Cardiovascular Actions of Magnesium: Importance in Etiology and Treatment of High Blood Pressure*)**)

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Zusammenfassung

Zahlreiche Untersuchungsbefunde aus Grundlagenforschung und Klinik zeigen, daß Mg-Mangel und/oder Störungen im Mg-Haushalt als wichtiger kausaler Faktor in der Pathogenese verschiedener Formen des Bluthochdrucks bisher wahrscheinlich übersehen wurden. Es ist heute gesichert, daß Mg^{2+} wichtige physiologische Wirkungen auf die Muskulatur des Herzens und der Gefäße besitzt. Mg^{2+} kann die Spannungsentwicklung und Kontraktilität dieser Gewebe beeinflussen durch Veränderungen des Membranpotentials, durch Beeinflussung von membrangebundenen und intrazellulär gebundenen Kationen (Na^+, K^+, Ca^{2+}) (sowie deren Transport), und zwar zusätzlich zu den bekannten Effekten auf kontraktile Proteine, auf den Transport von Ca^{2+} im sarkoplasmatischen Retikulum, auf die ATPase und auf energieabhängige zytoplasmatische und metabolische Wege. Neuere Daten aus mehreren Laboratorien zeigen, daß Mg^{2+} am Herzen elektrophysiologische, elektromechanische und hämodynamische Vorgänge modulieren kann. Mg^{2+} scheint eine Schlüsselstellung zu besitzen im Energiehaushalt des Herzens bezüglich anorganischem Phosphat, ADP und ATP, bezüglich der mitochondrialen und myofibrillären Creatinphosphokinase und saurer extrahierbarer Phospholipide. Verlust von intrazellulärem Mg^{2+} resultiert in Verlusten an kritischen, energiereichen Phosphatverbindungen, nämlich an Mg-ATP und Creatinphosphat. Unter Bedingungen, die zu einer Verarmung an intrazellulärem Mg^{2+} führen (z. B. Hypoxie, Anoxie, Ischämie, Zellschädigungen, Mg^{2+}-Mangel, Störungen des Mg^{2+}-Haushalts und -Transportes), sind die Na^+-K^+-Pumpe, die Phosphatvorräte und die Membranstruktur beeinträchtigt; hieraus resultiert ein herabgesetztes Membran-Ruhepotential mit gleichzeitiger Aufnahme von Na^+ und Ca^{2+} in die Zelle sowie Verlusten an intrazellulärem Mg^{2+}und K^+.

Außerdem wird Mg^{2+} im peripheren und zerebralen Blutkreislauf benötigt zur Aufrechterhaltung des Tonus der Arteriolen und eines normalen Blutdrucks. Eine Abnahme des extrazellulären und membrangebundenen Mg^{2+} kann Gefäßspasmen auslösen und die Wirksamkeit vasokonstriktiver Stoffe (und neurohumoraler Stimuli) potenzieren durch erhöhten Influx von extra-Ca^{2+}; gleichzeitig ist die Wirksamkeit vasodilatatorischer Substanzen vermindert. Änderungen des membranären Mg^{2+} verursachen in den Membranen von Arterien, Arteriolen (und wahrscheinlich auch des Herzens) eine erhöhte Durchlässigkeit und begünstigen so den intrazellulären Verlust an K^+ bei gleichzeitiger Zunahme von Ca^{2+} und Na^+. — Orale und parenterale Gabe von Mg-Salzen kann zur raschen, protrahierten Normalisierung erhöhter Blutdruckwerte führen. Klinische und experimentell erzeugte Hypertonieformen gehen mit einer Abnahme des Mg^{2+}-Gehaltes im Gewebe und Plasma einher, die Urin-Ausscheidung ist ebenfalls verändert. Die arterielle Hypertension scheint invers korreliert zu sein mit der intrazellulären Mg-Ionen-Konzentration und dem Plasma-Mg^{2+}.

Es ist fesselnd zu beobachten, daß Mg^{2+} aufgrund der Fähigkeit, eine ausgeprägte periphere Vasodilatation zu erzeugen und die Erregungszeit in Herzschrittmacherzellen zu verlangsamen, sich anscheinend als „echter", (natürlich vorkommender) Ca^{2+}-Antagonist verhält und entsprechend wirkt.

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Summary

Considerable experimental as well as clinical evidence has now accumulated to indicate that Mg^{2+} deficiency and/or errors in Mg^{2+} metabolism has probably been overlooked as an important causal factor in the etiology of several types of hypertensive diseases. It is now clear that Mg^{2+} exerts important, physiologic actions on both cardiac and vascular smooth muscle cells. Mg^{2+} can affect tension development and contractility of these cardiovascular tissues by altering membrane potentials, membrane and intracellular binding (and transport) of cations (Na^+,K^+, Ca^{2+}), in addition to its wellknown affects on contractile proteins, sarcoplasmic reticular membrane transport of Ca^{2+}, ATPase, and energy-dependent cytoplasmic and mitochondrial pathways. Recent data from a number of laboratories indicate that Mg^{2+} possesses important abilities to modulate cardiac electrophysiologic, excitation-contraction coupling and hemodynamic events. Mg^{2+} appears to be crucial in cardiac bioenergetics for stability of inorganic phosphorous, ADP, ATP, mitochondrial and myofibrillar creatine phosphokinase, and acid extractable phospholipids. Loss of cellular Mg^{2+} results in loss of critically important phosphagens: Mg ATP and creatine phosphate. Thus, under conditions where cellular Mg^{2+} is depleted (e.g., hypoxia, anoxia, ischemia, cellular injury, Mg^{2+} deficiency, errors in Mg metabolism and/or binding, transport), the Na^+-K^+ pump, phosphagen stores, and membrane structure will be compromised, leading to alterations in resting membranes, (e.g., membrane depolarization) with concomitant uptake of Na^+ and Ca^{2+}; Mg and K^+ will be lost. In addition, in the peripheral and cerebral circulation, Mg^{2+} is necessary for maintenance of arteriolar tone and normal blood pressure. A reduction in extracellular and membrane Mg^{2+} can produce vasospasm and potentiation of vasoconstrictor (neurohumoral stimuli) agents by allowing excess entry of Ca^{2+}; concomitantly the potency of vasodilators is reduced. Alterations in vascular (and probably cardiac) membrane Mg^{2+} result in arterial and arteriolar membra-

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nes which are "leaky," thus contributing to the cellular reduction in K^+ and gain of Ca^{2+} and Na^+. Oral and parenteral administration of Mg salts can result in rapid and sustained redcutions of hypertensive to normotensive blood pressure levels. Both clinical and experimental forms of hypertension are associated with tissue and plasma deficits of Mg^{2+}; urinary excretion also is altered. The arterial blood pressure elevation appears to be inversely related to the level of ionized intracellular and plasma Mg^{2+}. It is rather intriguing to note that Mg^{2+} by possessing the ability to produce sustained peripheral vasodilatation and slow conduction time in cardiac pacemaker cells appears to act and behave like a "true" (naturally-occurring) Ca^{2+} antagonist.

Résumé

A l'heure actuelle, un nombre considérable de preuves, obtenues tant expérimentalement qu'en clinique, montrent qu'une carence en Mg^{++} et/ou certaines altérations du métabolisme du Mg^{++} ont été probablement oubliées parmi les principaux facteurs responsables de l'apparition de certains états hypertensifs. Il est maintenant évident que le magnésium exerce d'importants effets physiologiques sur les cellules musculaires du cœur et des vaisseaux. Le Mg^{++} est susceptible d'affecter la tension et la contractilité de ces tissus cardiovasculaires en altérant les potentiels de membrane, la liaison (et le transport) intra-membranaires et intracellulaires de certains cations (Na^+, K^+, Ca^{++}), outre ses effets bien connus sur les protéines contractiles, le transport du Ca^{++} et de l'ATPase au niveau de la membrane du réticulum sarcoplasmique et les mécanismes cytoplasmiques et mitochondriaux sous la dépendance de l'énergie. De récentes données provenant de plusieurs laboratoires indiquent que le Mg^{++} est doué d'importantes propriétés de modulation de l'électrophysiologie cardiaque, du couplage excitation-contraction et des phénomèmes hémodynamiques. En bio-énergétique cardiaque, le Mg^{++} apparaît essentiel pour maintenir les taux de phosphore inorganique, d'ADP, d'ATP, de créatinine-phosphokinase mitochodriale et myofibrillaire et de phospholipides acides extractibles. Une perte cellulaire de Mg^{++} entraîne une perte de phosphagègenes essentiels: le Mg ATP et la phosphocréatine. En conséquence, dans des états pathologiques associés à une déplétion magnésique (hypoxie, anoxie, ischémie, lésion cellulaire, carence en Mg^{++}, altérations du métabolisme et/ou de la liaison et du transport de Mg), la pompe Na^+-K^+, les réserves en phosphagène et la structure membranaire vont se trouver compromis, entraînant alors des altérations de la membrane au repos (par exemple, une dépolarisation) avec un captage simultané de Na^+ et de Ca^{++} et une fuite de Mg^{++} et de K^+. En outre, le Mg^{++} est nécessaire au niveau de la circulation périphérique et cérébrale, car il maintient le tonus artériolaire et normalise la pression artérielle. Une diminution de la concentration extra-cellulaire et intramembranaire de Mg^{++} peut produire un angiospasme et potentialiser l'action de produits vasoconstricteurs (stimulus neurohumoral) en permettant l'entrée d'un excès de Ca^{++}; en même temps, l'activité des vasodilatateurs se trouve réduite. Des altération du taux de Mg^{++} dans les membranes vasculaires (et probablement cardiaques) rendent «poreuses» les parois artérielles et artériolaires, ce qui contribue à la diminution du K^+ et à l'augmentation du Ca^{++} et du Na^+ au sein de la cellule. L'administration de sels de magnésium, par voie orale ou parentérale, permet une diminution rapide et prolongée de la pression artérielle, le sujet hypertendu devenant normotendu. Qu'elle soit expérimentale ou clinique, l'hypertension artérielle est toujours associée à un déficit tissulaire et plasmatique en Mg, ainsi qu'à une altération de l'excrétion urinaire de Mg^{++}. L'augmentation de la pression artérielle semble être inversement proportionnelle au taux intra-cellulaire et plasmatique de Mg^{++} ionisé. Il est plutôt étonnant de constater que le magnésium, par l'intermédiaire de sa capacité à induire une vasodilatation périphérique prolongée et une vitesse de conduction lente au sein du noeud sino-auriculaire, semble agir et se comporter comme un inhibiteur calcique «vrai« (apparaissant de façon naturelle).

Introduction

It has generally been believed that the physiological roles for magnesium ions (Mg^{2+}) in cardiac and vascular smooth muscle are limited to the regulation of contractile proteins, sarcoplasmic reticular membrane transport of calcium ions (Ca^{2+}), co-factor in ATPase activities and metabolic regulation of energy-dependent cytoplasmic and mitochondrial pathways. In addition, up until recently [8, 15–17, 125, 166], it was not thought that small changes in free external ($[Mg^{2+}]_o$) or cytoplasmic Mg^{2+} could exert any significant effects on cardiac or vascular smooth muscle contractility. It is now clear, however, from the newer studies that $[Mg^{2+}]_o$ can affect tension and contractility of these muscle cells by altering membrane and intracellular organelle binding and transport of Ca^{2+} [15–17, 25–27, 46, 48, 49, 60, 78a, 79, 112, 132, 171, 180, 194], affecting hormone-receptor interactions [3–5, 10, 15–19, 38, 49, 53–55, 58, 63, 110, 113, 125, 171, 172, 183, 184], regulating electrolyte content and transport [1, 9, 10, 15, 16, 25–27, 39, 41–43, 55, 108, 109, 115, 117, 154, 173, 191, 197, 198], affecting resting membrane-generated and action potentials [10, 43, 94, 104, 121, 167, 174, 201, 202], altering excitation-contraction coupling events [16, 17, 20, 22–27, 32, 39, 49, 60, 66, 79, 84, 104, 112, 134, 166, 167, 180–184, 186, 188], and regulate peripheral and cerebral vascular tone and blood flows [6–10, 17, 20, 22–27, 30–37, 39–43, 46–49, 51–53, 58–67, 108, 109, 117, 122, 164, 181–183]. In addition, it is also now clear that small changes of free Mg^{2+} at the cardiac and vascular membranes can exert significant effects on mechanical and electrical activities of these cells (see ref. [24, 26, 27, 43, 82, 104, 165, 166] for reviews).

In view of such direct and indirect actions of Mg^{2+} on cardiac and vascular muscle celles, it has been suggested that Mg^{2+} deficiency may play an important role in the etiology of hypertensive disease [10, 22–24, 26, 34, 41, 42, 44, 47, 48, 51, 54, 57, 74, 120, 161, 162]. It has also been demonstrated that oral and intravenous administration of Mg^{2+} may be a useful, inexpensive tool in the treatment of high blood pressure in man [76, 93, 98, 128, 163, 177].

This review will be concerned primarily with the experimental and clinical evidence which implicates Mg^{2+} as a central cation

in both the etiology and treatment of hypertension via its actions on the cardiovascular system.

Importance of Cardiac Events in Hypertension

Hypertension is clearly an hemodynamic abnormality. Any factor(s) that result directly or indirectly in a sustained increase in either blood flow or vascular resistance will result in an increased intravascular pressure. The many diverse factors (e.g., neural, humoral, etc.) which interact to disturb pressure-flow-resistance relationships will serve to define the type and etiology of hypertension (Tab. 1). Irrespective of the etiology or variable (Tab. 2), the result will be a raised systemic arterial blood pressure. Of these variables, two — namely the cardiac output (CO) and the ratio of mean arterial blood pressure (MAP) to output (or resistance) — are quite important and have attracted a great deal of attention. Since measured arterial blood pressure (BP) in the formula BP = CO × TPR (total peripheral resistance) can be due to either an increased resistance or elevated flow, it has become clear that the level of CO in etiology, maintenance and treatment of high blood pressure is very important (for review see ref. [111]).

Recent experimental and clinical findings reveal that the intracellular and extracellular concentration of $[Mg^{2+}]_o$ can effect in diverse ways, directly and indirectly, the major factors that determine the level of arterial blood pressure (Tab. 1).

Tab. 1: Major Factors Determining Level of Arterial Blood Pressure

1. Total Peripheral Vascular Resistance
General vasomotor control; local vasomotor control mechanisms (neurohumors, hormones, local tissue hormones and ions)
2. Cardiac Output
Heart rate (pacemaker frequency, cardiac sympathetic and cholinergic discharge, neurohumors);
Stroke volume (systolic volume, ventricular ejection, diastolic volume, coronary blood flow, ventricular distensibility, cardiac sympathetic discharge, ventricular filling pressure, venous capacity, blood volume, neurohumors);
Speed of ejection
3. Aortic Compliance
4. Diastolic Arterial Blood Volume

Tab. 2: Factors Implicated in the Pathogenesis of Hypertension *)

Electrolyte Alterations
1. increased Na^+
2. increased, decreased Ca^{2+}
3. decreased K^+
4. decreased Mg^{2+}
5. increased Cl^-
Defects in Ion Transport
Neurogenic Mechanisms
Overproduction of Neurohumors
1. angiotensins-renin
2. vasopressins
3. catecholamines
4. serotonin
5. aldosterone, glucocorticoids
Increased Vascular Reactivity to Constrictors
Decreased Vascular Reactivity to Dilators
Genetics
Obesity
Diet-Lipids
Renal Alterations
Endothelial Cell Alterations
Psycho-Social Environmental Factors

*) Adapted from ref. [41]

Myocardial Effect of Mg^{2+}

In 1979, Shine reviewed the pertinent literature on the myocardial effects of magnesium [166]. Therefore, our review and remarks will be directed to those pertinent reports which have appeared since 1978.

Electrophysiologic actions. It is generally believed that Mg^{2+} has little effect on cardiac action potentials [124, 166], unless Ca^{2+} has been reduced or eliminated from the or external environment. However, in view of recent findings from several laboratories, this statement may have to be modified [94, 104, 129, 131, 133, 146b, 174, 201, 202]. Using canine false tendons, work from *Woods* et al. [129, 131, 201, 202], and *Moe* [146b] indicate that the extracellular $[Mg^{2+}]_o$ can modify cardiac resting membrane potentials as well as the action potential. Since Ca^{2+} antagonists and/or chelators can obviate the latter actions of Mg^{2+} [146b], we believe that Mg^{2+} may be acting on the Ca^{2+}-dependent inward current. In support of this notion, it has been demonstrated that hypoxic-induced depolarization [201], digitalis-induced oscillatory after potentials [146b], as well as K^+-induced depolarization [133] can all be prevented or ameliorated by elevation in $[Mg^{2+}]_o$. It is now known that the distortions produced in the cardiac action potentials in these pathophysiologic situations are dependent upon the inward current attributed to Ca^{2+}[104].

In 1979, *Späh* and *Fleckenstein* [174] reported that Mg^{2+} mediates the overshoot height and duration of the action potential in partially-depolarized guinea-pig papillary muscle. These experiments and others [104] led these investigators to postulate the existence of a transmembrane transport system that carries, preferentially Mg^{2+} into the ventricular myocardium. *Späh* and *Fleckenstein* suggested that this Mg^{2+} channel is intermediate in degree of activation lying between the fast Na^{2+} channel and the slow Ca^{2+} channel. More recently, *Kiyosue* and colleagues [131] have confirmed this work but conclude that the Mg^{2+}-increase in maximum rate of rise should be attributed to the change in voltage dependency of the inactivation process of the fast Na^+ channels, particularly since tetrodotoxin and low Na^+ abolished these action potential changes induced by elevated Mg^{2+}. Since Ca: Na manipulations were not made or ionic fluxes obtained, it

is difficult to completely accept this thesis.

With respect to nodal tissue, the earlier idea that Mg^{2+} can modulate chronotropicity of the sinoatrial node [159, 179, 186] was confirmed and extended by *Op't hof* and co-workers [150–153], using the isolated sinoatrial node preparations of the guinea-pig and rabbit. In addition to demonstrating a negative chronotropic effect for Mg^{2+}, these workers found that the major effects of Mg^{2+} on this nodal tissue appears to be a decrease in the rate of diastolic depolarization and production of pacemaker shifts.

Overall, these new findings on resting membrane potentials, action potentials and pacemaker cells would seem to strongly suggest that Mg^{2+}: 1. is important in regulating membrane-dependent electrical changes, 2. can act as a modulator of conduction, and 3. stabilizes membranes of cardiac muscle cells and pacemaker cells.

Excitation — contraction coupling, hypoxia and cardioplegia.

During the past decade, a considerable amount of interest has been generated with respect to the salutory effects of Mg on mechanical recovery after myocardial ischemia or anoxia in animals and man [30, 32, 39, 42, 73, 77, 79, 80, 82, 94, 96a, 97, 123, 124, 126, 137, 146b, 158, 160, 165, 166, 176, 177, 181, 201] as well as in drug-induced arrythmias and myocardial infarction (see references in [39, 42]). However, it is not clear as to how these benefiacial actions of Mg arise? Recently, it has been shown with ion-selective microelectrodes that graded degrees of hypoxia will produce reversible decreases in intracellular, free $[Mg^{2+}]_o$. Interestingly, this same group has found that elevating $[Mg^{2+}]_o$ from 0.5–10.0mM/L results in a reversible increase of $[Mg^{2+}]_i$ in cardiac cells. Others have recently reported in a preliminary communication that a similar elevation in $[Mg^{2+}]_o$ also increases efflux of $^{28}Mg^{2+}$ from isolated rat hearts [139]. However, during ischemia the rate of $^{28}Mg^{2+}$ was retarded markedly, but was not seen on reperfusion after ischemia [139].

Collectively, such findings are of potentially great importance for cardioplegia and the Ca^{2+} paradox phenomenon which occurs during reperfusion [205]. In this context, it has recently been shown that the concentration of $[Mg^{2+}]_o$ can significantly modify the Ca^{2+} paradox in the perfused isolated rat heart [132]. Moreover, these studies indicate that the protective effect of Mg^{2+} is probably related to Mg-Ca and Mg-K interactions at the sarcolemmal surface. With respect to cardioplegia, it has now been established that very high concentrations of Mg ions in themselves, in the absence of procaine or potassium cardioplegia, can stop hearts very rapidly [176, 192]. In this regard, it has been demonstrated that tissue enzymes and mitochondrial oxidative phosphorylation are preserved when high concentrations of Mg^{2+} are utilized to induce cardioplegia [192]. In addition to these salutory effects, Mg^{2+} is now known to produce direct vasodilatation of coronary arteries and arterioles [7, 30, 39, 48, 49, 70, 86, 109, 122, 160, 169b, 181] by modulating availability of Ca^{2+} influx, efflux and distribution in coronary vascular smooth muscle cells [27–27, 46, 48, 49, 181, 188].

Hemodynamics of Mg^{2+} in the Intact, Open-Chested Dog

Although dose-dependent vasodilator actions of Mg^{2+} have been clearly demonstrated in isolated blood vessels (see ref. 10, 26, 27, 30, 39, 43, 49, 60] for reviews), studies in intact animals and men have been inconclusive. Accordingly, in order to determine effects of $MgCl_2$, 0.1–4mM/min, administered IV, producing peak arterial [Mg] between 2.5–7.2 mg/dl, was given to α-chloralose anesthetized, open chest dogs. Measurements were made at spontaneous and constant rates. Mg lowered heart rate by 10–40 min^{-1}, CO by 0.3–0.9 L/min, left ventricular (LV) peak dp/dt, by 100–425 mmHg/-sec., mean aortic presure by 10–40 mmHg, and mean pulmonary arterial pressure by 1–5 mmHg, but did not change LV end-diastolic pressure or pulmonary resistance ([108], unpublished findings). Although coronary blood flow (CBF) (by 10–45 ml/min) and myocardial O_2 consumption (MVO_2) (by 1–4 ml/min) also decreased, coronary sinus O_2 saturation increased (by 3–15 %) ([108], unpublished findings). At a constant rate, Mg also decreased LV systolic pressure, LV dp/dt and CBF. Interestingly, increases of serum Mg were accompanied by rapid increases of serum Ca (by 0.5–1.8 mg/dl) and falls in serum K^+ (by 0.1–0.4 meg/L), but not by changes in serum changes in serum Na^+, myocardial electrolyte A-V differences, serum osmolality, or arterial O_2 saturation ([108], unpublished findings).

We believe these new findings indicate that: 1. $MgCl_2$ lowers systemic and pulmonary pressure, cardiac output and LV peak dp/dt in a dose-dependent fashion in normotensive, anesthetized dogs; 2. these effects cannot be explained only by bradycardia resulting from Mg^{2+}; 3. although Mg^{2+} produces a fall in CBF, this appears to be due to a fall in MVO_2, since coronary sinus O_2

increases; and 4. rapid changes in serum electrolytes accompany hemodynamic effects, at least in dogs. Somewhat similar observations have been made with Mg aspartate HCl [109]. Such preliminary results, when taken together, with the above provide evidence for the idea that Mg^{2+} can alter pressure-flow-resistance relationships by diverse actions on the myocardium and as such might lower arterial blood pressure in hypertensive individuals not only via effect on the peripheral blood vessels but via cardiac effects as well.

These effects notwithstanding, Mg has also been reported recently to affect the number of alpha-adrenergic receptors in canine myocardium [85].

When taken together, such findings indicate that Mg^{2+}, in addition to its well known affects on mitochondrial transport of ions, sarcoplasmic reticular membranes, ATPase activities and contractile proteins in cardiac muscle [8, 79, 114, 149, 171, 173, 191, 194], can modulate excitation-contraction coupling in these cells via additional actions on membrane permeability to Ca^{2+}, intracellular organelle functions, coronary blood flow (and cardiac cell nutrition) and amine receptors.

Mg Deficiency and Cardiac Bioenergetics

Mg^{2+} ions are important for regulation of Na^+ and K^+ transport across cell membranes, including those found in cardiac and vascular smooth muscle cells [1, 39, 41, 173, 191]. Mg^{2+} activates a Na^+, K^+ ATPase pump which in turn plays a major role in regulating Na^+-K^+ transport [173]. Loss of cellular Mg^{2+} has been demonstrated to result in loss of critically important phosphagens: Mg ATP and creatine phosphate [39, 79, 104, 115, 116, 123]. Recently, we have reported that 4 – 8 weeks of Mg deficiency in rats (serum Mg fell from 1.85 to 0.72 mg %) resulted in significant falls in inorganic phosphate, ADP, mitochondrial oxygen consumption, creatine phosphokinase (mitochondrial and myofibrillar) and several acid extractable phospholipid precursors from left ventricular cardiac muscle [79].

Thus, under conditions where cellular Mg^{2+} is depleted (e.g., hypoxia, anoxia, ischemia, cellular injury, Mg deficiency, errors in Mg metabolism and/or binding, tranport), the $Na^+ - K^+$ pump, phosphagen stores and cardiac cellular bioenergetics will be compromised, leading to alterations in resting membranes (e.g., membrane depolarization). Cellular Mg^{2+} depletion has been found to result in concomitant depletion of K^+ in a number of cells, including cardiac and vascular muscles [1, 39, 115, 191, 197, 198]. Myocardial and vascular Mg depletion (and/or cellular injury) thus will result in uptake of Na^+ and Ca^{2+}; Mg^{2+} and K^+ probably being lost first [30, 32, 39, 137]. The result of such abberations could be a sustained rise in arterial blood pressure (e.g., *Fig. 1;* see ref. [39, 41]).

In conclusion, it is now apparent that Mg^{2+} exerts direct actions on cardiac muscle cells, cardiac bioenergetics and modulates stability and excitability of these specialized cell membranes, attributes which would be important as tools in the therapy of hypertension.

Mg and Hypertensive Disease

Although it was first demonstrated in 1925 by *Blackfan* and *Hamilton* [76] that infusion of a Mg salt could reverse hypertension in some patients, this concept was not taken seriously until relatively recently. Experimentally, it is now known that dietary Mg deficiency can produce hypertension [51, 52] and aggravate preexisting hypertension [74, 88, 195]. Several reports have appeared which indicate that IV infusion, systemic or oral administra-

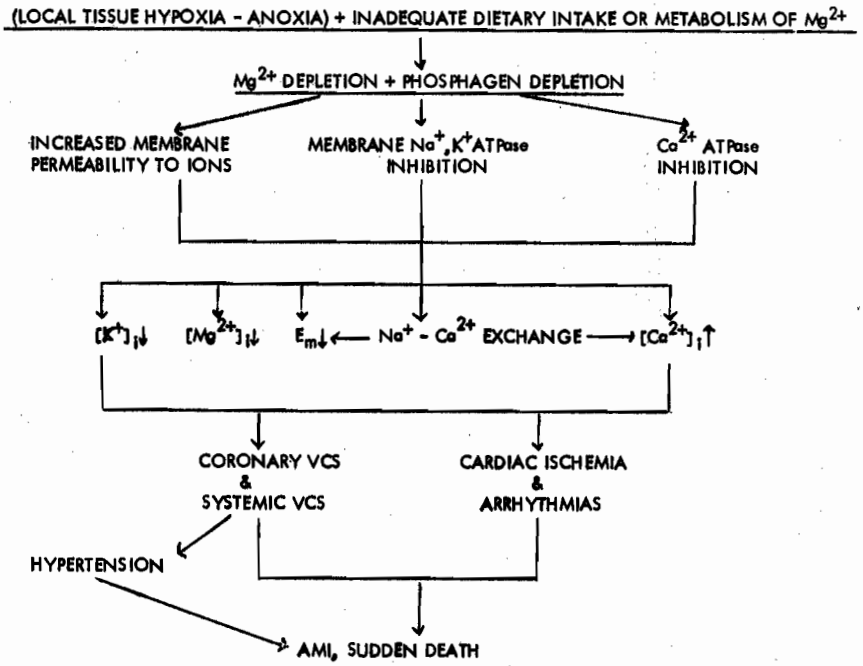

Fig. 1: Hypothetical scheme for the dysfunction of normal cardiovascular tone by deficits in dietary Mg^{2+} intake and/or inadequate metabolism of Mg^{2+}. VCS – vasoconstriction

tion of Mg salts can lower the the arterial blood pressure of renal hypertensive patients, patients, with essential hypertension, pregnancy-induced hypertension and diuretic-induced hypertension [76, 93, 98, 128, 163, 177, 200]. The recent findings of *Dyckner* and *Wester* [98], *Karppanen* et al. [128] and *Reyes* et al. [163] are particularly noteworthy since oral Mg supplementation (15 – 16 mmol/day) was seen to lower systolic and diastolic blood pressures up to 35 and 15mmHg, respectively. Arterial blood pressure was lowered in one of these studies even after only 3 – 5 weeks of Mg supplementation [128]. But, do hypertensive patients present with significant hypomagnesemia?

Up to the present, there are at least 16 independent studies which show that patients with hypertension of diverse etiologies exhibit hypomagnesemia either in serum or tissues [2, 71, 99, 100, 117b, 126, 130, 155, 161, 162, 165b, 168, 170, 178, 189, 196]. The reports by *Petersen* et al. [155], *Resnick* et al [161] and *Dyckner* and *Wester* [99] clearly demonstrate inverse correlations between serum (or tissue) Mg concentrations and arterial blood pressures. Other studies provide evidence for the idea that certain hypertensive patients exhibit reduced urinary excretion of Mg [100, 130] which is inversely correlated to diastolic blood pressure [100, 130]. Is there also epidemiologic evidence for a link between incidence of hypertensive disease and soil and/or drinking water content of Mg^{2+}?

Hardness of Drinking Water and Arterial Blood Pressure

It is clear from several studies done, so far *(Tab. 3)*, in which either water hardness or Mg^{2+} levels were ascertained, that there is an inverse relationship between water hardness or Mg and arterial blood pressure [138, 143, 144, 157, 175]. The lower the hardness or Mg in these studies, the higher the arterial blood pressure. Although 4 – 5 other epidemiologic studies also exist, which are not shown in Table 3, these in the main either did not accurately assess water hardness (or Mg content) or utilized boys and girls rather than middleaged men and women (e.g., see ref. [107]). So there does appear to be an inverse correlation between hardness of water or Mg content and incidence (development?) of hypertension, but can this concept be generalized to other initiating factors as well?

Tab. 3: Epidemiologic Studies Relating Drinking Water Hardness to Arterial Blood Pressure (BP)

References	Location	Subjects	Sampling Units	Relationship Between Hardness or Mg^{2+} and BP
Stitt et al. 1983 [175]	United Kingdom	Males 45—64 years	12 towns (hardness: 20—40, 253—358 ppm)	Inverse
Masironi et al. 1976 [144]	New Guinea	Males and Females Youths to Aged	3 river villages	Inverse
Paddu et al. 1980 [157]	Italy	Males 40—59 years	2 rural areas (215; 442 ppm hardness)	Inverse
Levin et al. 1981 [138]	USSR	Males and Females	Several towns (5—30 mg/L Mg^{2+})	Inverse

Association Between Mg Levels, Chronic Alcoholism, Diabetes Mellitus, Certain Drug Toxicities and Hypertension

A number of disease states, which result in elevation of the arterial blood pressure, are often associated with decreased levels of plasma and/or tissue Mg (for reviews see ref. [24, 30, 32, 39, 41]). Chronic alcoholism is associated with a serum, myocardial and vascular tissue loss of Mg [14, 40, 44, 73, 79, 96a, 105, 191]. In addition, 60 – 80 % of chronic alcoholics develop high blood pressure which remains to be explained [11, 12, 14, 29, 72, 156]. Chronic diabetes mellitus is also associated with a tissue and serum hypomagnesemia [1, 56, 96a, 101, 145, 146a, 165, 191]. Very recently, it has been reported that hypomagnesemia is present in diabetic children [101] and is accompanied by significant changes in the vascular reactivity [102]. Despite the use of insulin, the incidence of high blood pressure in long-term diabetics varies between 40 and 80 % in different studies (see ref. [56] for a review). We believe the hypomagnesemic state found in chronic alcoholics and diabetics (particularly those maintained long on insulin) is probably more than coincidental in the etiology of the accompanying angiopathy and hypertensive states; possible mechanisms for Mg-mediated etiologies have been discussed elsewhere [33, 182, 185, 187].

Recently, Mcnair et al. [146a] have shown that the degree of diabetic retinopathy is inversely related to the degree of hypomagnesemia in certain diabetic patients. These authors concluded that hypomagnesemia is a risk factor in the development and progress of diabetic retinopathy. More recently, *Ewald* et al. [101] in Sweden reported that the degree of hypomagnesemia found in 27 diabetic children correlated with the long-term diabetic com-

plications. *Cohen* et al. [91] reported that treatment of 8 young diabetic, hypomagnesemic patients with 750 mg/day of MgO for 3 months produced a complete reversal of the retinal vascular changes associated with high-renin essential hypertension; this occured concomitant with a restoration of normal serum Mg levels.

Certain drug toxicities, e.g., cyclosporine and cisplatin, also appear to be often associated with development of an hypomagnesemic state and concomitant hypertension and/or intense peripheral vasoconstriciton, viz., a *Reynaud's* type syndrome [30, 39, 178, 189]. Interestingly, hypercalcemic hypertension also appears to be associated with an hypomagnesemic state [204]. It will be important, in the near future, to try to correlate the degree of peripheral vasoconstriction, in these syndromes, with the degree of cellular Mg depletion.

Type A Behavoir: Relation to Ischemic Heart Disease, Hypertension and Mg Deficiency

Approximately 25 years ago, Friedman and Rosenman [109a] suggested that certain individuals displaying extremes of competitiveness, aggressiveness, haste, impatience and a striving for achievement could be grouped into a particular type of behavior pattern which they labeled 'type-A'. Such individuals often are under self-imposed great stress and show a great susceptibility to IHD and hypertension [109a]. One of us has suggested that such a type-A behavior would lead to an increase in blood free fatty acids as a result of self-induced stress and catecholamine secretion [59]. This was envisioned to lead to an apparent Mg deficiency state due to 2 major events: (a) formation of insoluble salts via chelation of Mg with free fatty acids [105a]; and (b) loss of Mg via the kidneys due to an overproduction of catecholamines. According to our hypothesis, the Mg-deficient state would result in an enhanced entry of Ca^{2+} into vascular smooth muscle cells, which in turn would result in increases in arteriolar tone, coronary spasms, hypertesion and IHD or SDIHD [7, 26, 48, 59, 180, 181].

During the past 2 years, 2 laboratories have indepen dently brought forth evidence, in type-A subjects, which supports the above hypothesis [118, 119, 169a]. Collectively, these studies reveal that the type-A subjects had lower red blood cell Mg and serum Mg than type-B subjects. It will thus be important to extend these studies over a duration of several years.

Vasospasm, Mg Deficiency and Hypertension

Several clinical vascular entities, including hypertension of unknown origin, preeclampsia-eclampsia of pregnancy, congestive heart failure, alcohol-induced hypertension and diabetes mellitus-induced hypertensive disease, are associated with hypomagnesemia [1, 2, 7, 10, 26, 30, 32, 39, 42, 45, 56, 57, 73, 105, 117b, 124, 127, 135, 136, 145, 146a, 155, 161, 162, 195, 196, 199]. In addition, an association between cerebral spinal fluid (CSF) Mg^{2+}, brain Mg^{2+} and the etiology of strokes has been reported (see [65, 66]). A number of these hypertensive vascular diseases (e.g., primary hypertension, preeclampsia, diabetes mellitus) often have the highest incidence ingeographic regions which contain Mg^{2+}-poor water and/or Mg^{2+}-poor soil [26, 30, 32, 39, 42, 87, 95, 126, 127, 136, 140–142, 165, 181]. On the basis of experimental data, it has been suggested that Mg^{2+}-deficiendy, either brought about by inadequate dietary intake, drug-induced or defects in Mg^{2+} metabolism, could produce vasoconstriction and ischemia of certain regional vasculatures (particularly the heart, brain, umbilical placental areas, splanchnic region), probably by allowing excess entry and intracellular release, of Ca^{2+} [7, 10, 13, 17,, 23, 26, 30, 31–37, 39, 41–49, 51, 58, 59–66, 180, 181]. The end result of the latt would be hypertensive diseases of differing severity, depending upon the extent of alterations in vascular muscle membrane and cellular Mg^{2+}/Ca^{2+} ratios. Recently, it has been reported by *Resnick* et al. [161] that a group of untreated hypertensive patients consistently demonstrated lower levels of intracellular free Mg^{2+}, using red blood cells, than either normotensive patients or hypertensive subjects whose blood pressure had been normalized with therapeutic agents. As predicted from our hypotheses, these investigators found: 1. and inverse relationship between intracellular free red blood cell Mg^{2+} and diastolic blood pressure; and 2. and inverse relationship between intracellular free Mg^{2+} an extracellular Ca^{2+} for all human subjects studied. These authors concluded that their findings "suggest a physiologic relationship between intracellular magnesium metabolism and blood pressure regulation and pathophysiologically suggest intracellular magnesium depletion to be common in human essential hypertension [161]."

Over the past 15 years, we have provided direct evidence [6, 7, 10, 13, 15–27, 30–37, 39, 46, 48, 49, 58, 60, 62, 65, 66, 180, 188], along with other investigators [70, 77, 84, 104, 134, 169b] that Mg^{2+} appears to be a very effective naturally occurring antago-

nist of activator Ca^{2+} in the vascular system. Utilizing this concept, several independent studies have now clearly shown that therapeutic trials with orally-administered Mg salts can be utilized effectively to treat several forms of hypertensive disease in human subjects [91, 98, 128, 163], transient ischemic attacks [103], and Prinzmetal's angina [89, 90].
Although two recent studies have appeared which indicated that blood pressures in several hypertensive subjects were not attenuated significantly with either oral Mg oxide or Mg aspartate HCl [83, 91], these studies did not demonstrate either a raised plasma or serum Mg. It is now known from experimental work with SHR [74] and DOCA-salt hypertension in rats [68] that unless the latter levels are elevated rather significantly, Mg administration won't necessarily reduce hypertensive blood pressures.

Experimental Evidence Demonstrating that Extracellular Mg^{2+} Concentration and Intracellular Free Mg^{2+} Control Vascular Tone and Reactivity of Vessels: Rationale in the Development of Hypertension

The following serves to summarize, briefly, the important extracellular and membrane actions of Mg^{2+} which are now known and are thought to be prime contributing factors in the etiology of diverse forms of hypertensive disease. The reader should consult the original studies and refiews on the subject for specific bits of information.
Artificial lowering of the Mg^{2+} content of isolated coronary, cerebral, umbilical-placental, as well as numerous types of peripheral blood vessels from rats, rabbits, piglets, dogs, and man induces rapid, contractile responses and potentiates the action of a variety of neurohumoral constrictor agents, including angiotensins, adrenergic amines, eicosanoids, serotonin, and ions such as K^+, and Ba^{2+} and Ca^{2+} [6, 7, 10, 15–17, 19–27, 30–37, 39, 43, 46–49, 53, 58–66, 70, 84, 106, 110, 112, 113, 125, 134, 181, 183]. Dietary deficiency of Mg^{2+} has also been reported to result in similar phenomena in the intact myocardium [124] and intact splanchnic, skeletal muscle and cerebral microvasculatures [23, 37, 51, 52, 66, 67, 68, 148, 164].
Collectively, these in-vitro and in-vivo studies indicate that the greater the deficit in extracellular Mg^{2+} concentration, the greater the degree of contraction or constriction and the greater the potentiation of constrictor agents. In addition, evidence has now accumulated to demonstrate that the vascular relaxant actions of certain neurohumoral substances, e.g., eicosanoids, adenosine, isoproternol, neurohypophyseal peptides, as well as certain nonspecific vasodilators (e.g., nitroglycerin, dilitiazen) are also greatly attenuated as Mg^{2+} is reduced [10, 19, 26, 27, 49, 53, 69, 70, 106, 183, 184]. At the microcirculatory level, invivo, it is now clear, at least for rats, that, physiologic micromolar changes in Mg^{2+} produce dose-dependent dilation of arterioles and venules [66, 67, 148).
Hypermagnesemia, on the other hand, inhibits the spontaneous tone of arteries, veins, arterioles and venules both in-vitro and in intact animals, and decreases arterial resistance to blood flow [7, 10, 17, 22, 23–27, 30–37, 39, 43, 46, 47–50, 58–67, 106, 117, 122, 148, 164, 181, 182, 188]. In addition, elevation of Mg^{2+} concentration attenuates, in a concentrationdependent manner, contractions induced by all known neurohumoral agents [7, 10, 16, 19, 23–27, 30–37, 39, 46, 47–49, 53, 58, 60, 63, 65, 169b, 181, 183].
Such data, collectively, lend support to the idea that reduction in plasma and CSF levels of free, ionized Mg^{2+} would narrow arterial and ateriolar lumen sizes by both direct and indirect actions on vascular smooth muscle excitability and contractility.

Dietary Deficiency of Mg Results in Hypertension and Exacerbation of Stress-Induced Hypertension: Relationship to Arteriolar and Venular Tone in Microcirculation

In view of the above experiments on blood vessels, and others on SHR and diabetic rats, we suggested that some forms of hypertension could be due to the direct effects of a hypomagnesemic state on arteriolar and venular tone [22–27, 48]. We reasoned that the hypomagnesemia could produce progressive vasoconstriction of arterioles, precapillary sphincters, and venules in the microcirculation, and curtail capillary blood flow, and result in hypertensive disease. To investigate the possibility that arteriolar, precapillary sphincter, and venular constriction can be produced in intact hypomagnesemic animals, we determined the influence of decreased dietary intake of Mg^{2+} on microvascular tone, blood pressure and serum Mg^{2+} concentrations [51, 52]. Rats maintained for 12 weeks on diets moderately or more severely deficient in Mg^{2+} showed significant elevations in arterial blood pressure compared with control animals. Examination of the mesenteric microcirculation **in situ** revealed that dietary Mg deficiency resulted in reduced capillary, postcapillary, and venular blood flow concomitant with reduced arteriolar, precapil-

lary sphincter, and venular lumen sizes. The greater the degree of dietary Mg deficiency, the greater the reductions in microvascular lumen sizes.

Since intense, environmental noise can result in hypertensive disease in man [92] and may produce hypomagnesemic states [57], we reasoned that such a stressful situation, if produced under controlled laboratory conditions, should exacerbate the hypertensive and microvascular changes we noted in animals made deficient in Mg. Very recently, in preliminary experiments, we have found that a superimposition of environmental noise stress in animals receiving dietary deficits in Mg exacerbates the elevation in arterial blood pressure and results in severe constriction of arterioles, precapillary sphincters and venules concomitant with a marked increase in sensitivity of these microvellels to vasoconstrictor stimuli [52]. It is of particular interest to note that we found: 1. the greater the reduction in serum Mg^{2+} concentration, the greater the microvascular reductions in lumen sizes; and 2. an inverse correlation between serum Mg^{2+} and arterial blood pressure. It is of interest to note here that others, using SHR's have recently shown that a similar Mg deficient diet increased blood pressure levels higher than those in SHR controls [74, 88].

Collectively, these findings together with those reviewed below, should provide a rationale for the etiology, as well as treatment, of some forms of hypertensive vascular disease.

Several reports have appeared, utilizing spontaneously hypertensive rats (SHR) and DOCA-salt-induced hypertension [26, 32, 33, 34, 41, 54, 68, 74, 75, 96b, 120, 193], which could be used to support the concept that derangements in Mg metabolism or Mg deficiency can result in high blood pressure [26, 32, 39, 41, 48, 56, 120, 193]. Collectively, these findings indicate several important implications for a role for Mg in hypertension: (1) reactivity of SHR blood vessels to $[Mg^{2+}]$ and neurohumoral agonists is altered in the directions one would predict [26, 32, 33, 34, 39, 48, 49, 54]; (2) SHR rats, as predicted [26, 33], have lower RBC and plasma Mg values than Wistar controls or WKY rats [33, 120]; (3) SHR rats exhibit elevated serum Ca/Mg and Na/Ca ratios [33, 120]; (4) numerous organs (e.g., heart, lungs, kidney, bone) from SHRs exhibit 6–16 % reductions in Mg content; in addition, an inverse relationship was noted between arterial blood pressure and tissue Mg content [193]; (5) dietary or acute administration of Mg lowers arterial blood pressure in SHR and DOCA-salt-hypertensive rats [64, 74, 88]; and (6) SHRs exhibit increased arterial and venous tone which is more resistant to Mg manipulation than in normal control tissues [26, 33]. Overall, these new findings support the hypothesis that the level of free, ionized $[Mg^{2+}]_o$ in the extravascular fluid and at the vascular smooth muscle cell membranes plays an important role in controlling vascular tone, contractility of blood vessels and preventing development of hypertension.

Diabetes and High Blood Pressure

With respect to experimental diabetes mellitus, several interesting studies were published during the past 5 years [26, 33, 49, 78b, 147, 182, 185, 187, 203]. Streptozotocin-induced diabetes mellitus in rats is clearly associated with an intense magnesuria, glycosuria and polyuria [203]. The increase in urinary Mg concentration paralleled the degree of glycosuria. This supports and extends numerous previous findings that diabetes mellitus results in hypomagnesemia [42, 56, 97]. Basal tension of aortas and portal veins excised from rats administered alloxan steadily increased from the 1st through the 8th week as the degree of diabetes (assessed by serum glucose, triglycerides, cholesterol, creatinine) become progressively worse [33, 182]. These studies also demonstrated alterations in vascular reactivity associated with elevated serum Na/Ca and Ca/Mg ratios. Twenty to twenty-five percent of the latter alloxan-diabetic rats exhibited significant elevations in arterial blood pressure by the 8th week after treatment [33]. This is particularly interesting since long-term diabetes mellitus in humans results in hypertension in 40–80 % of patients [see above]. It is of particular interest to note that elevation of $[Mg^{2+}]_o$ failed to relax the diabetic rat aortas; diabetic venous smooth muscle also demonstrated little response to high concentrations of Mg^{2+} [26, 33, 182]. Most importantly, the diabetic vessels of these rats showed marked elevation in total exchangeable and membrane-bound calcium [185]. Such data, overall, lend support to our concept that the vascular membranes in diabetic subjects probably have undergone alterations in their Mg-Ca exchange sites [26]. But, are these divalent cation permeability and membrane alterations a result of the diabetic state or are they linked to the etiology of the syndrome? In this context, it is of particular interest to note that Nelson and Boquist [78b, 147] have recently found that alloxan and streptozotocin can produce direct alterations in membrane permeability of mouse liver mitochondria in vitro. High concentrations of alloxan-

induced efflux of endogenous Mg^{2+}, K^+ and adenine nucleotides, efflux of accumulated Ca^{2+}, K^+ uptake inhibition, loss of membrane potential, and swelling [78b]. We were particularly interested to learn from these studies that the loss of Mg^{2+} precedes the release of accumulated Ca^{2+}, which paralleled the efflux of K^+ and swelling. This, thus resembles very closely what we have reviewed elsewhere for Mg-K-Ca interactions and control of vascular homeostasis [39]. It will be extremely important to extend such studies with alloxan and streptozotocin to isolated blood vessels and electrolyte transport.

Attenuation of Hypertension By Use of Mg Salts: Clinical and Experimental Evidence

Ever since 1925 [76], it has been suggested that Mg salts might be of value as a therapeutic tool in the treatment of hypertensive disease. As early as 1918, it was suggested that $MgSO_4$ might be the best way of treating preeclamptic hypertensive pregnant women [190]. The latter is now widely utilized in such cases. But, only recently has the mechanism of Mg's protection been elucidated [26]. Since the original clinical studies of Blackfan and Hamilton [76], there have been at least five different studies to demonstrate that either parenteral or oral administration of Mg salts can significantly lower arterial blood pressure of hypertensive patients [98, 128, 178, 189, 200]. If this is more than coincidental, and the above dietary-microcirculatory studies are valid, then reduced dietary intake of Mg in SHR's should exacerbate their blood pressures. At least two independent studies have confirmed this notion [74, 88]. In addition, these experimental studies have clearly shown that elevated dietary levels of Mg will lower the arterial blood pressure of SHR's. Moreover, in some very preliminary trials, we have found that oral administration of Mg salts will reduce the high levels of arterial blood pressure noted in DOCA-salt maintained, uni-nephrectomized rats [68].

Since the overwhelming laboratory data reviewed herein indicates that elevation of Mg^{2+} can attenuate induced vasospasm, regionally, and cause direct vasodilation, such a rationale, coupled with the above experiments on Mg^{2+} – vascular muscle interactions, dietary deficiency and production of hypertension, would aid in explaining why the administration of magnesium salts lowers arterial blood pressure [The cellular basis for magnesium's action on vascular tone and blood pressure is presented elsewhere in detail [24, 26, 39, 41].

Mg^{2+}-Deficiency Induces Alterations in Vascular Muscle Membrane Permeability to Ions: Membrane Leakiness and Ca^{2+} Movement

Considerable evidence has now been amassed to indicate that Mg^{2+} acts as a gate for entry and exit of Ca^{2+} at the vascular membrane [10, 16, 20, 22, 23–27, 32, 39, 46, 49, 58, 62, 65, 66, 84, 112, 113, 134, 180, 188], and most probably can also alter membrane permeability to ions [6, 20, 39, 49]. Briefly, the latter experiments indicate that removal of Mg^{2+} from 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 contractile responses. 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 suggest that other cellular cations (e.g., K^+) could in the absence, or in the face, of reduced Mg^{2+} exit the vascular smooth muscle cells, whereas other cations such as Na^+ and Ca^{2+} could probably gain entry. The end result would be cellular loss of K^+ and elevation in Na^+ and Ca^{2+}, events we know are observed in Mg-deficient states.

Conclusions

We believe the available clinial and experimental cardiac and vascular muscle data are most consistent with the hypothetical scheme shown in Fig. 1, whereby the prime factors for setting the dysfunctional cardiac and vascular events into motion are local tissue hypoxia, anoxia and cell injury combined with inadequate dietary intake or inadequate metabolism of Mg^{2+}, or drug-induced alterations and renal loss in Mg^{2+}.

The data reviewed herein are consistent with the hypothesis that the extracellular Mg^{2+} concentration, membrane Mg and intracellular level of Mg exert a regulatory role in vascular tone, vascular reactivity or peripheral vascular resistance, and probably has an important functional role in control of Ca^{2+} uptake, content, and distribution in smooth and cardiac muscle cells. Certain vascular disease states, e.g., hypertension, SDIHD, preeclampsia-eclampsia, stroke, diabetes, are associated with a deficiency of plasma and tissue ionized, free

Mg; the vascular and blood pressure changes here being, at least in part, reflections of the directascular actions of the lack, or reduction, of element 12.

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