Magnesium-Calcium Interrelationships in Vascular Smooth Muscle*)**)

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Zusammenfassung

Die Kontraktilität aller Arten von Wirbeltier- und Nichtwirbeltier-Muskulatur ist abhängig von Wirkungen und Wechselwirkungen des Calciums (Ca^{2+}) und Magnesiums (Mg^{2+}). Obwohl über die Rolle, die beide Kationen bei der Zellmotilität, bei neurosekretorischen Prozessen, im Rahmen der Tätigkeit von Nervenzellen und bei der Regulation von metabolischen Prozessen spielen, viel zu sagen wäre, beschränkt sich der vorliegende Übersichtsbeitrag auf die Darstellung von Befunden, die zeigen, daß die Funktion der glatten Gefäßmuskulatur und damit der Gefäßtonus direkt von der modulatorischen Rolle des Mg^{2+} auf die Bewegung und Verschiebung von Ca^{2+} abhängen, und zwar an der Zellmembran wie auch intrazellulär. Bemerkenswerte Beweise werden dafür erbracht, daß Mg^{2+} ein „echter", natürlicherweise vorkommender Ca^{2+}-Antagonist an der glatten Gefäßmuskulatur ist. Unterscheidungskriterien dafür, was ein Ca^{2+}-Antagonist bzw. ein Ca^{2+}-Kanalblocker oder ein Ca^{2+}-Einstromhemmer ist, werden vorgestellt. Wir haben Ca^{2+}-Antagonisten in mindestens 8 Unterklassen aufgeteilt: 1. Gewisse di- und trivalente Kationen; 2. Lokalanästhetika, 3. gewisse Antibiotika, 4. Anästhetika, 5. trizyklische Verbindungen, 6. gewisse Antiepileptika, 7. verschiedene synthetische Moleküle, 8. Magnesium. Nichtsdestoweniger wirken die Vertreter aller Klassen, wenn auch unterschiedlich, über Interaktionen mit den Wirkungen und/oder der Freisetzung von Ca^{2+}. Einige ersetzen Ca^{2+}, einige wirken auf langsame Ca^{2+}-Kanäle, einige interferieren mit der Ca^{2+}-Bindung an oberflächlichen Bindungsstellen, einige wirken auf Troponin oder Calmodulin, einige verändern Rezeptor-Interaktionen, während andere die „wirkliche" Aufnahme und den Efflux von Ca^{2+} in bzw. aus Zellen beeinflussen. In der Gefäßmuskulatur kann aktivierendes Ca^{2+} über potentialabhängige Kanäle, über Rezeptor gesteuerte Kanäle und sogar über einfach erhöhte Durchlässigkeit der Membran zur Verfügung gestellt werden. Es scheint, als ob Mg^{2+} die einzige Substanz ist, die auf allen 3 Ebenen an der Gefäßmuskulatur wirksam wird. Insgesamt bestätigen die vorliegenden Daten die Hypothese, daß $(Mg^{2+})_0$ und Membran-Mg^{2+} einen regulatorischen Einfluß auf den Muskeltonus ausüben, ebenso wie auf Gefäßreaktivität, auf physiologische Herzfunktionen und auf den peripheren Gefäßwiderstand. Mg hat möglicherweise eine wichtige funktionelle Bedeutung bei der Regulation der Ca-Aufnahme sowie auf Ca-Gehalt und -Verteilung in Herz- und Gefäßmuskelzellen. Eine Anzahl pathophysiologischer Zustände und Symptome scheinen — wahrscheinlich kausal — mit Mg-Mangel ursächlich verknüpft zu sein.

Zusammenfassend weisen die vorliegenden Daten klar aus, daß Mg^{2+} einen speziellen Typ von Ca^{2+}-Kanalblockern darstellt. Über den Angriff an den Membranen der Gefäßmuskulatur kann Mg^{2+} 1. den Ca^{2+}-Einstrom hemmen und den peripheren und zerebralen Gefäßwiderstand senken, 2. den peripheren und zerebralen Durchfluß verbessern, 3. zerebrale, koronare und periphere Vasospasmen lösen und 4. den arteriellen Blutdruck senken (wenn ausreichend hohe Mg^{2+}-Mengen zugeführt werden). Somit ist Mg^{2+} anscheinend ein spezielles Kation mit schwachen und potentiell nützlichen Ca^{2+}-antagonistischen Eigenschaften.

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Summary

Contractility of all types of invertebrate and vertebrate muscles is dependent upon the actions, and interactions, of two divalent cations, viz., calcium (Ca^{2+}) and magnesium (Mg^{2+}). Although much space could be devoted to the role these cations play in motility of cells, excitation-secretion coupling events, activity of nerve cells, regulation of cellular metabolic processes, transport and secretion of fluids and ions, among other important functions, this review is concerned primarily with the evidence that suggests that vascular smooth muscle (and blood vessel tone) function is a direct consequence of the modulatory role of Mg^{2+} on the movement and translocation of Ca^{2+} at the vascular muscle cell membranes and intracellularly. Considerable evidence is provided for the idea that Mg^{2+} is a "true" (and naturally-occurring) Ca^{2+} antagonist on vascular smooth muscle. The concept of what is and is not a Ca^{2+} antagonist (Ca^{2+} channel blocker, Ca^{2+} entry blocker) is reviewed. We have categorised Ca^{2+} antagonists into at least 8 different subclasses:

1. certain di- and trivalent cations,
2. local anesthetics,
3. certain antibiotics,
4. anesthetics,
5. tricyclics,
6. certain antileptics,
7. diverse synthetic molecules,
8. Mg^{2+}.

However, each class of these molecules acts on cardiac and vascular muscles differently to interfere with the actions and/or release of Ca^{2+}. Some substitute for Ca^{2+}, some interfere with slow Ca^{2+} channels, some interfere with Ca^{2+} binding at superficial binding sites, some act on troponin or calmodulin, some alter receptor interactions, while others affect "true" Ca^{2+} uptake and efflux from cells. In vascular muscle, activator Ca^{2+} can be generated from potential-operated channels, receptor-operated channels, and even leak-operated channels. Mg^{2+} appe-

ars to be the only agent which can clearly act at all 3 sites in vascular muscle. Overall, the available data are consistent with the hypothesis that $[Mg^{2+}]_o$ and membrane Mg^{2+} exert a regulatory role in vascular tone, vascular reactivity, cardiac physiology and peripheral vascular resistance. Mg may have an important functional role in regulating Ca uptake, content and distribution in cardiac and vascular smooth muscle cells. A number of pathophysiologic vascular states and syndromes appear to be associated with, and possibly attributed to, a Mg deficient state.

Collectively, the data acquired, so far, clearly indicate that Mg^{2+} is, indeed, a special kind of Ca^{2+} channel blocker. At vascular membranes it can:

1. block Ca^{2+} entry and lower peripheral and cerebral vascular resistance,
2. improve peripheral and cerebral blood flows,
3. relieve cerebral, coronary and peripheral vasospasm,
4. lower arterial blood pressure (provided enough Mg^{2+} is administered).

In conclusion, Mg^{2+} appears to be a special cation with weak and potentially useful Ca^{2+} antagonist properties.

Résumé

Chez les invertébrés comme chez les vertébrés, la contractilité de tous les types de muscles est sous la dépendance des actions, et des interactions, de deux cations bivalents, le calcium (Ca^{++}) et le magnésium (Mg^{++}). Bien qu'il faudrait consacrer plus de place aux rôles de ces cations dans la motilité cellulaire, les phénomènes de couplage excitation-sécrétion, l'activité des cellules nerveuses, la régulation de certains processus métaboliques cellulaires, le transport et la sécrétion de liquides et d'ions, ainsi que dans d'autres fonctions importantes, cette revue se focalise essentiellement sur la preuve que le fonctionnement du muscle vasculaire lisse (et donc le tonus du vaisseau sanguin) est directement lié au rôle de modulation du Mg^{++} sur les mouvements et le transport membranaires et intra-cellulaires du Ca^{++} au niveau de la cellule musculaire du vaisseau. De très nombreuses preuves indiquent que l'ion Mg^{++} est un antagoniste calcique «véritable» et naturel au niveau du muscle vasculaire lisse. Cet article tend à préciser ce qu'est exactement un antagoniste calcique (bloqueur des canaux du Ca^{++}, bloqueur de l'entrée de Ca^{++}). Nous avons réparti les antagonistes calciques en au moins 8 sous-catégories:

1. certains cations bi- et tri-valents,
2. les anesthésiques locaux,
3. certains antibiotiques,
4. les anesthésiques,
5. les anti-dépresseurs tricycliques
6. certains anti-épileptiques,
7. différentes molécules de synthèse,
8. le Mg^{++}.

Les modes d'action de ces diverses classes de produits sur les effets ou la libération de calcium au niveau de la musculature cardiaque et vasculaire sont cependant différents. Certaines molécules se substituent au Ca^{++}, d'autres agissent au niveau des canaux lents du Ca^{++}, d'autres interfèrent avec la liaison du calcium aux sites superficiels de cette liaison, d'autres ont un effet sur la troponine ou la calmoduline, d'autres encore altèrent les interactions avec les récepteurs, d'autres enfin ont un rôle sur le captage et la sortie cellulaires du Ca^{++}. Dans le muscle vasculaire, l'activation du Ca^{++} peut passer par des canaux dépendant du potentiel, des récepteurs, voire même des fuites de calcium. Le Mg^{++} semble être le seul agent nettement actif sur ces trois sites au niveau du muscle vasculaire. Globalement, les données disponibles semblent indiquer que le $(Mg^{++})_o$ et le Mg^{++} membranaire exercent un effet régulateur sur le tonus et la réactivité vasculaires, ainsi que sur la physiologie du muscle cardiaque et les résistances vasculaires périphériques. Le magnésium pourrait avois une fonction importante dans la régulation du captage, de la concentration et de la répartition du calcium au sein des cellules musculaires lisses du coeur et des vaisseaux. Certains états physiopathologiques vasculaires et certains syndromes semblent être associés, et peut-être même imputables, à une carence en magnésium.

L'ensemble des données acquises à ce jour montre sans aucune équivoque possible que le Mg^{++} est un bloqueur particulier des canaux calciques. Au niveau de la membrane vasculaire, ses actions sont les suivantes:

1. Blocage de l'entrée du Ca^{++} et diminution des résistances vasculaires périphériques et cérébrales,
2. Amélioration des débits sanguins périphériques et cérébraux,
3. Levée de l'angiospasme cérébral, coronaire et périphérique,
4. abaissement de la pression artérielle (sous condition d'être administré en quantité suffisante).

En conclusion, le magnésium semble être un cation particulier, possédant de faibles mais potentiellement utiles propriétés d'inhibition calcique.

Introduction

Contractility of all types of invertebrate and vertebrate muscles (e. g. cardiac, skeletal and smooth) is dependent upon the actions, and interactions, of two divalent cations, viz., calcium (Ca^{2+}) and magnesium (Mg^{2+}). Interestingly, motility of cells, excitation-secretion coupling events (e. g., release of hormones and neurotransmitters), as well as activity of nerve cells and neurons are also dependent upon an interaction of these two divalent cations. These Ca^{2+} and Mg^{2+} messenger systems also have central roles in regulation of metabolic processes, transport and secretion of fluids and ions, regulation of DNA and RNA, as well as cellular growth processes [3, 12, 13, 24, 44, 55, 81, 85, 88, 93, 98, 99, 111, 124, 135, 197].

Although much space could be devoted to cellular divalent cation metabolism, recent views of the intricacies of these messenger systems, and regulation of enzyme kinetics, these and other important functions of Ca^{2+} and Mg^{2+} are beyond the scope of this review. This review will be concerned primarily with the evidence that suggests that vascular smooth muscle and blood vessel tone function is a direct consequence of the modulatory role of Mg^{2+} on the movement and translocation of Ca^{2+} at the vascular muscle cell membranes and intracellularly. We shall provide considerable evidence for the idea that Mg^{2+} is a „true" (and naturally occurring) Ca^{2+} antagonist on vascular smooth muscle [11, 14, 16, 24, 25, 27, 34, 38, 40, 44, 57, 58, 61, 74, 86, 88, 104, 105, 113, 133, 141, 146].

What are Ca^{2+} antagonists, Ca^{2+} entry blockers or slow channel blocking agents?

Much emphasis has recently been placed on the use and de-

sign of drugs which can antagonize or prevent the access of activator, free Ca^{2+} ions to the contractile apparatus in muscles, including cardiac and vascular smooth muscle cells [38, 87, 100, 118, 131, 151]. These so-called Ca^{2+} antagonists (i. e., Ca^{+2} entry blockers, slow channel blocking agents) have been suggested as therapeutic agents for the treatment of a variety of cardiovascular disorders including hypertension, angina, strokes, cerebrovasospasm, transient ischemic attacks, congestive heart failure, arrhythmias, *Raynaud's* phenomenon, migraine headaches, etc. This suggestion is based upon the assumption that these so-called Ca^{2+} antagonists will produce peripheral vasodilation and slow conduction time in cardiac pacemaker cells, thus alleviating ischemia and vasospasm. In other terms, this assumes that slow channel electrical activity in cardiac pacemaker cells and vascular tone is due to an influx of Ca^{2+} across these specialized cell membranes.

However, if we examine the various diverse agents and drugs which exert so-called Ca^{2+} antagonist activities, we note that these substances range from small molecules, like ions (e. g., Mn^{2+}, La^{3+}, to large molecules like tricyclics and dihydropyridine derivatives (Tab. 1). We believe there are at least eight different subclasses of molecules which can be termed Ca^{2+} antagonists (Tab. 1). But, if one closely examines the specific sites of localized cellular action, one notes that only two subclasses inhibit slow Ca^{2+} inward current and can alter membrane receptor interactions, viz. those we have termed synthetic and natural Ca^{2+} blockers, i. e., **Group I** includes 1,4 dihydropyridines, verapamil-like drugs and diphenylmethylalkylamines, and group II compromises Mg^{2+}.

The picture, however, in vascular smooth muscle cells becomes complicated because there are at least three different pathways by which these cells can become activated: potential-operated channels, receptor-operated channels, and leak-operated channels. Each Ca^{2+} pathway seems to be dependent upon a different type of activation (Tab. 2). Thus, we believe that in order to have an excellent Ca^{2+} antagonist for vascular smooth muscle, the molecule should act on all three pathways. It is becoming apparent that Mg^{2+} may have these attributes.

The remaining part of this report will be concerned with identifying the vascular actions and mechanisms of action of Mg^{2+} and how it relates intimately to Ca^{2+} entry, exit and mobilization in vascular muscle cells.

Tab. 1: Molecules which have been designated as calcium antagonists

Class	Action
Di- and Trivalent Cations (e.g., Mn^{2+}, La^{3+})	Substitute for Ca^{2+} at Ca^{2+} binding sites Generally competitive w/Ca^{2+}
Local Anesthetics (e.g., procaine)	Interferes with slow Ca^{2+} channel and produces membrane stabilization
Antibiotics (e.g., Neomycin c)	Interferes w/Ca^{2+} binding at superficial sites
Anesthetics (e.g., barbiturates, alcohols, ketamine halothane, etc.)	Alter troponin regulation of Ca^{2+} and inhibit Ca^{2+} influx
Tricyclics (e.g., trifluoperazine, antipsychotic agents)	Bind to Calmodulin
Antileptics (e.g., dilantin)	
Ca^{2+} Channel Antagonists (Blockers)	Decrease Ca^{2+} binding sites on calmodulin
1. *Synthetic*, e.g., 1,4-dihydropyridines verapamil, diphenylmethylalkylamines	Inhibits slow Ca^{2+} inward current Alters receptor interactions
2. *Natural*, e.g., Mg^{2+}	Inhibits slow Ca^{2+} inward current, alters Ca^{2+} uptake and efflux Alters receptor interactions

Peripheral Vascular Effects of Magnesium

In 1980 and 1981, two reviews appeared which attempted to place into perspective the effects and actions Mg^{2+} exerts on the peripheral circulation [24, 100]. In addition, the review written by *Mordes* and *Wacker* in 1978 [119] contains valuable information on some of the actions excess Mg^{2+} is known to exert on the circulation. Our remarks will therefore focus on information primarily published after 1978. Since none of the previous reviews is directed towards the microcirculation or cerebral circulation, we will also address these specialized areas of the circulation.

Tab. 2: Entry pathways for calcium in vascular smooth muscle cells

Pathway	Dependent Upon?
Potential-Operated Channels	Degree of Membrane Depolarization
Receptor-Operated Channels	Agonist and Concentration
Leak-Operated Channels	Unstimulated?

Regional blood flow

Although systemic administration of pharmacologic amounts of Mg^{2+} has been known to produce vasodilation and hypotension for more than 100 years, until relatively recently [52, 84, 100, 120, 132] very little was known about this divalent cation's effects on specific organ blood flows. In addition, up until recently, a wide range of diverse concentrations of Mg^{2+} was not explored for effects on blood flow, vascular resistance, vascular reactivity or conductance.

During the past four years, several studies using rats, dogs and rabbits have been published which collectively, clearly show that administration of Mg^{2+} can produce dose-dependent reductions in arterial blood pressure, reductions in vascular resistance across several organ beds (i. e., heart, kidney, intestine, muscle, brain) and increased vascular perfusion (across coronary and renal vasculatures) [52, 84, 100, 120, 126, 132]. The data of Charbon in the intact dog seem to indicate that Mg can reduce total peripheral vascular resistance and not produce any increase in left ventricular volume output [84]. Using the perfused isolated Langendorff rat heart, others have found that that it can produce very significant increases in coronary blood flow and yet not affect heart rate or myocardial activity [126]. *Yaeger* and *Masters* using thermography and rapid dialysis found that rapid lowering of plasma Mg^{2+} produced coronary vasoconstriction or vasospasm [153]. These findings, when taken in concert with recent studies demonstrating that infusion of Mg^{2+} can attenuate vascular responsiveness to pressor doses of angiotensin II and norepinephrine in intact rabbits, concomitant with dose-dependent reduction in arterial blood pressure [112], suggest that Mg^{2+} has both direct and indirect actions on arteriolar tone in many vascular beds, thus supporting findings of others on isolated blood vessels and the microcirculation [17, 19, 22–27, 30–36, 38, 40, 42, 46, 49, 50, 54, 56–62, 69, 80, 91, 92, 95, 96, 103, 105, 120, 132, 134, 137, 141–145].

Microcirculatory findings in-vivo

Although there have been a number of interesting studies done with Mg^{2+} on small blood vessel blood flow across some organ regions (e. g., heart, kidney, skin and muscle) in the intact dog as long as 25 years ago by Haddy and co-workers (see [100] for review), such studies do not allow one to discern whether particular types of microscopic resistance and capacitance vessels (e. g., arterioles, venules, metarterioles, precapillary sphincters) are affected selectively by particular concentrations of a vasoactive substance [6, 10]. In addition, since the anion in a Mg salt may be important, it is also necessary to examine different organic and inorganic compounds. During the past 10 years, our group has attempted to provide such information for the microcirculation in living animals [13, 22, 23, 38, 52, 53, 59, 69, 120]. Using the intact rat, we have found that irrespective of the Mg salt (e. g., $MgSO_4$, $MgCl_2$, Mg Aspartate · HCl, Mg acetate), this divalent cation produces dose-dependent reductions in systolic, diastolic and mean arterial blood pressure on intravenous administration [120]. The rapidity and magnitude of the blood pressure drops are, however, somewhat dependent upon the salt and anion coupled to Mg^{2+} [120, unpublished findings]. In addition, irrespective of the route of administration (i. e., local perivascular, intraarterial infusion, intravenous infusion), increasing doses of Mg^{2+} salts produce concentration-dependent dilation of arterioles, venules and precapillary sphincters (where they exist) in skeletal muscle, intestinal and cerebral (cortical) microvasculatures [69, 120].

Moreover, as has been shown for isolated vascular smooth muscles [16, 17, 27, 30, 46, 49, 50, 105, 142, 144], increasing concentrations of Mg salts attenuate arteriolar and venular spasms induced by catecholamines, phenylephrine and Ba^{2+} in these vasculatures, including that of the cerebral circulation [69, 120]. Others have also recently reported that Mg^{2+} can produce vasodilation of cerebral arterioles in the intact cat brain [132]. Our experiments also show that intraarterial (via an internal carotid artery), or even sometimes intravenous, administration of Mg salts can produce rapid (within seconds) vasodilation of cerebral arterioles and venules [69, 120]. It is of considerable interest to note here that all of these vascular effects can be obtained with micromolar changes in blood $[Mg^{2+}]$. This would seem to suggest the posibility that Mg^{2+} can possibly get across certain areas of the blood-brain-barrier, in contradistinction to what has been suggested by others on the basis of only a meager number of indirect studies (see [76], for references). Our findings would also seem to support the older findings of *McCall* and *Sass* on human subjects that systemic administration of Mg^{2+} can cause cerebral vasodilation [117].

Interestingly, when $[Mg^{2+}]_o$ is reduced or withdrawn from the blood or perfusate, arterioles and venules, in the peripheral and cerebral microcirculations will undergo profound vasoconstriction [22, 23, 34, 132]. Collectively, such findings when taken in con-

cert with those discussed above provide impetus to the idea that Mg^{2+} may be an important regulator of the microcirculation and a modulator of organ blood flow. In this context, it also must be considered that reductions in vascular membrane, blood vessel, or free ionic blood levels of Mg^{2+} will result in vasospasm, leading possibly to several types of vascular disease (see ref. [43], for review).

Effects of Magnesium on Blood Vessels and Vascular Smooth Muscles

This section will be directed to recent evidence that suggests that excess Mg^{2+} lowers blood pressure and induces peripheral vasodilation by its actions on vascular smooth muscle cell membranes and intracellularly. In addition, we also review recent findings that indicate that reductions in $[Mg^{2+}]_o$ increases blood pressure and induces peripheral and cerebral vasospasm. These actions of hyper- and hypomagnesemia seem to be in large measure a reflection of Mg^{2+}'s actions on movement and/or translocation of Ca^{2+} across vascular smooth muscle cell membranes and intracellularly [9, 11, 16, 17, 20, 25, 27, 40, 42, 49, 50, 61, 65, 67, 69, 70, 95, 141].

Spontaneous mechanical activity and basal tone

Mg^{2+} appears to be able to directly alter baseline tension or tone [9, 11, 13, 14, 16, 17, 19–27, 30, 33–36, 40, 42, 46, 50, 52, 54, 56–62, 64, 65, 69, 72, 91, 95, 107, 132, 142]. Decrements in $[Mg^{2+}]_o$ result, in a dose-dependent manner, in rapid elevations in tension development in a variety of mammalian arteries (e. g., coronary, cerebral, umbilical-placental, piglet mesenteric arteries, rat aorta) and arterioles that are either spontaneously active or exhibit tone (e. g., mesenteric, cerebral, coronary, umbilical-placental). Similar results have also been reported in ileal smooth muscle [106]. Raising the $[Mg^{2+}]_o$ above normal physiological levels (i. e., >1.2mM) inhibits spontaneous mechanical activity and lowers baseline tension; none of these findings are due to changes in osmolarity or the release (or inhibition of release) of any known vasoactive substance from the vascular walls [11, 16, 21, 26, 27, 40, 49, 59, 57, 69, 80, 92, 95, 142, 144, 146]. The elevations in mechanical activity when $[Mg^{2+}]$ is lowered are markedly reduced and rapidly disappear as $[Ca^{2+}]_o$ is lowered or chelated; addition of calcium ethylenediaminetetracetic acid (calcium EDTA) to the bath fluid or perfusate potentiates these contractile responses, whereas ethylene glycol-bis (B-aminoethylether)-N, N-tetra acetic acid (EGTA) promotes rapid relaxations. Such findings suggest that influx of Ca^{2+} is necessary for these contractile responses [9, 16, 17, 20, 22, 25, 26, 27, 80, 146]. Conversely, lowering baseline tone with excess extracellular Mg^{2+} can be reversed by elevating the $[Ca^{2+}]_o$ [9, 17, 22, 25–27, 146].

In vitro studies using spontaneously active venous smooth muscle (e. g., portal veins) indicate that withdrawal of $[Mg^{2+}]_o$ results in a rapid enhancement of the spontaneously evoked mechanical responses and increases in rhythmic contractility [9, 19, 22–27, 49, 50, 54, 55, 62, 95, 141, 146]. Elevations in $[Mg^{2+}]_o$ above the physiological level lower, in a dose-dependent manner, the frequency and the contractile tension. Addition of approximately 9–10 mM Mg^{2+} usually obliterates development of all spontaneous mechanical events; these findings are not the results of hyperosmolarity or release of any known vasoactive agent from the vascular walls. Like the arteries and arterioles, the magnitude of each mechanical spike elevation, when $[Mg^{2+}]_o$ is lowered, is almost directly proportional to $Ca^{2+}]_o$ [9, 17, 22, 23]. The attenuation of spike activity by elevations in $[Mg^{2+}]_o$ can be surmounted to a large extent by an elevation in $[Ca^{2+}]_o$ or by the addition of extracellular Sr^{2+} [9, 17, 22, 23, 49, 50, 146]. Divalent cations such as Ni^{2+}, Co^{2+} Cd^{2+}, and Mn^{2+}, which inhibit uptake of Ca^{2+} in exciteable tissues can completely block the rise in contractile tensions when Mg^{2+} is lowered, both in venous and arterial smooth muscles [9, 20, 22, 23].

Overall, such data would seem to indicate that Mg^{2+}can certainly inhibit slow Ca^{2+} inward current and act on the leak-operated channels (Tab. 1 and 2).

Influence of magnesium ions on contractions elicited by neurohumoral agents and potassium ions

In addition to its direct actions on myogenic tone, Mg^{2+} may cause vasodilation by inhibition of the constrictor actions of endogenous neurohumoral substances that help to maintain vascular tone [13, 16, 17, 19, 22–27, 30–34, 36, 38, 40, 42, 46, 49, 50, 57, 61, 62, 65, 69, 95, 96, 134, 142, 144]. Since the vasodilation induced by hypermagenesemia is extremely rapid [3, 13, 23, 27, 100, 119], it is likely that it is due to some alteration at the cell surface of the arteries, arterioles, metarterioles and precapillary sphincters [9, 11, 20, 22–27]. In-vitro studies performed over the past 15 years clearly indicate that the contractile actions on isolated arterial and venous smooth muscles, and that of the microvasculature, to a variety of

agonists, including neurohumoral agents (e. g., catecholamines, angiotensin II, serotonin, vasopressin, prostaglandins, other eicosanoids, neuropeptides), K^+, Ba^{2+} and ouabain are depressed by even a slightly elevated $[Mg^{2+}]_o$ (i. e., > 1.2mM). Such results have been noted for a wide variety of arteries (e. g., pulmomary, coronary, mesenteric, renal, femoral, cerebral, celiac, carotid, splenic, umbilical placental) from rabbits, dogs, rats, piglets, guinea pigs, cats and humans [7, 8, 13, 17, 19, 23–27, 30, 31, 34–36, 46, 49, 50, 54, 57, 59, 65, 69, 95, 134, 142, 144, 145], as well as for microscoic resistance and capacitance vessels [22, 23, 42, 69, 120], and several types of veins [9, 19, 24–27, 46, 50, 59, 95, 134]. These results cannot be attributed to hyperosmolarity, alteration of Na^+, K^+-ATPase activity, or release of any known vasoactive mediator from the smooth muscle or endothelial cells. It is of additional interest to note that similar inhibitory effects of elevated $[Mg^{2+}]_o$ have been observed on other types of smooth muscles, e. g. uterine, bladder, vas deferens and respiratory [102, 106, 109, 130].

Conversely, hypomagnesemia could elevate blood pressure and/or increase vascular resistance in certain vascular regions by potentiating the constrictor actions of endogenous circulating neurohumoral substances (e. g., catecholamines, angiotensin II, acetylcholine, serotonin and eicosanoids) and ions (e. g., K^+) known to play important roles in regulation of blood flow [6, 10]. Lowering or removing the Mg^{2+} from the perfusate of medium bathing isolated arterial and venous vessels (e. g., coronary, pulmonary and renal arteries, umbilical arteries and veins, rat mesenteric arterioles, and rat and rabbit portal veins) enhances reactivity of these blood vessels to a number of these neurohumoral agents [11, 13, 16, 17, 19, 22–27, 30–36, 40, 42, 46, 49, 50, 52, 53, 54, 57, 62, 65, 69, 92, 95, 142, 144]. Interestingly, even reactivity of non-blood vessel smooth muscle (e. g., urinary bladder) can be enhanced by low $[Mg^{2+}]_o$ [106].

Influence of extracellular Mg^{2+} on relaxants and vasodilator s. Interestingly, certain relexants (e.g., isoproterenol, nitroprusside) and endogenous vasodilators (e.g., K^+, adenosine, prostaglandins, other eicosanoids, neurohypophyseal hormones) are greatly attenuated as $[Mg^{2+}]_o$ is reduced. An elevation in $[Mg^{2+}]_o$ potentiates the actions of these vasodilators on numerous large and small blood vessels [11, 19, 25–27, 40, 42, 44, 50, 54, 72, 91, 96, 144, 145].

Overall, such data, collectively, would seem to indicate that Mg^{2+} acts on potential-operated (K^+ stimulation) and receptor-operated channels (Tab. 2).

Insights Into Mechanisms Whereby Mg^{2+} Controls and Stabilizes Vascular Tone and Reactivity

Hormone and drug-receptor interactions. It has been suggested that extracellular Mg^{2+} potentiates and inhibits (dependent upon $[Mg^{2+}]$, blood vessel and vasoactive agent) the contractile and relaxant actions of several hormones on vascular smooth muscle by enhancing or inhibiting the ability of these agonists to bind at their receptors (i.e., alter hormone-receptor affinity) [5, 7, 8, 16, 18, 39, 136, 137]. Although the ED50's, and binding-affinity constants can be shown to be altered for certain contractile as well as relaxant hormones by $[Mg^{2+}]_o$, the maximal responses are also seen to be changed by the $[Mg^{2+}]_o$ and often the concentration-effect curves are not parallel to one another with change in $[Mg^{2+}]_o$ [5, 7, 8, 16, 18, 39]. Thus, although Mg^{2+} may be important for some binding of the agonist (s) to the receptor-membrane, the latter actions of Mg^{2+} would suggest other mechanisms are involved.

Modulation of membrane permeability to Ca^{2+} and its cellular translocation. Several types of experiments, both direct and indirect, can be cited to support the premise that Mg^{2+} can modulate Ca^{2+} entry, binding and translocation in vascular smooth muscle.

1. Ca^{2+}-induced contractions of K^+-depolarized vascular muscles are sensitive to changes in the concentration of $Mg^{2\,N}$ [13, 17, 25–27, 34, 49, 50, 57, 61, 62, 80, 134, 144, 146].
2. Calcium-induced contractions of cerebral arteries, exposed to Ca^{2+}-free but otherwise normal media show similar responses to change in $[Mg^{2+}]_o$ as in 1., above [25–27, 65, 69].
3. Reductions in extracellular Mg^{2+} raise smooth muscle Ca content, whereas elevations in Mg^{2+} lower Ca content in smooth muscle, including arterial and venous smooth muscles [2, 9, 11, 13, 16, 20, 24–27, 40, 42, 45, 50, 65, 69, 80, 95, 96, 103, 106, 110, 141]. The observation that high $[Mg^{2+}]_o$ decreases total exchangeable and membrane-bound Ca^{2+} suggests that Mg^{2+} can displace and compete with Ca^{2+} at smooth muscle cell membranes for some functional binding sites. Coronary and cerebral vascular smooth muscle Ca^{2+} appear to be particularly sensitive to regulation by Mg^{2+}.
4. Experiments using ^{45}Ca-loaded arteries and veins indicate that reduction in Mg^{2+} enhances ^{45}Ca efflux, whereas elevation in Mg^{2+} above 1.2mM markedly re-

tards efflux of ^{45}Ca [25, 26, 50, 141]. Collectively, these findings and those reviewed above suggest that specific membrane Mg^{2+} sites can act physiologically to control and regulate intracellular content, distribution, entry and exit of Ca in vascular muscle.

Overall, the available, data demonstrate that Mg^{2+} inhibits slow inward current, alters Ca^{2+} uptake and efflux, and alters receptor interactions-all important attributes for Ca^{2+} antagonistic activity (Tab. 1).

Absence of involvement of any known neurotransmitter or humoral substance. As reviewed above, it is very unlikely that changes in receptor affinities, per se, could cause the increased or decreased contractile tensions or relaxations in response to changes in extracellular Mg^{2+}. This is bolstered by experiments which demonstrate that changes in tension to non-specific vasoactive agents (i.e., K^+, Ba^{2+}), as well as to specific agonists, are obtained in the presence of a variety of specific pharmacologic antagonists, cyclo-oxygenase inhibitors as well as lipoxygenase inhibitors [16, 17, 25, 27, 50, 57, 144].

Alterations in membrane Na^+-K^+, ATPase activity? Since Mg^{2+} is known to be an important cofactor for activation of Na^+-K^+, ATPase activity [135], and membrane Na^+, K^+, ATPase can play important roles in regulating vascular tone and reactivity [100, 150], one should entertain the possibility that alterations in Mg^{2+} concentrations might alter the Na^+-K^+ pump in vascular muscle. However, the evidence, so far, for acute changes in extracellular Mg^{2+} (i.e., within 30 to 60 min) have failed to indicate alterations in Na^+, K^+ or water content [2, 16, 18, 27, 50]. In addition, ouabain or other inhibitors of Na^+, K^+, ATPase failed to mimic the actions of Mg^{2+} on vascular tone and reactivity [2, 21, 40, 50]. However, long-term vascular changes noted with Mg deficiency are probably in part related to alterations in membrane Na^+, K^+-ATPase, since $Na^+$and K^+ contents are altered in directions one might expect if the latter were inhibited [99, 100, 114, 115, 122].

Role of Mg^{2+} in vascular muscle membrane permeability to ions and their cellular contents. In view of the above evidence, it is becoming clear that Mg^{2+} can act as a gate for entry and exit of Ca^{2+} a special sites in the vascular membrane. It is also clear that the intracellular [Mg^{2+}] also plays an important role in regulating binding of Ca^{2+} to organelles and contractile proteins as well as cellular bioenergetics [17, 75, 77, 78, 99, 121, 128, 136, 149]. But, in addition to these important functions, Mg^{2+} most probably can also alter membrane permeability to ions in vascular muscle [2, 9, 13, 16, 25, 40, 44, 50, 61, 99]. To illustrate, recently it has been shown that removal of Mg^{2+} from the vascular membranes can allow divalent and trivalent cations (e.g., Be^{2+}, Fe^{3+}, AL^{3+}), which have atomic radii smaller than Mg^{2+}, to gain access to the cytoplasm to promote release of intracellular Ca^{2+}, thereby causing huge contractions [9, 40, 50]. In addition, trivalent cations such as La^{3+}, which are larger than Mg^{2+} and which normally do not penetrate the cell membrane, will be able to pass into the vascular smooth muscle cells in the absence of membrane Mg^{2+}. The result of this effect is also one of contraction.

Such experiments, and others [2, 13, 16, 40, 42, 50, 61, 69, 116], lead us to speculate that other cellular cations (e.g., K^+) could in the absence, or in the face, of reduced membrane Mg^{2+} exit the vascular smooth muscle cells, whereas other cations, such as Na^+ and Ca^+ could probably gain entry. The end result would be cellular loss of K^+ and elevation in Na^+ and Ca^{2+}, events we now know are seen in chronic Mg^{2+} deficiency.

Mg^{2+}, cyclic AMP and membrane Ca^{2+}-ATPase. The influence of Mg^{2+} on vascular muscle tone and reactivity could also possibly be explained in terms of an effect of adenosine 3', 5'–monophosphate (cyclic AMP) formation within the cells--Mg^{2+} being an activator of adenylate kinase, an enzyme involved in the synthesis of cyclic AMP. There is some experimental evidence to suggest that increased and decreased cyclic AMP concentrations participate in coronary vasodilation and constriction, respectively [150]. A decrease in cyclic AMP in the absence of enough free-Mg^{2+} could result in an increased concentration of free Ca^{2+} within the cytoplasm because there would be less cyclic-AMP-mediated Ca^{2+} sequestration. Thus, this mechanism could, in part, be responsible for the increased tone and reactivity noted in Mg^{2+}-deficient states [142].

An alternative and contributing mechanism could be an inhibition of a Ca^{2+}-dependent ATPase at the membrane [142] that is Mg^{2+}-dependent and that presumably extrudes Ca^{2+} [123].

Coronary Vasospasm and Myocardial Hypoxia

The association of Mg^{2+} with ischemic heart disease is too persistent and turns up in too many places to be merely a coincidence (see [43] for review). In our minds, the question is not whether magnesium levels affect myocardial perfusion (see [42, 44]), but how they do so; it is not

whether hypomagnesemia causes ischemia, or whether Mg^{2+} supplements relieve it, but how magnesium does this. Is this related to Ca^{2+} movement and/or translocation?

There are much semi-quantitative data suggesting that Mg^{2+} can prevent atheroma, platelet aggregation, and thrombosis (see [3, 86, 97, 125, 133, 139, 140[for reviews and references). But, we believe that Mg^{2+} primarily affects myocardial perfusion by affecting arterial and arteriolar tensions. For this reason, we have studied the effects of varying $[Mg^{2+}]_o$ levels on arteries from different parts of the body in several species, including man (see refs. in [24–27, 40, 42[). We have found that all arteries are influenced by Mg^{2+}, but that the coronary vessels are particularly sensitive to its effect [30, 40, 57, 142]. Others have corroborated this [72, 91, 105, 134].

In simple terms, these studies have shown that the more Mg^{2+} in and around arterial and arteriolar tissue, the lower the wall tensions; the less the Mg^{2+}, the greater the tensions. This happens in part because the reduction in Mg^{2+} increases coronary arterial and arteriolar tensions resulting in coronary vasospasm and potentiates the constrictor actions of angiotensin, the catecholamines, potassium ions, and other endogenous neuro-humoral agents, reinforcing and exacerbating the vasospasm [30, 57, 72, 105, 134, 142]. As reviewed elsewhere [26, 30, 40, 43] and below, this change in wall tension also happens because Mg^{2+} serves as a calcium channel regulator by operating a particular gate to a calcium channel in the vascular membranes. In a healthy artery, with an adequate supply of Mg^{2+}, the gates are closed, and the entry of Ca^{2+} into the cells is severely restricted. But, with a decrease in the number of magnesium ions, calcium flows into the cell, promoting contraction. Furthermore, in a hypomagnesemic state, Ca^{2+} and Na^{+}, but not K^{+}, are selectively accumulated leading to even more contractility. In support of this concept, several new in-vivo studies have appeared which collectively demonstrate that dietary magnesium deficiency of several weeks to months duration or acute withdrawal of $[Mg^{2+}]_o$ in hearts of dogs or hamsters results in reduction in coronary arterial and arteriolar lumen sizes concomitant with calcification in these blood vessels [74, 82, 83]. In addition to these very important studies, *Buja* and co-workers have recently reported that when perfused rabbit ventricular tissue was exposed to hypoxia, x-ray microanalysis showed that the sarcoplasm and mitochondria of the myocytes exhibited significant alterations of the diffusible elements; i.e., decreases in Mg, K and P were observed concomitant with increases in Na and chloride [79]. Those myocytes that were the most severely affected by the hypoxia demonstrated clear evidence of Ca^{2+} overloading, particularly in the mitochondria. It is interesting in this context to recall that massive mitochondrial overloading with Ca^{2+} is typically seen in damaged myocytes during and after reperfusion after ischemic injury [101, 108, 128, 129, 154).

These findings do not prove definitively that Mg^{2+} plays a key role in maintaining coronary vascular tone, or that hypomagnesemia plays a crucial role in the development of myocardial injury and ischemic heart disease. However, the association of Mg^{2+} levels and coronary vasospasm and ischemic heart disease is too close to be ignored. It tells us that a degree of hypomagnesemia should be suspected in any case of myocardial ischemia or in any disease associated with coronary vasospasm. It should also be understood that even though the total assessed Mg level may not be altered, this doesn't necessarily imply that the free, ionic (or ultrafiltrable) level of Mg^{2+} is not altered [1, 3, 127, 147, 148].

Alcohol and Substances of Abuse

Considerable data is accumulating to indicate that alcohol and several abused drugs (e.g., phencyclidine HCl-PCP, PCP analogs, cocaine) can produce significant cerebral and/or peripheral vasoconstriction and hypertension leading to encephalopathies and tissue injury [28, 29, 33, 37, 41, 45, 47, 48, 51, 63, 64, 66, 67, 68, 70, 71]. Interestingly, all of these cerebral and peripheral vasospasms result in increased uptake of Ca^{2+} in the vascular smooth muscle cells. Alcohol has long been known to produce hypomagnesemia [90]. Since some of these drug-induced vasospasms have now been shown experimentally to be amenable to treatment with Mg^{2+} or calcium antagonists [29, 33, 37, 38, 45, 51, 63, 67], one must entertain the possibility that Mg-Ca interactions play some role in the cerebral and peripheral vasospasms associated with some of the abused substances. It is of considerable importance to note, here, that we have recently found that rats ingesting alcohol, chronically, for periods up to 24 weeks, show increased Ca content in blood vessels concomitant with decreased vascular muscle cell Mg^{2+} [45].

Vasospastic Syndromes

During the past decade, considerable experimental and clinical data has appeared which indicates that vasospasm plays an important role in Raynaud's disea-

se, classical migraine, transient ischemic attacks, stroke, head injuries, preeclampsia eclampsia, angina and sudden-death ischemic heart disease [4, 11, 30, 34, 43, 45, 65, 88, 94]. Since influx and release of Ca^{2+} is thought to play a role in most of these syndromes, the reports that Mg^{2+} can alleviate and relax constricted cerebral and coronary blood vessels in experimental cerebral ischemia and stroke-like events [11, 26, 30, 40, 42, 45, 65, 69, 88, 117, 138, 142, 152], should be extended to other types of experimental vasospastic phenomena. Moreover, one should carefully examine the Mg : Ca relationship in the vessels and their membranes.

Mg^{2+} — the Naturally Occurring or Mimic Ca^{2+} Antagonist

As mentioned in the Introduction, much emphasis has recently been placed on the use and design of drugs which can antagonize or prevent the access of activator, free calcium ions (Ca^{2+}) to the contractile apparatus in muscles, including cardiac myocytes and vascular smooth muscle cells. These so called Ca^{2+} antagonists (i.e., Ca^{2+} entry blokkers, slow channel blocking agents) have been suggested as therapeutic agents for the treatment of a variety of cardiac and vascular disorders including angina, cardiac arrhythmias, hypertension, strokes, transient inschemic attacks, cerebrovasospasm, migraine, *Raynaud*'s phenomenon, etc. [4, 63, 88, 89, 87, 118, 131, 151, 152]. This suggestion is based, primarily, on the assumption that these so-called Ca^{2+} antagonists will produce peripheral, coronary and cerebral vascular dilation, thus reversing or preventing vasospasms as well as restoring normal cardiac rhythm. But, most of these drugs are not without risk and may not result in vasodilation.

In the 1970s, we demonstrated that Mg^{2+} clearly affected uptake, distribution and content of Ca^{2+} in vascular smooth muscle cells [15, 16, 20, 26, 27, 64, 141]. We also suggested that Mg^{2+} might be the naturally-occurring Ca^{2+} antagonist [11, 14, 16, 17, 24–27, 34, 38, 49, 50, 141, 146]. During the past five years, this idea seems to have caught the attention of numerous investigators and clinicians [73, 74, 84, 86, 88, 104, 105, 107, 113, 127, 133, 134, 152]. Is Mg^{2+} a naturally-occurring or mimic Ca^{2+} antagonist? By definition, if a drug prevents only uptake of Ca^{2+} into cells, it can be labeled a Ca^{2+} antagonist [87, 88]. Although this simple definition is being contested at the present time [151], Mg^{2+} by current standards can be labeled a weak Ca^{2+} antagonist, since it is several orders of magnitude less potent than the verapamil, nifedipine and other dihydropyridine Ca^{2+} antagonist drugs [88, 134, 146]. However, in the cardiovascular system, Mg^{2+}, unlike most other Ca^{2+} antagonists (Tab. 1), can act on potential-operated channels, receptor-operated channels and leak-operated channels (Tab. 2), possibly making it an ideal cardiac and vascular muscle Ca^{2+} antagonist. Collectively, the available data presented here, together with that reviewed elsewhere [43], and that published elsewhere (see above), appear to clearly indicate that Mg^{2+} is, indeed, a special kind of Ca^{2+} channel blocker. At vascular membranes it can: 1 block Ca^{2+} entry and lower peripheral and cerebral vascular resistance, 2 improve peripheral and cerebral blood flows, 3 relieve cerebral, coronary and peripheral vasospasm, and 4 lower arterial blood pressure (provided enough Mg^{2+} is administered).

Conclusions

In summary, the data reviewed herein and elsewhere [43], are consistent with the hypothesis that $[Mg^{2+}]_o$ and membrane Mg exerts a regulatory role in vascular tone, vascular reactivity, cardiac physiology and peripheral vascular resistance. Mg may have an important functional role in regulating Ca uptake, content and distribution in cardiac and vascular smooth muscle cells. A number of pathophysiologic vascular states and syndromes appear to be associated with, and possibly attributed to, a Mg deficient state. Mg^{2+} appears to be a weak and useful Ca^{2+} antagonist.

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