Role of Magnesium Ions in Contractility of Blood Vessels and Skeletal Muscles [1]

By *Burton M. Altura* and *Bella T. Altura*

Department of Physiology, SUNY Downstate Medical Center, Brooklyn, New York 11203, U.S.A.

Zusammenfassung

Es wird ein Überblick gegeben über den Einfluß intrazellulärer und exrazellulärer Magnesium-Ionen (Mg^{2+}) auf die Kontraktilität sowie die Lokalisation (und Verteilung) divalenter Kationen in der Skelett- und glatten Gefäßmuskulatur. Weiterhin wird der Einfluß extrazellulärer Mg^{2+} ($(Mg^{2+})_o$) auf Tonus, Kontraktilität und Reaktivität von Blutgefäßen abgehandelt. Mit Hilfe empfindlicher Färbungs- und Elektrodentechniken ist der Anfang gemacht, Mg-Kompartimente in verschiedenen Muskelzelltypen darzustellen; trotzdem kann nur die Konzentration an freiem cytoplasmatischem Mg^{2+} abgeschätzt werden. Orte des Mg-Ca-Austausches scheinen in sarkoplasmatischem Retikulum und Plasmamembranen sowohl von Skelett- als auch von Gefäßmuskelzellen zu existieren. Eine Anzahl Mg^{2+}-Bindungsstellen sind auf kontraktilen (und regulatorischen) Proteinen lokalisiert worden wie Troponin C, Parvalbumin und Calmodulin. Verschiedene unterschiedliche ATPasen existieren in diesen Muskelzellen, die verschiedene Abhängigkeiten von Mg^{2+} besitzen. Eine kausale Beziehung scheint zu bestehen zwischen Serum-(und Gewebe-) Mg^{2+}, dem Tonus (und der Reaktivität) von Blutgefäßen und der Ätiologie gewisser peripherer Gefäßerkrankungen, z.B. dem plötzlichen ischämischen Herztod, der Eklampsie, dem Diabetes mellitus, dem Kreislaufschock, Nierenerkrankungen und bestimmten Formen der Hypertonie. Direkte Studien an Blutgefäßen zeigen, daß Hypermagnesämie eine Vasodilation induziert und die Reaktivität auf zirkulierende gefäßverengende neurohumorale Überträgerstoffe abschwächt, wohingegen Mg-Mangel (oder Hypomagnesämie) Gefäßspasmen verursachen kann und die Kontraktilität potenziert. $(Mg^{2+})_o$ ändert direkt die Aufnahme, den Gehalt, die Bindung und die Verteilung von Ca-Ionen in der Gefäßmuskulatur. Der Efflux von Ca^{2+} kann ebenfalls durch $(Mg^{2+})_o$ moduliert werden. Funktionelle Mg-Ca-Austausch- (und Mindungs-) orte in der glatten Gefäßmuskulatur von diabetischen und spontan hypertensiven Versuchstieren sind verändert. Insgesamt gesehen zeigen die hier vorgelegten Daten, daß Mg^{2+} eine zentrale Bedeutung zukommt bei der Regulation und Kontrolle von Kontraktibilität und Gefäß-Homeostase.

Summary

The influence of intracellular and extracellular magnesium ions (Mg^{2+}) on contractility and divalent cation localization (and distribution) in skeletal and vascular smooth muscle is reviewed. In addition, the influence of extracellular Mg^{2+} ($[Mg^{2+}]_o$) on tone, contractility and reactivity of blood vessels is reviewed. Sensitive dye and electron probe techniques are beginning to reveal sites of compartmentalization of Mg in different types of muscle cells; despite this, the free cytoplasmic Mg^{2+} concentration can only be estimated. Mg-Ca exchange sites appear to exist in the sarcoplasmic reticulum and plasma membranes of both skeletal and vascular muscle cells. A number of Mg^{2+} binding sites have been localized on the contractile (and regulatory) proteins, including troponin C, parvalbumin and calmodulin. Several different ATPases exist in these muscle cells which have different dependencies on Mg^{2+}. A causal relationship appears to exist between the serum (and tissue) Mg^{2+}, the tone (and reactivity) of blood vessels, and the etiology of certain peripheral vascular diseases, e.g., sudden-death ischemic heart disease (SDIHD), eclampsia, diabetes mellitus, circulatory shock, renal disorders and certain forms of hypertension. Direct studies on blood vessels indicate that hypermagnesemia induces vasodilatation and attenuation of reactivity to circulating contractile neurohumoral substances, whereas Mg-deficiency (or hypomagnesemia) can produce vasospasm and potentiation of contractility. $[MG^{2+}]_o$ alters, directly, uptake, content, binding and distribution of calcium ions in vascular smooth muscle. Efflux of Ca^{2+} can also be modulated by $[Mg^{2+}]$. Functional Mg-Ca exchange (and binding) sites in vascular smooth muscle from diabetic and spontaneously hypertensive animals are altered. Overall, the data reviewed here indicate that Mg^{2+} is central to the regulation and control of contractility and vascular homeostasis.

Résumé

Nous avons passé en revue l'influence des ions Mg^{++} intracellulaires et extracellulaires sur la contractilité et la localisation (et la répartition) des cations divalents dans le muscle du squelette et le muscle lisse des vaisseaux. De plus nous avons passé en revue l'influence de Mg^{++} ($[Mg^{++}]_o$) sur le tonus, la contractilité et la réactivité des vaisseaux sanguins. Des techniques sensibles avec colorant et électroniques ont été élaborées pour révéler les sites de compartimentalisation du Mg dans différents types de cellules musculaires; malgré cela, la concentration du Mg^{++} cytoplasmatique libre peut seule être évaluée. Des sites d'échange Mg-Ca semblent exister dans le reticulum sarcoplasmatique et les membranes plasmatiques des cellules des muscles du squelette et des vaisseaux. Un certain nombre de sites de fixation du Mg^{++} ont été localisés sur les protéines contractiles (et régulatrices); y compris la troponine C, la parvalbumine et la calmoduline. Il existe plusieurs ATPases différentes dans ces cellules musculaires qui présentent des magnésio-dépendances différentes. Une relation causale semble exister entre le Mg^{++} sérique (et tissulaire) le tonus (et la réactivité) des vaisseaux sanguins et l'étiologie de certaines affections vasculaires périphériques, entre autres la maladie cardiaque avec mort subite, l'éclampsie, le diabète sucré, le choc circulatoire, les perturbations rénales et certaines formes d'hypertension. Des études directes sur les vaisseaux sanguins indiquent que l'hypermagnésémie provoque une vasodilatation et une atténuation de la réactivité envers les substances neurohumorales contractiles circulantes, alors que le déficit magnésique (ou l'hypomagnésémie) peuvent produire un vasospasme et une potentialisation de la contractilité. Le $[Mg^{++}]_o$ altère directement la captation, la teneur, la fixation et la répartition des ions Ca dans le muscle lisse vasculaire. L'efflux de Ca^{++} peut aussi être modulé par $[Mg^{++}]_o$. Les sites fonctionnels d'échange (et de fixation) Mg-Ca sont altérés dans le muscle lisse vasculaire des animaux diabétiques et avec hypertension spontanée. Au total, les données passées en revue ici, indiquent que le Mg^{++} est au centre de la régulation et du contrôle de la contractilité et de l'homéostase vasculaire.

During the past decade, a considerable amount of information has accumulated concerning the physiological and biophysical roles of magnesium in contractility

of skeletal, cardiac and smooth muscles (particularly on blood vessels) [see 9, 18, 20, 21, 56, 66, 68, 71, 89, 96, 97, 99, 107, 109, 114, for recent reviews]. Collectively, these findings have revealed that intra- as well as extracellular Mg^{2+} ($[Mg^{2+}]_o$) play important roles in the basic contractile properties of muscles. The transport of this divalent cation across muscle membranes and muscle mitochondria has yielded interesting and important information. Sensitive dye and electron probe techniques are beginning to reveal sites of compartmentalization of Mg^{2+} in different types of muscle cells. A number of Mg^{2+} binding sites have been localized on the contractile proteins and several different ATPases have been localized, in muscles, which exhibit different dependencies on Mg^{2+}. The external and membrane concentration of this divalent cation may control calcium ion (Ca^{2+}) movements and distribution in several types of muscles, including vascular smooth muscles. Finally, the muscle and serum concentrations of Mg^{2+} appear to play important roles in the etiology and progression of certain diseases, especially those concerned with the cardiovascular system.

We have made an attempt in this review to bring together information on a number of those aspects referred to above. We have tried to focus, primarily, on the literature over the past 15 years; the orientation of the selected subject matter reflects some of our own prejudices and often is focused on only some aspects of a particular theme due, primarily, to limitations of space. The reader should therefore consult a number of the recent reviews and monographs, mentioned above, for other points not covered here.

Cellular and cytoplasmic measurements and localization of muscle Mg

By now, it is well recognized that Mg^{2+} ions are important, and vital, constituents of cell cytoplasm and participate in many intracellular enzyme reactions [1, 9, 41, 53, 80, 81, 126]. As a soft tissue cation, Mg ranks second to potassium in quantity in the body, and also resembles potassium (K) in its distribution [1, 126]. Although total cellular (and muscle) Mg can be easily and accurately determined by atomic absorption spectroscopy, including that present in vascular smooth muscle [10, 12, 93, 94], it is rather difficult to precisely determine the free cytoplasmic Mg^{2+} because of its binding to ionic constituents, proteins and intracellular organelles. Moreover, little is known about the concentration of free Mg^{2+} under physiologic conditions, especially in mammalian skeletal muscle and vascular smooth muscle [1, 9, 39a, 40, 57a, 93, 94, 96, 101, 114, 126].

Although several techniques have been used to estimate the intracellular ionized Mg^{2+} in muscle cells (see ref. 101 for recent review), the methods utilized require too much guesswork and are fraught with errors and assumptions (see ref. 101 for review). Among these "indirect" methods are: 1) the estimation of diffusible Mg^{2+} in the sarcoplasm of barnacle muscle cells after replacement microinjection — such a method is however not suitable for mammalian skeletal or vascular muscle; 2) the estimation of Mg^{2+} quenching on the light emission of aequorin in the presence of Ca^{2+} in vitro and in barnacle sarcoplasm — again not very suitable for mammalian muscle cells; 3) the measurement of various cellular *in situ* equilibrium concentration of reactants and enzymatic reaction products whose apparent equilibrium constants are known to be dependent on Mg^{2+} — again not precise; 4) a consideration of the binding constants of all intracellular muscle cell components known to form complexes with Mg^{2+} — again, a method of doubtful validity; 5) the measurement of relaxation parameters of phosphocreatine in muscles in order to compare them to ideal model (or theoretical) solutions; vascular muscle cells have, however, little or no phosphocreatine; 6) the use of an ionophone to measure and control free and bound cytoplasmic Mg^{2+} — this might be of use in a red blood cell, but is doubtful for muscle cells; and more recently 7) the use of a Mg^{2+} metallochromic indicator (e.g., Eriochrome Blue) in the cytosol — however, it can't be utilized with small muscle cells like most mammalian skeletal and vascular muscles, nor can it be used as the pH varies. Obviously, at present, there is a great need to develop a specific Mg^{2+} ion electrode, without which it is impossible to determine mammalian skeletal and vascular muscle free Mg^{2+}.

The total Mg content of vascular smooth muscle is approximately 30—40 mM/kg dry wt. muscle [10, 114]; only about 50—60% of this can be removed by exposure to Mg^{2+}-free solutions and metabolic inhibition [10, 93, 94, 114, 115]. The vascular muscle cytoplasmic estimation of $[Mg^{2+}]$ is, at present, approximately 0.1—1.0 mM [114]. This compares with estimates of 0.9 mM in frog striated muscle [57a] and 4 mM in barnacle striated muscle [39a].

Electron probe studies of most organelles in resting vascular muscle reveal that the total Mg contents are not really different frome one another [114]. For example, the mitochondrial Mg content of rabbit anterior-mesenteric portal vein (38 ± 1.5 mM/kg dry wt) is similar to that of the adjacent cytoplasm (43 ± 1.9 mM/kg dry wt). Studies with resting frog semitendinosus muscle indicate that the cytoplasmic Mg content (49 mM/kg dry wt) may be higher than the mitochondrial Mg content (23 mM/kg dry wt) [114]. Although the nuclear Mg contents are also similar to the cytoplasmic levels, vascular smooth muscle lysosomal and residual body Mg contents are much lower (e. g., $\cong$ 5 mM/kg dry wt) [114].

In addition to the free $[Mg^{2+}]$, [Mg ATP] and other Mg chelates, it is believed that about 1.0 mM/kg wet wt of Mg^{2+} is bound to Ca:Mg sites on the contractile protein troponin and parvalbumin [99, 114].

Recent electron probe findings suggest that when skeletal muscle is tetanized, for about 1.2 sec, the calcium

release from the terminal cisternae is accompanied by a small (e. g., 25 meq/kg dry wt) uptake of Mg into the terminal cisternae [114]. Such findings suggest, at least for stimulated striated muscle, that Ca:Mg exchange can take place in the sarcoplasmic reticular membranes (see also below).

Magnesium and calcium release by sarcoplasmic reticulum

Ever since Hasselbach discovered the Ca^{2+} pump in sarcoplasmic reticular membranes [70], it has been known that this requires the presence of both Ca^{2+} and Mg^{2+} for its operation; neither Ca^{2+} transport nor Ca^{2+}-stimulated ATP cleavage can be observed in the absence of Mg^{2+} [71].

Since the presence of Mg is known to affect both the sensitivity of muscle to stimulants as well as the degree of biologic response, in this case contraction, one must consider the possibility that this divalent cation could modulate the amount of Ca^{2+} released by the sarcoplasmic reticulum (SR) [71, 97, 114]. Some evidence could be cited for this concept based on findings in skeletal muscle. For example, in 1968, Weber [128] reported that caffeine-induced Ca^{++} release from vesicles of rabbit skeletal muscle fragmented SR was reduced by increasing the $[Mg^{2+}]$ from 0.2 to 4 mM. Using skinned fibers of frog skeletal muscle, Ford and Podolsky [59] found that an increase in $[Mg^{2+}]_o$ from 0.02 to 1.4 mM would inhibit the tension spike elicited by Ca^{2+}; this was attributed to a decrease in the total amount of Ca^{2+} released by the SR. More recently, some work on rat uterine smooth muscle may also be indicative of a role for Mg in modulating Ca^{++} release by the SR. Osa [91] has reported that relaxation after potassium-contracture in pregnant rat myometrium became significantly faster when $[Mg^{++}]_o$ (0.5 — 20 mM) was added to the bathing media. Since it has been demonstrated that: 1) Ca binding to the SR, in skeletal as well as vascular smooth muscle, is Mg-dependent [55, 56, 70, 71, 99, 108, 112, 114]; 2) that a distinct SR does exist in smooth muscles, including vascular smooth muscle [51, 74, 114], it would seem likely that the latter is at least in part a reflection of events at the SR.

Contractile proteins and magnesium

Although the primary activator of muscle contraction is Ca^{2+}, both Mg^{2+} and ATP must be present in order to generate Ca^{2+}-activated tension in all types of muscle [38, 41, 56, 62, 71, 74, 112, 114]. Potter and Gergely [98] have shown, at least for skeletal muscle, that six divalent cation binding sites appear to exist on the calcium sensitive regulatory protein, troponin C. Two of these sites exhibit a high affinity for Ca^{2+} and also competitively bind Mg^{2+} (Ca^{2+} - Mg^{2+} sites); two sites that bind Mg^{2+} but not Ca^{2+} but not Ca^+ (Mg^{2+} - specific sites); and two sites with lower affinities for Ca^{2+} than the Ca^{2+} - Mg^{2+} sites that cannot bind Mg^{2+} (Ca^{2+}-specific sites). Evidence has accrued to indicate that Mg^{2+} interacts with troponin, as Mg^{2+} when it is present in solution with troponin can change the latter's electrophoretic mobility [46] and bring about a change in its conformation [65, 70]. Although a troponin-tropomyosin system has been found to exist in some arterial smooth muscles [108], it appears to have different characteristics than the system in skeletal muscle [90, 111]. In addition, the calcium-binding regulatory proteins in arterial smooth muscle appear to be associated with myosin rather than with actin as in striated muscle [90, 111]. Even though such differences may exist in the contractile proteins of vascular smooth muscle, and it is unknown as to whether the calcium binding regulatory protein in vascular muscle has CA^{2+}-Mg^{2+} binding sites which modulate the ATPase activity, alterations in $[Mg^{2+}]$ could affect contractility by altering the binding of Ca^{2+}. Moreover, although the Ca^{2+} binding regulatory proteins of vascular muscle may be different from those in skeletal muscle [90, 111]., Ca^{2+} binding to to the regulatory proteins probably allows actin form a complex with myosin, which in the presence of Mg^{2+}, will exhibit a high ATPase activity, as in skeletal muscle; the result would be hydrolysis of ATP, liberation of energy, and shortening of the myofibrils. One must also consider the possibility that Mg^{2+} might alter Ca^{2+} binding to myosin sites. For example, Bremel and Weber [39], at least for skeletal muscle, have reported that an inrease in $[MG^{2+}]$ from 3 µM to 5mM alters the degree of cooperativity and decreases the sensitivity of Ca^{2+} binding sites on rabbit myosin. A similar type of reaction has been reported recently by Sobieszek and Small [111] for chicken gizzard smooth muscle.

It should also be pointed out that, as in skeletal and cardiac muscle, there is a Mg^{2+} dependent SR Ca ATPase, which is needed for active transport of Ca in relaxation processes in blood vessels [74, 112]. It therefore seems reasonable to believe that alterations in $[Mg^{2+}]$ might affect contraction-relaxation of both skeletal and vascular muscle via affects on the SR Ca Atpase.

The possible interactions of Mg^{2+} with the Ca^{2+} binding (and regulating) proteins, parvalbumin and calmodulin, should also be mentioned. Parvalbumins are low molecular weight, water soluble calcium binding proteins which appear to exist freely in muscle sarcoplasm, while calmodulin, another Ca^{2+} binding protein, also present in skeletal and vascular muscles [100, 114], has a structure very similar to troponin C[100]. Parvalbumin appears to have sites which can bind Mg^{2+} competitively, while calmodulin has sites which bind Mg^{2+} in a non-competitive manner [100]. Thus, it would appear from such data that parvalbumin, at least, could play an important role in Ca: Mg exchange mechanisms.

Cell membrane Na$^+$, K$^+$-ATPase and magnesium

Active transport of sodium and potassium across mammalian membranes is dependent upon a splitting of ATP, which in turn is dependent on a special enzyme (i. e., Na$^+$, K$^+$ ATPase) having an obligatory requirement for Mg^{2+}[1]. Withdrawal of [Mg^{2+}]$_o$ from the bathing medium is known to result in a loss of potassium and again of sodium in skeletal muscle and in at least one type of vascular smooth muscle [93, 130]. Such data would appear to suggest that the Na$^+$, K$^+$ ATPase activated transport pump may be compromised in at least some vascular muscles in the absence of [Mg^{++}]$_o$. Since this pump is electrogenic in vascular smooth muscle, (i. e., increasing the rate of pumping will hyperpolarize the cell membrane while decreasing the rate of pumping will do the reverse [105, 112]), it has been suggested that magnesium-free solution could depolarize the membrane, thereby increasing Ca^{2+} permeability and influx [68]; as mentioned below, removal of [Mg^{2+}]$_o$ does increase content of Ca in vascular muscle. Additional indirect evidence for this concept can be derived from experiments on isolated rat aortic smooth muscle: 1) although the latter tissue is known to contract rapidly when the [Mg^{2+}]$_o$ is lowered (see below), rat aorta will not respond in such a manner when it is placed in high [K$^+$]$_o$, e. g., 179 mM [11]. 2) These contractile responses obtained on lowering [Mg^{2+}]$_o$ are directly linked with permeability of the cell membrane to [Ca^{2+}]$_o$ [7, 8, 13, 19 — 21, 31, 117]. Aortic smooth muscle from the rabbit, however, does not exhibit any significant alteration in either Na$^+$, K$^+$ or water content when placed in a Mg^{2+}-free environment for 60 minutes, despite the fact that reactivity to a variety of vasoactive stimulants is differentially altered [10]. It is thus obvious that a considerable amount of work remains to be done in this particular area before one can safely say that alterations in vascular muscle membrane Na$^+$, K$^+$-ATPase play a role in the Mg^{2+}-dependent vascular responses. Recent studies in rat aorta, at least, using ouabain and K$^+$-free solutions, fail to support a role for Na$^+$, K$^+$-ATPase [15].

Magnesium deficiency and cardiovascular disease

Up until relatively recently, it had been assumed that serum as well as tissue Mg remains stable over a variety of patho-physiological conditions. It is now known that a variety of systemic stresses, both acute and chronic, can result in a significant elevation or lowering of serum and tissue Mg [8, 21, 23, 24, 25, 27, 34 — 36, 40, 42, 44, 45, 48, 52, 54, 61, 66, 69, 73, 78, 79, 83 — 85, 86, 88, 89, 95, 102 — 104, 116, 124, 126). Many of these changes in Mg appear to be either reflections of alterations in or result in changes in cardiovascular function. Ventricular fibrillation brought about by acute anoxia, in guinea pigs, was reported to be associated with a rapid lowering of myocardial Mg, which appeared to parallel the resultant cardiac dilatation [73]. Serum Mg has been observed to be lowered following myocardial infarction in man and after experimentally-induced infarction in dogs [36, 40, 83, 85, 103, 107, 115a, 116, 126]. Cardiac diseases are also associated with a lowering of serum Mg [40, 44, 45, 78, 79, 84, 85, 103, 107, 115a, 116].

Several recent investigations point to causal relation between decreased Mg content (e. g., up to a loss of 20 — 35%) of cardiac muscle and coronary arteries and mortality from (non-occlusive) sudden-death ischemic heart disease (SDIHD), the incidence of which is highest in geographic areas with soft drinking water or magnesium-poor soil [8, 21, 25, 32, 33, 35, 44, 45, 47, 50, 78, 79, 84, 85, 103, 116, 118]. Interestingly, the intake of water for man can result in imbibition of a wide range of Mg concentrations (i.e., from 6 to 175 mg/day), depending upon geographic region [1, 84, 85].

Acute hypomagnesemia in animals and man is often associated with rises in blood pressure and elevations in peripheral vascular resistance in a variety of regions in the circulation. In addition, convulsions often result, the mechanism of which in unknown [54]. Recently, it has been suggested that the latter may be the result of cerebral hypoxia due to constriction of cerebral resistance vessels [27]. A number of disease states (e. g., alcoholism, atherosclerosis, eclampsia, diabetes mellitus, essential hypertension) which result in elevation of blood pressure are often associated with decreased serum levels of Mg [21, 23, 24, 25, 48, 61, 81, 85, 86, 95, 102 — 104, 116, 126]. Interestingly, there appears to be an inverse relationship between the serum level of Mg and cholesterol; the lower the [Mg]$_o$, the higher the cholesterol or viceversa [85, 103]. Some experiments suggest that dietary elevation of Mg intake can prevent elevation in serum cholesterol, and prevent atheroma formation [85, 103].

Hypermagnesemia, on the other hand, which is frequently noted in renal vascular disorders, uremias and circulatory shock, is often associated with hypotensive episodes [20, 21, 34, 42, 68, 69, 72, 88, 89, 103, 124]. Circulatory shock and trauma are thought to produce significant alterations in the metabolism of body Mg. Almost four decades have passed since Beecher and co-workers [34] reported that increased serum Mg levels appeared to correlate with the severity and duration of shock as seen in battlefield casualties. Similar results have been reported more recently for several different forms of circulatory shock and trauma [42, 52, 124]. In fact the recent work of Valencic et al. [124] suggests that reversibility of the shock syndrome may be associated with a restoration of plasma Mg to normal levels.

Several important hemodynamic alterations are known to occur in animals and man during various states of magnesium deficiency, e. g., ventricular tachycardia

and fibrillation, increased coronary and renal vascular resistances, modification of arterial blood pressure, hypertension, modification of peripheral blood flow, degenerative lesions in the vascular wall, arteriosclerosis, calcification of arterial walls, modification of red blood cell as well as leukocyte functions, alterations in blood levels of neuro-humoral substances, and marked alterations in the responsiveness of peripheral vessels to neuro-humoral agents, to name a few (see 1, 68, 85, 102 — 104, 116 for recent reviews). Despite this large body of data, there have been little attempt, to our knowledge, to integrate the avialable information with how it might relate to vascular responsiveness and basal tone.

The maintenance of circulatory homeostasis depends to a large extent on the responsiveness of the peripheral blood vessels to the sympathetic nervous system and circulating neuro-humoral substances [3, 6, 87, 105]. Changes in blood vessel walls brought about through alterations in Mg metabolism could interfere with the normal responses of the peripheral vessels thereby seriously affecting blood pressure, tissue blood flow, and cardiac output, especially in patients subjected to stress. An attempt is made below to bring together the important available information on the alterations that take place in mammalian blood vessels subjected to hypo- and hypermagnesemic environments.

Acute hyper- and hypomagnesemia and peripheral blood flow

It has been known ever since the work of Hazard and Wurmser [72] that increases in $[Mg^{2+}]_o$ can produce vasodilatation in intact or perfused vascular beds (see ref. 68 for review). Since the vasodilatation induced by changes in extracellular Mg^{2+} is extremely rapid, and since the intracellular free Mg^{2+} in vascular muscle is relatively insensitive to changes in $[Mg^{2+}]_o$ [93, 94, 114], it is likely that this hypermagnesemic-induced relaxation is due to some alteration at the cell surface [7, 8, 11, 13, 16, 17, 20, 21, 26, 118], e. g., displacement of Ca^{2+} [7 — 11, 13, 16, 18, 19 — 21, 26 — 31, 117, 118], hyperpolarization and/or interference with the constrictor action of circulating neuro-humoral agents [68, 109, 110, 117, 118, 121, 122, 125].

Infusion of solutions which induce acute hypomagnesemia can raise blood pressure [57] and elevate vascular resistance in a variety of beds [67, 68], the exact opposite of that seen in acute hypermagnesemia (see above). Since this elevation in blood pressure also takes place rapidly [57], and since as already mentioned (above) the intracellular free $[Mg^{++}]$ in blood vessels is relatively insensitive to changes in $[Mg^{2+}]_o$, it is likely that this hypomagnesemic-induced constriction is also due to an alteration at the vascular smooth muscle membrane for several reasons: 1) acute withdrawal of $[Mg^{2+}]_o$ *in vitro* produces rapid contraction or spasm, of a number of arterial smooth

muscles, which is directly dependent upon the $[Mg^{2+}]_o$ and $[Ca^{2+}]_o$ [7, 8, 10, 11, 13, 15, 16, 18, 20, 21, 26, 27, 118]. 2) Reduction in the perfusate concentration of $[Mg^{2+}]$ produces constriction of arterioles, $17 - 25 \ \mu m$ i. d. [16, 18]. 3) These directly produced *in vitro* contractile responses cannot be prevented by anti-adrenergic, anti-serotonergic, anti-cholinergic or anti-histaminic agents [8, 11, 15, 20, 21, 26, 118, 129]. 4) Addition of EGTA but not EDTA to the bathing medium will result in rapid, and complete, relaxation of the contractile responses elicited by withdrawal of $[Mg^{2+}]_o$ [13]. 5) Addition of EDTA but not EGTA to the bathing solution will result in a potentiation of the contraction observed by withdrawal of $[Mg^{++}]_o$ [13]. 6) Addition of a variety of divalent cations which are known to block inward movement of $[Ca^{++}]_o$ at the cell membrane (e. g., Mn^{2+}, Co^{2+}, Cd^{2+}, Ni^{2+}) result in a rapid relaxation of these contractile responses [7, 13, 16, 18, 19].

It is important to point out that some of the effects of acute alterations of $[Mg^{2+}]_o$ observed in intact vascular beds *(vide supra)* may also be due in part to actions of Mg^{2+} on circulating neuro-humoral constrictor substances, membrane stability, membrane potential and physiologic state of host [2, 4, 5, 7, 11, 13, 14, 16 — 19, 21 — 23, 25, 43, 68, 82, 110, 113 — 115, 118, 121, 129]. Some of these points are discussed in detail below.

Magnesium defiency and peripheral blood flow

Rats placed on a Mg deficienct diet exhibit significant alterations in organ blood flow between the eighth and sixteenth day of Mg dietary deprivation [49]. Blood flow was found to decrease in the spleen, kidney, skin, and testes, but to increase in the anterior pituitary and gut regions. These changes so balanced one-another out that the overall peripheral vascular resistance did not change. Forty days of Mg deficiency, however, resulted in an approximately 50% reduction of most organ blood flows including that to the brain [49].

In man hypomagnesemic states are frequently associated with rises in blood pressure and increased peripheral vascular resistance [67, 69, 103], while severe hypermagnesemia seems to be associated with hypotension [68, 88, 89, 116]. One is prompted to ask whether these alterations are due to direct effects of Mg^{2+} on the vascular wall *(vide supra, vide infra)*, basal tone, or to indirect effects on circulating vasoactive substances *(vide infra)*.

Magnesium deficiency, arterial smooth muscle morphology and cation content

Mg^{2+} deficiency induces arterial injury and dysfunction (see 102 — 103 for reviews).
Some of these lesions resemble what is seen early in the development of arteriosclerosis in man; i.e., calcified

plaques are usually seen. Interestingly, experimental dietary supplementation with Mg tends to decrease atheroma formation [85, 102, 103]. Hungerford and Bernick [76] have recently reported that magnesium deficiency in rats induces coronary arterial intimal cell damage, edema, hyperplasia, internal elastica fragmentation as well as medial (smooth muscle cell) hyperplasia. Mg^{2+} deficiency causes Ca^{2+} and Na^+ to be retained, while K^+ is lost [103, 104].

Magnesium deficiency in dogs has been demonstrated to raise aortic calcium tenfold (from 116 mg% to 1076 mg%) [58]. Serum calcium is lowered from 11.3 mg% to 7,88% while the serum Mg was lowered from 1.89 mg% to 0.89 mg% [58]. Other types of smooth muscle exhibit increased Ca content and transport during experimental Mg deficiency (127). Mg depletion (or deprivation) also induces an increase in cellular myocardial Ca and Na; myocardial Mg and K fall under these conditions [83].

Magnesium and responsiveness of vascular muscle to vasoactive stimulants

Up until recently, it was believed that the influences of $[Mg^{2+}]_o$ on blood pressure and blood flow were reflections of this metal's effects on cardiac muscle electrical activity, neuronal function, blood coagulation system, metabolism at the cellular level, and an activation of the contractile proteins in cardiac and vascular smooth muscles [1, 40, 54, 97, 107, 116]. We shall review here some recent experiments which are beginning to suggest that $[Mg^{2+}]_o$ can exert direct actions on vascular reactivity, vascular tone and divalent cation movements, in smooth muscles. In addition, we will attempt to demonstrate how such actions on smooth muscle cells could have bearing on the aforementioned Mg-associated alterations in blood pressure and peripheral vascular flows.

A Hypermagnesemia attenuates contractions elicited by neurohumoral agents, potassium ions and ouabain

Since the vasodilatation induced by hypermagnesemia is extremely rapid [20, 21, 68, 72, 89], it is likely that this hypermagnesemic-induced response is due to some alteration at the cell surfaces of the arteries and arterioles. Recent studies clearly indicate that the contractile actions of a variety of agonists, including agents such as potassium ions and ouabain, are depressed, on isolated arterial smooth muscle, by even slightly elevated levels of $[Mg^{2+}]_o$. Such results have been noted on a variety of arteries (e. g., pulmonary, coronary, mesenteric, renal, femoral, cerebral) excised from rabbits, rats, dogs, piglets, guinea pigs and man [8, 10, 11, 14-18, 20, 21, 26, 29, 30, 43, 63, 68, 82, 118, 121, 129], unpublished findings] as well as on single perfused rat mesenteric arterioles (17 — 22 µm i. d.) [16, 18]. These results cannot be attributed to

hyperosmolarity, alteration of Na^+, K^+-ATPase activity or release of any known vasoactive mediator from the smooth muscle cells [8, 10, 11, 15, 16, 18 — 21, 26, 28, 29, 43, 63, 85, 118, 129].

B Hypomagnesemia enhances contractions elicited by certain neurohumoral agents and potassium ions

Hypomagnesemia could elevate blood pressure and/or increase vascular resistance in certain vascular regions by potentiating the constrictor action of endogenous circulating neurohumoral substances (e. g., catecholamines, angiotensin, acetylcholine, serotonin) and ions (e. g., K^+) which are known to play important roles in regulation of blood flow [3, 6, 87, 105]. If one removes Mg^{2+} from the external medium, reactivity of a number of isolated arterial and venous vessels (i. e., rabbit aortae, canine coronary, pulmonary, splanchnic [e. g., celiac, splenic, gastric, hepatic, mesenteric], and renal arteries, human umbilical arteries and veins, rat and rabbit portal veins) [8, 10, 11, 16, 18, 20, 21, 25, 26, 28, 29, 30, 63, 118, 121, 129], unpublished data) to a number of these neurohumoral agents is enhanced. Similar findings have recently been observed also for single perfused rat mesenteric arterioles (17 — 23 µm i. d.) [16, 18, 26]. Such findings, collectively, lend support to the idea that reductions in serum levels of $[Mg^{2+}]$ could narrow arterial and arteriolar lumen sizes by enhancing activity of circulating (or released) constrictors, thus possibly accounting for the aforementioned elevations in peripheral vascular resistance and changes in systemic blood pressure. It is of additional interest to note that even reactivity of non-blood vessel smooth muscle cells (e. g. urinary bladder) can be enhanced by low $[Mg^{2+}]_o$ [77]. It should be pointed out here, however, that contractions induced by neurohypophyseal hormones are depressed, rather than enhanced, in the absence of $[Mg^{2+}]_o$ [2 — 5, 113 — 115]. These peptides may be exceptions to the rule; this will, however, have to await future investigation.

C Hypomagnesemia attenuates relaxations of blood vessels elicited by prostaglandins and isoproterenol

Decreased serum and tissue levels of Mg could also elevate blood pressure and vascular resistance by influencing circulating and/or released neurohumoral substances which normally promote dilatation or relaxation of peripheral blood vessels such as prostaglandin (PG) compounds and beta-adrenergic amines (e. g., isoproterenol). There is now some evidence that both PG- and ioproterenol-induced relaxations are attenuated in the absence of $[Mg^{2+}]_o$ on rat aortic and canine coronary arterial smooth muscle, respectively [14, 22], unpublished data. Although further work is needed to verify that PG and beta-adrenergic-induced relaxation of vascular smooth muscle is Mg-dependent,

these findings do provide some evidence that a portion of the increased noted in hypomagnesemic states may be reflection of a reducedability of certain neuro-humoral substances to elicit vasodulatation.

Extracelluar magnesium ion concentration influences, directly, basal tone in isolated blood vessels

Besides modulating drug — and hormone-induced contractions in smooth muscle cells, $[Mg^{2+}]_o$ also appears to be able to directly alter baseline tension or tone [7—11, 13—16, 18—21, 25—30, 68, 75, 110, 118, 129]. Lowering the $[Mg^{2+}]_o$ by 0.6 mM, in isolated rat aorta, induces a rapid rise in tension development; the maximal contractile response being attained within 15 seconds [7, 11, 13]. Total withdrawal of $[Mg^{2+}]_o$ enhances tensions further, which are maintained for as long as the medium lacks magnesium ions [7, 11, 13]. In contrast to the contractions seen on lowering the $[Mg^{2+}]_o$, an elevation of $[Mg^{2+}]_o$ to as little as 2.4 mM inhibits spontaneous mechanical activity [11]. Raising the $[Mg^{2+}]_o$ to 6 mM not only completely inhibits all prior spontaneous mechanical events but, in addition, lowers baseline tension. Similar findings have been made on canine coronary and cerebral arteries [20, 27], piglet arteries [8, 20, 21], human umbilical arteries [20, 21] as well as on rat ileal smooth muscle preparations [75]. It thus appears that a variety of smooth muscle preparations which either exhibit a basal tone or develop spontaneous activity are susceptible to alterations in baseline mechanical activity soleley by altering $[Mg^{2+}]_o$. However, it is important to determine whether such results, on isolated arteries and veins, can be extrapolated to the major sites of peripheral vascular resistance, namely the spontaneously active arterioles. Recently, using an isolated perfused mesenteric preparation and an image-splitting closed circuit television microscope recording system, at magnifications up to 3000x, it has been demonstrated that removal of Mg^{2+} from both the superfusate and perfusate results in a rapid and progressive reduction in arteriolar lumen sizes with a simultaneous sharp reduction in venous outflow [16, 18]. Do such findings on spontaneously active arterial and arteriolar vascular muscle cells, however, also apply to spontaneously active venous smooth muscle cells (e. g., portal veins, human umbilical veins)? Withdrawal of, or lowering, the $[Mg^{2+}]_o$ results in a rapid enhancement of the spontaneously evoked mechanical responses and increases in rhythmic activity in such spontaneously active veins [7, 14, 16, 18, 19—21, 26, 29, 63, 110, 117, 122, 129]. Interestingly, although withdrawal of $[Mg^{2+}]_o$ can increase rhythmic contractility and amplitude in spontaneously active mammalian veins, such venous vessels do not go into a spasm (contracture?) as is seen on arteries (above). Elevations of the $[Mg^{2+}]_o$ above the normal physiologic level (e. g., > 1.2 mM) dose-dependently lower

the frequencies and the contractile tensions. Similar findings have been observed on spontaneously active human umbilical veins [20, 21]. It should be noted that none of these reductions in contractility produced by elevated $[Mg^{2+}]_o$ are related to osmolarity, inhibition of Na^+, K^+-ATPase activity or release (or inhibition of release) of vasoactive mediators from within the arterial, arteriolar or venous walls [8, 18, 20, 21, 60, 118, 129]. If none of the latter can account for the direct and rapid effects changes in $[Mg^{2+}]_o$ exert on basal tone, spontaneous mechanical and reactivity to both constrictor and dilator substances, then how do alterations in extracellular (and membrane) $[Mg^{2+}]$ bring these actions about? Since vascular smooth muscle cells, like heart muscle cells [40, 92, 97, 107], in the absence of acute loss of $[Mg^{2+}]_o$ still retain 50—60% of their Mg content [10, 12, 21, 93, 94, 114, 115], which is probably between 0.1—1 mM (above) and more than enough for activation of Mg-dependent enzymes and contractile proteins [1, 38, 39A, 53, 56, 57a, 66, 96, 99, 108, 114], a mechanism which is central to Mg^{2+}-dependent changes in spontaneous mechanical activity, drug-induced activation and inhibition of contractility in smooth muscles must be sought. A likely point of action might be on the availability of calcium ions (Ca^{2+}) for the contractile process.

Evidence that extracellular magnesium influences membrane permeability to calcium ions and the distribution and exchange of calcium ions in vascular smooth muscle

Several lines of experimental evidence, both indirect and direct, can be marshalled to support the idea that $[Mg^{2+}]_o$ does indeed, affect uptake, binding and/or distribution of cellular Ca in vascular smooth muscle. First, a simple exposure of aortic smooth muscle to a Ca^{2+}-free versus a Ca^{2+}, Mg^{2+}-free Krebs-Ringer solution for 2 hours, followed by a cumulative readmittance of Ca^{2+} to acetylcholine- or angiotensin-induced residual contractions results after only Ca depletion in 60 and 40% maximal responses, respectively, whereas after Ca, Mg depletion one sees very dramatic 250 and 150% maximal contractile responses [e. g., 18, 28]. The potentiation of maximum responses in normal Krebs-Ringer, containing $2.5 mM[Ca^{2+}]_o$, in the absence of $[Mg^{2+}]_o$ is, however, only 30 and 10% respectively [10]. Enhanced entry or translocation of $[Ca^{2+}]_o$ in the absence of both Ca and Mg could account for the increased maximal responses noted with acetylcholine and angiotensin stimulations of vascular muscle [10, 18, 21, 28]. The inhibitory effects of elevated $[Mg^{2+}]_o$ (above) can also be explained as a result of a block of Ca^{2+} influx at the membrane.

Experimtents with different cation chelators (i. e., Ca EDTA and EGTA), and divalent and trivalent cations, have provided additional evidence that $[Mg^{2+}]_o$

can exert influences on Ca^{2+} influx at vascular smooth muscle cell membranes [7, 13, 16, 18, 19, 20, 21]. With rat aortic strips, addition of 5 mM Ca EDTA potentiates contractions induced by $[Mg^{2+}]_o$ withdrawal, while 5 mM EGTA promotes rapid relaxations [13]. Ca EDTA which has an affinity for Mg^{2+} is probably chelating and removing surface membrane Mg from the arterial smooth muscle cells. This results in a further influx of $[Ca^{2+}]_o$, thus potentiating the response. EGTA (5 mM) completely inhibits development of rhythmic contractile activity in spontaneously active arterial and venous smooth muscle, as one might expect from the dependence of these tissues on $[Ca^{2+}]_o$ [7, 26, 105]. Rapid relaxations of contractions induced by $[Mg^{2+}]_o$ withdrawal in arteries and veins can also be induced by Mn^{2+}, Ni^{2+}, Co^{2+}, Cd^{2+} but not by Sr^{2+} [13, 18]. Addition of trivalent cations (e. g., La^{3+}, Fe^{3+}, Al^{3+}) will also inhibit contractions induced by $[Mg^{2+}]$ withdrawal in portal venous smooth muscle [7, 19]. All of these foreign divalent and trivalent cations, expect for Sr^{2+}, are known to block entry of $[Ca^{2+}]_o$. Sr^{2+} is known to substitute for Ca^{2+} in many chemical and physiological reactions and would not be expected to inhibit contractions of vascular muscle induced by withdrawal of $[Mg^{2+}]_o$. Collectively, such data suggest that these cations are competing for surface binding sites at the smooth muscle cell membranes [7, 13, 18, 19], which are most likely, to some extent, normally occupied by Mg^{2+}.

If Mg^{2+} does compete with Ca^{2+} for binding sites then one should expect extracellular magnesium to influence tissue Ca content. Several studies do indeed support this hypothesis, e. g., 1) calcium-induced contractions of K^+-depolarized vascular muscles are sensitive to inhibition by elevated levels of $[Mg^{2+}]$, i. e., one observes increases in EC50's, and threshold concentrations with reductions in maximal tension [20, 21, 43, 121, 129]. The reverse is seen when $[Mg^{2+}]$ is lowered, i. e., $CaCl_2$-induced contractions are potentiated as is confirmed by the observed decreases in EC50's, threshold concentrations and increases in the maximal tensions [20, 21, 43, 121, 129]. 2) Acute reductions in $[Mg^{2+}]_o$ raise smooth muscle Ca content whereas acute elevations in $[Mg^{2+}]$ lower Ca content in several types of smooth muscle [10, 12, 20, 21, 64, 93]. These findings have been strengthened by recent experiments in which ^{45}Ca was utilized [20, 21, 31, 63, 117, 129]. Collectively, these newer experiments indicate that when $[Mg^{2+}]_o$ is lowered, ^{45}Ca influx (and intracellular content) is increased. The observation that high $[Mg^{2+}]_o$ decreases total exchangeable and membrane-bound Ca, without any effect on intracellular Ca, suggests that $[Mg^{2+}]_o$ can indeed displace and/or compete with Ca at smooth muscle cell membranes for some functional binding sites. Overall, these findings suggest that membrane Mg sites can act, physiologically, to control and regulate entry of Ca in smooth muscle.

Can $[Mg^{2+}]_o$ also influence exit of Ca^{2+} in smooth muscle cells? In order to test such an hypothesis, we loaded rat portal venous smooth muscle with ^{45}Ca in the presence of normal Krebs-Ringer bicarbonate containing $[Ca^{2+}]_o$ (2.5 mM) and $[Mg^{2+}]_o$ (1.2 mM) [20, 21]. After effluxing ^{45}Ca into normal Krebs, the tissues were effluxed into modified Krebs-Ringer bicarbonate containing either 0,1.2 or 9.6 mM Mg^{2+}. Such an experiment indicates that use of zero Mg^{2+}-Krebs enhances ^{45}Ca efflux considerably, while use of high Mg^{2+}-Krebs decreases ^{45}Ca efflux when compared to that observed in normal (1.2 mM) Mg^{2+}-Krebs [20, 21]. In other experiments, wie effluxed the ^{45}Ca into the three different Mg^{2+}-Krebs solutions from zero time after loading the cells with ^{45}Ca [20, 21]. These data add further support to our tenet and indicate that high $[Mg^{2+}]_o$ can exchange with cellular radiolabeled Ca from the beginning of the experiment in this tissue. These findings suggest that membrane [Mg] can affect exit of Ca^{2+} from vascular smooth muscle cells. Collectively, the data aquired so far, clearly indicate that $[Mg^{2+}]_o$ can control and regulate Ca^{2+} flux and content in several different types of smooth muscle. Whether such a mechanism extends to the resistance vessels, i. e., arterioles, will have to await further experimentation. If the latter does obtain, then one would have to consider the possibility that reciprocal changes in arteriolar and plasma Mg and Ca could take place pathophysiologically under a variety of conditions.

A Alternative and contributing mechanisms

The influence of Mg^{2+} could also, possibly, be explained in terms of an effect on the cyclic nucleotide system within the cells. Mg^{2+} is an activator of adenylate cyclase, an enzyme involved in the synthesis of adenosine 3', 5'-mono phosphate (cyclic AMP). There is some evidence, albeit controversial, to suggest that increased and decreased cyclic AMP concentrations participate in vasodilation and vasoconstriction, respectively [81]. A decrease in cyclic AMP in the absence of $[Mg^{2+}]_o$ could result in an increased concentration of free Ca^{2+} within the cytoplasm because there would be less cyclic AMP-mediated calcium sequestration. Thus, such a mechanism could, in part, be responsible for the increased tone and reactivity obtained in the absence of Mg^{2+}, provided of course, that intracellular $[Mg^{2+}]$ could fall far enough to influence cyclic AMP formation. It is also possible that $[Mg^{2+}]_o$ could exert some influence on resting membrane potentials [109, 110]. An alternative and contributing mechanism could be an inhibition of a Ca^{2+}-dependent adenosine-triphosphatase at the membrane that is Mg^{2+}-dependent and that presumably extrudes Ca^{2+} [100]. The reader should also consult recent reviews for a discussion of other, possible contributing mechanisms of action [20, 21, 26, 68].

B Evidence for modification of Mg-Ca exchange sites at diabetic and hypertensive vascular muscle membranes

Evidence is accumulating to suggest that structural changes can occur in arterial walls in the early stages of diabetes mellitus and several forms of hypertensive vascular disease which progressively increase as the diseases advance [24, 61]. Several types of arterial vessels from diabetic and hypertensive animals have been shown to contain an increased Ca content [24, 37, 61, 120]. This could, at least in part, result in the elevated vascular tone and contractility seen in these disease states. In 1942, Winkler and co-workers [131] reported that infusion of Mg^{2+} into patients with renal and eclamptic hypertension produced, in most cases, a lowering of blood pressure. Patients with essential hypertension are, however, in most cases resistant to the blood-pressure-lowering action of infusion of Mg^{2+} [89, 131]. Why doesn't Mg^{2+} infusion consistently lower blood pressure in subjects with essential hypertension? The effects of different forms of hypertensive diseases, both experimental and clinical, on vascular muscle Mg content and exchange is at the present time unclear [61].

In progressive diabetes mellitus, not only is there an increased loss of urinary Mg^{2+}, but, in addition, there have been numerous reports of a progressive plasma hypomagnesemia [24, 48, 103, 126]. Is the marked curtailment of local blood flow, arteriolar constriction, elevated vascular tone and high incidence of hypertension, noted in patients and animals with diabetes (for review see 24), causally related to the hypomagnesemic state and its effects on the vascular walls? Recent in vitro experiments, using alloxan-diabetic rats [123] and spontaneously hypertensive rats (SHR) [21, 23, unpublished findings], suggest that the altered vascular tone noted in these experimental animal models may, at least in part, be due to modification of Mg-Ca exchange sites at the vascular smooth musle cell membranes. Although a sudden withdrawal of $[Mg^{2+}]_o$ usually elicits potent contractions of normal rat aortae [7, 11, 13], aortae excised from either alloxan-diabetic rats or SHR exhibit weaker, or little (no more than $25-35\%$ of control), contractile responses to $[Mg^{2+}]_o$ withdrawal as the syndromes advance in severity [119]. Relaxation due to high $[Mg^{2+}]_o$ (4.8 mM) is seen in control aortae, not at all in diabetic aortae [119], and only somewhat in aortae of SHR [21]. Although diabetic portal veins from SHR exhibit basal contractile tensions than controls, the increased and decreased contractile tensions usually noted in response to withdrawal and elevation in Mg^{2+}, respectively, is not observed in either diabetic or SHR portal veins [121]. These data could indicate that in aortic smooth muscle of alloxan-diabetic rats and SHR: 1) membrane permeability to Ca^{2+} might be decreased, 2) cellular or membrane Ca is present in a more tightly bound form, and/or 3) the functional Mg-Ca exchange sites are either fewer in number or are altered.

Utilizing ^{45}Ca, it has been demonstrated recently that aortic smooth muscle from diabetic rats exhibited a progressive increase in both membrane and intracellular Ca content, from the first through eight weeks after treatment with alloxan [120]. Experiments with SHR also reveal a progressive, increased aortic smooth muscle uptake of ^{45}Ca and Ca content as the hypertensive syndrome advances with age of the animals [37]. In addition, Ca^{2+}-induced contractions of potassium-depolarized aortic smooth muscle of diabetic rats and SHR were decreased significantly [21, 119, unpublished findings]. It is well known that membrane stabilization by Ca^{2+} influences its own ability to permeate the membrane or to be released. Thus, collectively, these findings support our contention that in vascular smooth muscle from rats with experimental diabetes mellitus and spontaneous (essential?) hypertension, increased Ca^{2+} binding, coupled with a decreased membrane permeability to this divalent cation, probably limits the influence of withdrawal or lowering of $[Mg^{2+}]_o$.

Elevated $[Mg^{2+}]_o$ (4.8 mM) lowered basal tension significantly more in the control aortae compared to either the diabetic [119] or SHR aortae [21] and portal veins (unpublished data). High $[Mg^{2+}]_o$ significantly lowers membrane-bound Ca in rat aortae [21]. If the Ca present on the diabetic and SHR vascular membranes is tightly bound and cannot be released by Mg^{2+}, one would expect less degree of relaxation in the presence of high $[Mg^{2+}]$, which is what we observe [119]. Alternatively, the findings that $[Mg^{2+}]$ exerts less influence in basal tension of arterial and venous smooth muscle from diabetic rats and SHR could be due to fewer and/or altered functional Mg-Ca exchange sites at the diseased vascular muscle membranes [119]. Either of these mechanisms could explain why systemic infusion of $[Mg^{2+}]$ exerts little or variable effects on blood pressure of subjects with essential hypertension.

Conclusions

In summary, these data are consistent with the hypothesis that $[Mg^{2+}]_o$ and membrane Mg may exert a regulatory role in vascular tone, vascular reactivity or peripheral vascular resistance and may have an important functional role in control of Ca uptake, content, release and its distribution in striated and smooth muscle cells. Certain vascular disease states that are associated with a deficiency (e. g., sudden-death ischemic heart disease, diabetes mellitus, hypertension) or excess (e. g., circulatory shock, renal vascular disorders) in plasma and tissue Mg may be reflections of the direct vascular actions of the lack, or excess of, this metal, respectively.

References

[1] *Aikawa, J. K.:* The relationship of Magnesium to Disease in Domestic Animals and in Humans. Thomas, Springield (1971).

[2] *Altura, B. M.:* Influence of magnesium and cysteine on vasopressin-induced contractions in various canine blood vessels. Experientia **26**, 1089 – 1090 (1970).

[3] —: Chemical and humoral regulation of blood flow through the precapillary sphincter. Microrasc. Res. **3**, 361 – 384 (1971).

[4] —: Neurohypophyseal hormones and analogues: Magnesium dependence and contraction of arterial smooth muscle. Proc. Soc. Exp. Biol. Med. **148**, 1031 – 1037 (1975).

[5] —: Magnesium-neurohypophyseal hormone interactions in contraction of vascular smooth muscle. Am. J. Physiol. **228** 1615 – 1620 (1975).

[6] —: Pharmacology of venular smooth muscle: New insights. Microvasc. Res. **16**, 91 – 117 (1978).

[7] —: Magnesium withdrawal and rhythmic contractility of arterial vs. venous smooth muscle. Differential effects of multivalent cations and EDTA. Artery **4**, 512 – 517 (1978).

[8] —: Sudden-death ischemic heart disease and dietary magnesium intake; Is the target site coronary vascular smooth muscle? Med. Hypotheses **5**, 843 – 849 (1979).

[9] —: (ed.) Role of magnesium ions in regulation of muscle contraction. Am. Physiol. Soc. Symposium, Anaheim, Calif. (April 1980). Federation Proc., in press (1981).

[10] *Altura, B. M., B. T. Altura:* Influence of magnesium on drug-induced contractions and ion content in rabbit aorta. Am. J. Physiol. **220**, 938 – 944 (1971).

[11] *Altura, B. M., Altura, B. T.:* Magnesium and contraction of arterial smooth muscle. Microvasc. Res. **7**, 145 – 155 (1974).

[12] —;—: Magnesium-neurohypophyseal hormone interactions in contraction of arterial smooth muscle. In: Walter, R., J. Meienhofer (eds.) Peptides: Chemistry, Structure and Biology, Ann Arbor Science Publ., Ann Arbor p. 719 – 726 (1975).

[13] —; —: Magnesium withdrawal and contraction of arterial smooth muscle. Effects of EDTA, EGTA and divalent cations. Proc. Soc. Exp. Biol. Med. **151**, 752 – 755 (1976).

[14] —; —: Vascular smooth muscle and prostaglandins. Federation Proc. **35**, 2360 – 2366 (1976).

[15] —; —: Ouabain, membrane Na$^+$, K$^+$-ATPase and the extracellular action of magnesium ions in arterial smooth muscle. Artery **3**, 72 – 83 (1977).

[16] —; —: Extracellular magnesium and contraction of vascular smooth muscle. In: Casteels, R., Godfraind, T., Rüegg, J. C. (eds) Excitation-Contraction Coupling of Smooth Muscle, North-Holland Publ. Co., Amsterdam (1977).

[17] —; —: Vascular smooth muscle and neurohypophyseal hormones. Fed. Proc. **36**, 1853 – 1860 (1977).

[18] —; —: Magnesium and vascular tone and reactivity. Blood Vessels **15**, 5 – 16 (1978).

[19] —; —: Differential interactions of divalent and trivalent cations with magnesium ions in rhythmic contractility of arterial versus venous smooth muscle. In: Hemphill, D. D. (ed.), Trace Substances in Environmental Health-XIII, University of Missouri, Columbia p. 408 – 416 (1980).

[20] —; —: General anesthetics and magnesium ions as calcium antagonists on vascular smooth muscle. In: Weiss, G. B. (ed.) New Perspectives on Calcium Antagonists. Am. Physiol. Soc., Wash., D. C., in press (1981).

[21] —;— : Magnesium ions and contraction of vascular smooth muscles: Relationship to some vascular diseases. Federation Proc., in press (1981).

[22] *Altura, B. M., Altura, B. T., Waldemar, Y.:* Prostaglandin-induced relaxations and contractions of arterial smooth muscle: Effects of magnesium ions. Artery **2**, 326 – 336 (1976).

[23] *Altura, B. M., Carella, A., Altura, B. T.:* Magnesium ions control prostaglandin reactivity of venous smooth muscle from spontaneously hypertensive rats. Prostaglandins and Med. **4**, 255 – 262 (1980).

[24] *Altura, B. M., Halevy, S., Turlapaty, P. D. M. V.:* Vascular Smooth muscle in diabetes mellitus and its influence on reactivity of blood vessels. In: Davis, E., (ed.), The Microcirculation in Diabetes Mellitus, Karger, Basel p. 118 – 150 (1979).

[25] *Altura, B. T.:* Type-A behavior and coronary vasospasm: a possible role of hypomagnesemia. Med. Hypotheses **6**, 753 – 758 (1980).

[26] *Altura, B. T., Altura, B. M.:* Factors affecting vascular responsiveness. In: Kaley, G., Altura, B. M. (eds.), Microcirculation, Vol. II, University Park Press, Baltimore p. 547 – 615 (1978).

[27] —; —: Withdrawal of magnesium causes vasospasm while elevated magnesium produces relaxation of tone in cerebral arteries. Neuroscience Letters **20**, 323 – 327 (1980).

[28] —; —: Magnesium-calcium interactions and contraction of isolated arterial smooth muscle. In: *Cantin M., Seelig, M. S.* (eds.), Magnesium in Health and Disease, Spectrum Publications, New York, p. 703 – 711 (1980).

[29] —; —: Influence of magnesium on contractile activity in isolated rat arterial and venous muscle. In: *Cantin, M., Seelig, M. S.,* (eds.) Magnesium in Health and Disease, Spectrum Publications, New York p. 695 – 702 (1980).

[30] *Altura, B. T., Altura, B. M., Turlapaty, P. D. M. V.:* Magnesium modulates contractile reactivity of canine coronary, renal and intrapulmonary arteries to neurohumors and potassium ions. Brit. J. Pharmacol., submitted.

[31] —; —; —: Magnesium modulates calcium entry in coronary arterial smooth muscle. J. Mol. Cell. Cardiol. submitted.

[32] *Anderson, T. W., Leriche, W. H., Mackay, J. S.:* Sudden death and ischemic heart disease. Correlation with hardness of local water supply. New Engl. J. Med. **280**, 805 – 807 (1969).

[33] *Anderson, T. W., Neri, L. C., Schreiber, G. B., Talbot, F. D. F., Zdrojewski, A.:* Ischemic heart disease, water hardness and myocardial magnesium. Can. Med. J. **113**, 199 – 203 (1975).

[34] *Beecher, H. K., Simeone, F. A., Burnett, C. H., Shapiro, S. L., Sullivan, E. R., Mallory, T. B.:* Internal state of several wounded men on entry to most forward hospital. Surgery **22**, 672 – 711 (1947).

[35] *Behr, G., Burton, P.:* Heart-muscle magnesium. Lancet **2**, 450 (1973).

[36] *Beisel, W. R., Pekarek, R. S.:* Acute stress and trace element metabolism. Int. Rev. Neurobiol. Supl. **1**, 53 – 82 (1972).

[37] *Bhalla, R. C., Webb, R. C., Singh, D., Ashley, T., Brock, T.:* Calcium fluxes, calcium binding, and adenosine cyclic 3',5'-monophosphate-dependent protein kinase activity in the aorta of spontaneously hypertensive and Kyoto-Wistar normotensive rats. Mol. Pharmacol. **14**, 468 – 477 (1978).

[38] *Bendall, J. R.:* Muscles, Molecules and Movement. American Elsevier, New York (1969).

[39] *Bremel, R. D., Weber, A.:* Calcium binding to rabbit skeletal myosin under physiological conditions. Biochim. Biophys. Acta **376**, 366 – 374 (1975).

[39a] *Brinley, F. J., Scarpa, A., Tiffert, T.:* The concentration of ionized magnesium in barnacle muscle fibers. J. Physiol., London **266**, 545 – 565 (1977).

[40] *Burch, G. E., Giles, T. D.:* The importance of magnesium deficiency in cardiovascular disease. Am. Heart J. 94, 649 – 657 (1977).

[41] *Burton, R. F.:* Adenosine triphosphate as a determinant of magnesium in cytoplasm. Comp. Biochem. Physiol. 65A, 1 – 4 (1980).

[42] *Canepa, J. F., Gomez-Povina, O. A.:* Electrolyte changes in the ventricular myocardium following experimental haemorrhagic hypotension in dogs. J. Surg. Res. 5, 355 – 340 (1965).

[43] *Carrier, O., Jr., Hester, R. K., Jurevics, H. A., Tenner, T. E., Jr.:* Influence of magnesium on calcium- and potassium-related responses in vascular smooth muscle. Blood Vessels 13, 321 – 337 (1976).

[44] *Chipperfield, B., Chipperfield, J. R.:* Heart-muscle magnesium, potassium and zinc concentrations after sudden death from heart disease. Lancet 2, 293 – 295 (1973).

[45] —; —: Differences in metal content of the heart muscle in death from ischemic heart disease. Am. Heart J. 95, 732 – 737 (1978).

[46] *Chowrashi, P., Kaldor, G.:* Studies on the electrophoretic mobility of troponin in the presence of Ca^{++}, Mg^{++} and $(MgATP)^{2-}$. Proc. Soc. Exp. Biol. Med. 133, 969 – 972 (1970).

[47] *Crawford, T., Crawford, M. D.:* Prevalence and pathological changes of ischaemic heart-disease in a hard-water and in a soft-water area. Lancet 1, 229 – 232 (1967).

[48] *Cruikshank, D. P., Pitkin, R. M., Reynolds, W. A., Williams, G. A., Hargis, G. K.:* Altered maternal calcium homeostasis in diabetic pregnancy. J. Clin. Endocrinol. Metab. 50, 264 – 267 (1980).

[49] *Dagirmanjian, R., Goldman, H.:* Magnesium deficiency and distribution of blood in the rat. Am. J. Physiol. 218, 1464 – 1467 (1970).

[50] *Dawson, E. B., Frey, M. J., Moore, T. D., McGanity, W. J.:* Relationship of metal metabolism to vascular disease mortality rates in Texas. Am. J. Clin. Nutrition 31, 1188 – 1197 (1978).

[51] *Devine, C. E., Somlyo, A. V., Somlyo, A. P.:* Sacroplasmic reticulum and excitation-contraction coupling in mammalian smooth muscles. J. Cell. Biol. 52, 690 – 718 (1972).

[52] *Dileo, P.:* Rapporto tra modificaziono della potassemia e tasso di magnesio plasmatico nello stress. Boll. Soc. Ital. Biol. Sper. 44, 850 – 852 (1968).

[53] *Dixon, M., Webb, E. C.:* Enzymes, 2nd Ed. Academic Press, New York (1964).

[54] *Durlach, J.:* Neurological manifestations of magnesium imbalance. In: *Vinken, P. J., Bruyn, G. W.,* eds. **Handbook of Clinical Neurology, Vol. 28. Metabolic and Deficiency Diseases of the Nervous System.** North-Holland Publ. Co., Amsterdam, p. 545 – 579 (1976).

[55] *Ebashi, S.:* Calcium binding and relaxation in the actomyosin system. J. Biochem. 48, 150 – 151 (1960).

[56] *Ebashi, S., Endo, M.:* Calcium ion and muscle contraction. Progr. Biophys. Mol. Med. 18, 123 – 183 (1968).

[57] *Emerson, T. E., Jr., Scott, J. B., Haddy, F. J.:* Effects of acute multiple changes in plasma electrolyte levels on dog blood pressure. Am. J. Physiol. 218, 233 – 240 (1970).

[57a] *Endo, M.:* Mechanism of action of caffeine on the sarcoplasmic reticulum of skeletal muscle. Proc. Jap. Acad. 51, 479 – 484 (1975).

[58] *Featherstron, W. R., Morris, Jr., M. L., Phillips, P. H.:* Influence of lactose and dried skim milk upon the magnesium deficiency syndrome in the dog. I. Growth and biochemical data. J. Nutrition 79, 431 – 436 (1963).

[59] *Ford, L. E., Podolsky, R. J.:* Intracellular calcium movements in skinned muscle fibres. J. Physiol., London 223, 21 – 33 (1972).

[60] *Fujiwara, M., Kitagawa, H., Kurahashi, K.:* Effects of magnesium on contractile responses induced by electrical transmural stimulation and noradrenaline in rabbit thoracic aorta. Brit. J. Pharmacol. 63, 51 – 56 (1978).

[61] *Genest, J., E. Koiw, Kuchel, O.* eds.: Hypertension. McGraw-Hill Book Co., (1977).

[62] *Gillis, J. M., O'Brien, E. J.:* The effect of calcium ions on the structure of reconstituted muscle thin filaments. J. Mol. Biol. 99, 445 – 459 (1975).

[63] *Goldstein, S., Zsotér, T. T.:* The effect of magnesium on the response of smooth muscle to 5-hydroxyptamine. Brit. J. Pharmacol. 62, 507 – 514 (1978).

[64] *Goodford, P. J.:* The calcium content of the smooth muscle of guinea pig taenia coli. J. Physiol., London, 142, 145 – 157 (1967).

[65] *Gruda, J., Thérien, H.-M. Cermakian, E.:* The effects of calcium and magnesium ions on the secondary structure of calcium binding component of troponin. Biochem. Biophys. Res. Comm. 52, 1307 – 1313 (1973).

[66] *Günther, T., Averdunk, R., Ising, H.:* Biochemical mechanisms in magnesium deficiency. In: *Cantin, M. Seelig, M. S.,* eds. Magnesium in Health and Disease. Spectrum Publ., Holliswood p. 57 – 65 (1981).

[67] *Haddy, F. J., Scott, J. B.:* Mechanism of the acute pressor action of hypokalemia, hypomagnesemia, and hypoosmolality. Am. Heart J. 85, 655 – 661, (1973).

[68] *Haddy, F. J., Seelig, M. S.:* Magnesium and the arteries II. Physiologic effects of electrolyte abnormalities on arterial resistance. In: *Cantin, M. Seelig, M. S.,* eds. Magnesium in Health and Disease. Spectrum Publ., Holliswood p. 639 – 651 (1980).

[69] *Hall, R. C. W., Joffe, J. R.:* Hypomagnesemia. Physical and Psychiatric Symptoms. J.A.M.A. 224, 1749 – 1751 (1973).

[70] *Hasselbach, W., Makinose, M.:* Die Calciumpumpe der Erschlaffungsgrana" des Muskels und ihre Abhängigkeit von der ATP-spaltung. Biochem. Z. 333, 518 – 528 (1961).

[71] *Hasselbach, W., Fassold, E., Migala, A., Rauch, B.:* Magnesium dependence of sarcoplasmic reticulum calcium transport. Federation Proc., in press (1981).

[72] *Hazard, R., Wurmser, L.:* Action de sels de magnésium sur les vasoconstricteurs rénaux. C. Seance Soc. Biol. 110, 525 – 528 (1932).

[73] *Hochrein, H., Kuschke, H. J., Zagga, Q., Fahl, F.:* Das Verhalten der intracellularen Magnesium Konzentration im Myokard bei Insuffizienz, Hypoxie und Kammerflimmern. Klin. Wochenschr. 45, 1093 – 1096 (1967).

[74] *Huddart, H., Price, N. R.:* Calcium movements during excitation-contraction coupling in muscle cells. Comp. Biochem. Physiol. 54A, 375 – 386 (1976).

[75] *Huddart, H., Saad, K. H. M.:* The effect of sodium and magnesium and their interaction with quinine and lanthanum on spontaneous activity and related calcium movements of rat ileal smooth muscle. J. Comp. Physiol. 126, 233 – 240 (1978).

[76] *Hungerford, G. F., Bernick, S.:* Response of rat coronary arteries to dietary magnesium deficiency with and without cholesterolemia. In: *Cantin, M., Sellig, M. S.,* eds. Magnesium in Health and Disease. Spectrum Publications, Inc., Holliswood, p. 659 – 670 (1980).

[77] *Johns, A.:* The effect of magnesium-free solutions on the responses of the guinea pig urinary bladder to adenosine 5'-triphosphate and nerve stimulation. Can. J. Physiol. Pharmacol. 57, 1320 – 1323 (1979).

[78] *Johnson, C. J., Peterson, D. R., Smith, E. K.:* Myocardial tissue concentrations of magnesium and potassium in men dying suddenly from ischemic heart disease. Am. J. Clin. Nutrition. 32, 967 – 970 (1979).

[79] *Karpanen, H., Pennanen, R., Passinen, L.:* Minerals, coronary heart disease and sudden coronary death. Adv. Cardiol. 25, 9 – 24 (1978).

[80] *Kirk, J. E.:* Enzymes of the Arterial Wall: Academic Press, New York (1969).

[81] *Kramer, G. L., Hardman, J. G.:* Cyclic nucleotides and blood vessel contraction. In: *Bohr, D. F., Somlyo, A. P.,*

Sparks, H. V., eds. Handbook of Physiology, Circulation, Vol. 2 Williams and Wilkins, Baltimore, p. 179–199 (1980).

[82] *Lefkowitz, B. S., Goldson, H., Rashkin, A., Kay, H., Valcin, A., Mathur, A., Laguerre, J. N.:* Magnesium ion blockade of regional vasoconstriction. Ann. Surgery 172, 33–40 (1970).

[83] *Lehr, D., Blaiklock, R., Brown, A.:* Magnesium loss as a reliable measure of acute myocardial injury. In: *Cantin, M., Seelig, M. S.*, eds., Magnesium in Health and Disease, Spectrum Publications, Inc., Holliswood, p. 499–506 (1980).

[84] *Marier, J. R.:* Cardio-protective contribution of hard waters to magnesium in-take. Rev. Can. Biol. 37, 115–125 (1978).

[85] *Marier, J. R., Neri, L. C., Anderson, T. W.:* Water hardness, human health, and the importance of magnesium. Nat. Research Council Canada Publi. No. 17581, 1–119 (1979).

[86] *McNair, P., Christiansen, C., Madsbad, S., Lauritzen, E., Faber, O., Binder, C., Transbil, I.:* Hypomagnesemia, a risk factor in diabetic retinopathy. Diabetes 27, 1075–1077 (1978).

[87] *Mellander, S., Johansson, B.:* Control of resistance, exchange, and capacitance functions in the peripheral circulation. Pharmacol. Rev. 20, 117–196 (1968).

[88] *Mordes, J. P., Swarz, R., Orky, R. A.:* Extreme hypermagnesemia as a cause of refractory hypotension. Ann. Int. Med. 83, 657–658 (1975).

[89] *Mordes, J. P., Wacker, W. E. C.:* Excess magnesium. Pharmacol. Rev. 29, 273–300 (1978).

[90] *Murphy, R. A.:* Structural proteins in the myofilaments and regulation of contraction in vertebrate smooth muscle. Federation Proc. 35, 1302–1306 (1976).

[91] *Osa, T.:* Effects of magnesium and temperature during the recovery process from the potassium contracture of the pregnant rat myometrium. Kap. J. Physiol. 25, 185–199 (1975).

[92] *Page, E., Polimeni, P. I.:* Magnesium exchange in rat ventricle. J. Physiol., London 224, 121–139 (1972).

[93] *Palatý, V.:* Distribution of magnesium in the arterial wall. J. Physiol. London 218, 353–368 (1971).

[94] —: Regulation of the cell magnesium in vascular smooth muscle. J. Physiol. London 242, 555–569 (1974).

[95] *Peterson, B.:* Serum and erythrocyte magnesium in normal elderly Danish people. Relationsship to blood pressure and serum lipids. Acta Med. Scand. 201, 31–34 (1977).

[96] *Paul, R. J., Rüegg, C. J.:* Biochemistry of vascular smooth muscle: Energy metabolism and proteins of the contractile apparatus. In: *Kaley, G., Altura, B. M.*, eds. Microcirculation, Vol. 2, University Park Press, Baltimore, p. 41–82 (1980).

[97] *Polimeni, P. I., Page, E.:* Magnesium in heart muscle. Circulation Res. 33, 367–374 (1973).

[98] *Potter, J. D., Gergely, J. J.:* The calcium and magnesium binding sites on troponin and their role in the regulation of myofibrillar adenosine triphosphatase J. Biol. Chem. 250, 4628–4633 (1975).

[99] *Potter, J. D., Robertson, S. P., Johnson, J. D.:* Magnesium and the regulation of muscle contraction. Federation Proc., in press (1981).

[100] *Popescu, L. M.:* Cytochemical study of the intracellular calcium distribution in smooth muscle. Surface microvesicles and cellular calcium homeostasis. In: *Casteels, R., Godfraind, T., Rüegg, J. C.*, eds. Excitation-Contraction Coupling in Smooth Muscle. Elsevier/North-Holland, Amsterdam, p. 13–23 (1977).

[101] *Scarpa, A., Brinley, F. J.:* In situ measurements of free cytosolic Mg. Federation Proc., in press (1981).

[102] *Seelig, M. S.:* Magnesium deficiency with phosphate and vitamin D excess: Role in pediatric cardiovascular disease? Cardiovasc. Med. 3, 637–650 (1978).

[103] —: Magnesium Deficiency in the Pathogenesis of Disease. Plenum, New York (1980).

[104] *Seelig, M. S., Haddy, F. J.:* Magnesium and the arteries. I. Magnesium deficiency, arterial lesions, and electrolyte retention. In: *Cantin, M., Seelig, M. S.*, eds. Magnesium in Health and Disease. Spectrum Publications, Holliswood, p. 605–638 (1980).

[105] *Shepherd, J. T., Vanhoutte, P. M.:* Veins and Their Control. Saunders, Co., Philadelphia (1975).

[106] *Shibata, N., Hollander, W.:* Calcium uptake, ATPase and relaxing activity of arterial micorsomal vesicles. Fed. Proc. 26, 598 (1967).

[107] *Shine, I. I.:* Myocardial effects of magnesium, Am. J. Physiol. 237, H413–H423 (1979).

[108] *Shoenberg, C. F., Needham, D. M.:* A study of the mechanism of contraction in vertebrate smooth muscle. Biol. Rev. 51, 53–104 (1976).

[109] *Siegel, G., Walter, A., Gustavsson, H., Lindman, B.:* Magnesium and membrane fuction in vascular smooth muscle. Artery, in press (1981).

[110] *Sigurdsson, S. B., Uvelius, B.:* The effects of variations in extracellular magnesium concentration on electrical and mechanical activity in rat portal vein. Acta Physiol. Scand. 99, 368–376 (1977).

[111] *Sobieszek, A., Small, J. V.:* Myosin-linked calcium regulation in vertebrate smooth muscle. J. Mol. Biol. 101, 75–92 (1976).

[112] *Somlyo, A. P., Somlyo, A. V.:* Vascular smooth muscle, I. Pharmacol. Rev. 20 197–272 (1968).

[113] —; —: Vascular smooth muscle. II. Pharmacol. Rev. 22, 249–353 (1970).

[114] —; —: Effects and subcellular distribution of magnesium in smooth and striated muscles. Federation Proc., in press (1981).

[115] *Somlyo, A. V., Woo., C., Somlyo, A. P.:* Effect of magnesium on posterior pituitary hormone on vascular smooth muscle. Am. J. Physiol. 210, 705–714 (1966).

[115a] *Speich, M., Bousquet, B., Nicolas, G.:* Concentrations of magnesium, calcium, potassium, and sodium in human heart muscle after acute myocardial infarction. Clin. Chem. 26, 1662–1665 (1980).

[116] *Szelényi, I.:* Magnesium and its significance in cardiovascular and gastrointestinal disorders. World Rev. Nutr. Diet. 17, 189–224 (1973).

[117] *Turlapaty, P. D. M. V., Altura, B. M.:* Extracellular magnesium ions control calcium exchange and content of vascular smooth muscle. Eur. J. Pharmacol. 52, 421–423 (1978).

[118] —; —: Magnesium deficiency produces spasms of coronary arteries: Relationship to etiology of sudden death ischemic heart disease. Science 208, 198–200 (1980).

[119] —; —: Magnesium ions and contractions of alloxandiabetic vascular muscle. Artery 6, 375–384 (1980).

[120] *Turlapaty, P. D. M. V., Altura, B. T., Altura, B. M.:* Ca^{2+} uptake and distribution in alloxan-diabetic rat arterial and venous smooth muscle. Experientia 36, 1298–1299 (1980).

[121] —; —; —: Influence of magnesium on responses of coronary arteries to vasoactive agents. Federation Proc. 40, Part I, 563 (1980).

[122] *Turlapaty, P. D. M. V., Carrier, O., Jr.:* Influence of magnesium on calcium-induced responses of atrial and vascular muscle. J. Pharmacol. Exp. Ther. 187, 86–98 (1973).

[123] *Turlapaty, P. D. M. V., Lum, G., Altura, B. M.:* Vascular responsiveness and serum biochemical parameters in alloxan-diabetes mellitus. Am. J. Physiol. 239, E412–421 (1980).

[124] *Valencic, F., Dodich, B. N., Hill, O. A., Strain, W. H.,*

Pories, W. J., Flynn, A.: Arterial-venous magnesium gradients in hypovolemic shock: An indication of the irreversible state. Proc. Soc. Exp. Biol. Med. **150**, 660—663 (1975).

[125] *Viveros, H., Somjen, G. G.:* Magnesium-calcium antagonism in the contraction of arterioles. Experientia **24**, 457—459 (1968).

[126] *Wacker, E. C.:* Magnesium and Man. Harvard Univ. Press. Cambridge (1980).

[127] *Walling, M. W., Favus, M. J., Kimberg, D. V.:* Effect of magnesium deficiency and thyroparathyroidectomy on calcium active transport by rat duodenum. Proc. Soc. Exp. Biol. Med. **148**, 1038—1043 (1975).

[128] *Weber, A.:* The mechanism of the action of caffeine on sarcoplasmic reticulum. J. Gen Physiol. **52**, 760—772 (1968).

[129] *Weiner, R., Turlapaty, P., Altura, B. M.:* Influence of extracellular magnesium on contractility and calcium uptake in venous smooth muscle. Federation Proc. **38**, 1136 (1979).

[130] *Whang, R., Welt, L. F.:* Observations in experimental magnesium depletion. J. Clin. Invest. **42**, 305—313 (1968).

[131] *Winkler, A. W., Smith, P. K., Hoff, H. E.:* Intravenous magnesium sulfate in the treatment of nephritic convulsions in adults. J. Clin. Invest. **21**, 207—216 (1942).