mg²⁺ recompile and supplementation in chronic Mg²⁺ deficiency

Smooth muscles	Vasodilatory, antihypertensive, bronchodilatory, antiasthmatic, tocolytic, laxative
Skeletal muscles	Myorelaxant, relieving cramps
Heart	Antiarrhythmic, anti-ischemic, cardioprotectant
Nervous system	Anticonvulsant, antimigrainic, analgesic, neuroprotectant, anxiolytic, antidepressant

It may seem paradoxical how beneficial effects numbered in Table 5, all are clinically overt while the very chronic Mg²⁺ deficiency may be clinically latent. The explanation lies in the present-day inadequacy in discovering the latent intracellular Mg²⁺ deficiency that is causing or contributing to the specific clinical condition. Therefore, clinicians should bear in mind that magnesium can be used in the prevention and treatment of many different clinical forms of hyperexcitability, especially knowing that an underlying subclinical chronic magnesium deficiency is frequently present.

Conclusion

Magnesium is a bioessential mineral with multiple functions that contribute to maintaining an optimal state of health. Magnesium is ubiquitous in all body structures and is especially abundant in intracellular fluid. Unfortunately, magnesium undernutrition is widespread, and magnesium deficiency, although often clinically silent and difficult to measure accurately, is very prevalent today in the general population. Subclinical magnesium deficiency can cause or at least partially contribute to the emergence of numerous, even leading diseases in the modern world.

Excitability and conductivity, two crucial biophysical features of excitable membranes, underlie the basis of neuromuscular excitability as one of the vital body functions. Magnesium is strongly implicated in the regulation of membrane excitability, as Mg²⁺ regulates cation homeostasis. Magnesium can be considered responsible for the fine-tuning and integration of energy metabolism and ionic homeostasis, as indicated by both extensive fundamental research and clinical trials. Although there are no electrically significant Mg²⁺-driven ionic currents through the membranes, Mg²⁺ disturbances affect all excitable structures in the body and can lead to human excitability disorders. The effects of Mg²⁺ on the properties and electrical activity of excitable tissues are much less well known than its generally better known structural roles and many metabolic effects. The mechanisms of many of these electrophysiological and electropathophysiological effects of Mg²⁺ are still understudied but attract the focus of numerous ongoing biomedical research studies, including basic, translational and clinical studies.

One may say that we are clinically generally still quite unaware of the many points and steps of electrophysiological

processes at which Mg²⁺ is interposed as a regulatory cation for cell membrane intrinsic excitability, impulse generation and conduction, pacemaker cell function, subcellular membranes' function, neurotransmitter release and action, gap junction regulation, etc. However, Mg²⁺ remains essential for normal excitability. Magnesium helps regulate cardiovascular, respiratory and nervous system vital body functions through a plethora of both electrophysiological and metabolic effects. The role of Mg²⁺ in the pathogenesis and management of hyperexcitability disorders is considerable. Multiple mechanisms mediate the electrogenesis of membrane hyperexcitability in Mg²⁺-deficient conditions. The acute and chronic changes in intrinsic and synaptic excitability evoked by low Mg²⁺ that contribute to neuronal and muscle hyperexcitability are numerous, complex and only partially explained. Magnesium recompensation provides improved and adequate treatment for the many forms of hyperexcitability that occur due to underlying Mg²⁺ deficiency. This literature review shows that Mg²⁺ ions play important regulatory roles in the membrane excitability of smooth and skeletal muscles, the heart and the nervous system. It also strives to elucidate current knowledge on the basic mechanisms behind the adverse effects of chronic negative Mg²⁺ balance, as well as the therapeutic effects of its recompense.

The versatile effects of magnesium in electrophysiology are clinically well known, as magnesium is a drug or supplement for multidisciplinary indications. Magnesium is used as an adjunct vasodilator, antihypertensive agent, bronchodilator, antiasthmatic agent, tocolytic agent, laxative agent, antiarrhythmic agent, cardioprotectant, neuroprotectant, anticonvulsant agent, antimigrainic agent, analgesic, anxiolytic agent and antidepressant drug. Magnesium also shows other therapeutically relevant effects, including anti-inflammatory, anti-epileptogenic, anti-arrhythmogenic and general myorelaxant effects; it helps to improve cognitive deficits, alleviates conditions of primary and secondary neurodegeneration, improves sleep, etc. Therefore, Mg²⁺ homeostasis should be assessed in any case of disorders of excitable organs. Maintaining Mg²⁺ within optimal ranges should be a therapeutic target in those diseases, as Mg²⁺ repletion, where needed, removes the background hyperexcitability caused by its deficiency, which aggravates the condition.

These findings remind and warn us of the importance of adequate dietary magnesium intake. Since the impact

of Mg^{2+} on excitable tissues is high, clinicians should consider alterations in Mg^{2+} homeostasis wherever signs and symptoms of excitability disorders are present. The possible presence of subclinical or clinical magnesium deficiency should be considered a potential risk factor for a number of conditions and diseases, due to its growing prevalence. When affecting excitable tissues and organs, long-lasting Mg^{2+} depletion leads to multiple disorders with a common pathophysiological feature of hyperexcitability. Including Mg^{2+} -rich foods and waters is an excellent way to boost magnesium intake naturally. Magnesium supplementation can also be considered in these conditions. However, despite being available and affordable and having a wide therapeutic index and many indications, preparations of magnesium (peroral, parenteral and transdermal) are unfortunately still underused clinically. The awareness of the great therapeutic potential of magnesium should increase, and its supplementation, if needed, should be provided wherever possible. Correction of the background level of hyperexcitability caused by underlying (clinical or subclinical) Mg^{2+} deficiency is certainly beneficial for a number of the conditions and diseases discussed in this review.

Abbreviations ATP: Adenosine triphosphate; SLC: Solute carrier; CNM: Cyclin M; TRPM: Transient receptor potential melastatin; AP: Action potential; RDA: Recommended dietary allowance; tMg^{2+} : Total Mg^{2+} ; iMg^{2+} : Ionized Mg^{2+} ; $[iMg^{2+}]$: Concentration of ionized Mg^{2+} ; Mg^{2+}_o : Extracellular (outer) Mg^{2+} ; Mg^{2+}_i : Intracellular Mg^{2+} ; $[iMg^{2+}]_i$: Concentration of ionized intracellular (inner) Mg^{2+} ; $[iMg^{2+}]_o$: Concentration of ionized extracellular (outer) Mg^{2+} ; RBC: Red blood cells; DM: Diabetes mellitus; $[Mg^{2+}]_o$: Concentration of extracellular (outer) Mg^{2+} ; $[Mg^{2+}]_i$: Concentration of intracellular (inner) Mg^{2+} ; SMC: Smooth muscle cell; BP: Blood pressure; NO: Nitric oxide; VGCC: Voltage-gated Ca^{2+} channel; $[Ca^{2+}]_i$: Intracellular Ca^{2+} concentration; K_{Ca} : Ca^{2+} -activated K^+ channel; $[iCa^{2+}]_i$: Concentration of ionized intracellular Ca^{2+} ; pH: *Potentia Hydrogenii*, lat.; COPD: Chronic obstructive pulmonary disease; ACh: Acetylcholine; SP: Substance P; *i.v.*: Intravenous; BBB: Blood-brain barrier; VGSC: Voltage-gated sodium channel; SR: Sarcoplasmic reticulum; RyR: Ryanodine receptor; CAD: Coronary artery disease; ECG: Electrocardiogram; RMP: Resting membrane potential; K_{ir} : Inwardly rectifying K^+ channel; K_{v7} : Voltage-gated K^+ M channel; K_{ATP} : ATP-sensitive K^+ channel; GJ: Gap junction; Cx: Connexin; AMI: Acute myocardial infarction; Ch: Cholesterol; HMG-CoA: β -Hydroxy β -methylglutaryl-CoA; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; LCAT: Lecithin cholesterol acyl transferase; CNS: Central nervous system; CSF: Cerebrospinal fluid; iMg^{2+}_i : Ionized fraction of intracellular Mg^{2+} ; ISF: Interstitial fluid; I_{NaP} : Persistent Na^+ current; ADP: Afterdepolarization; TRP: Transient receptor potential; TRPV: Transient receptor potential vanilloid; TRPA: Transient receptor potential ankyrin; TRPC: Transient receptor potential canonical; IP_3 : Inositol 1,4,5-triphosphate; GABA: γ -Aminobutyric acid; NMDA: N-Methyl-D-aspartate; R: Receptor; $GABA_A$ R: GABA type A receptor; AMPA: α -Amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; aSAH: Aneurysmal subarachnoid haemorrhage; PNS: Peripheral nervous system; nAChR: Nicotinic acetylcholine receptor; CSD: Cortical spreading depolarization; BDNF: Brain-derived neurotrophic factor; SN: Substantia nigra; ADHD: Attention deficit hyperactivity disorder

Author Contribution MS designed and supervised the project. MS, NDj and DP performed the literature search and wrote the main text of the manuscript. MS, MP, MB, SS, SL, SK and JNO edited the manuscript. All authors reviewed and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Declarations

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