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Archives of Biochemistry and Biophysics xxx (2006) xxx–xxx
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Role of magnesium in hypertension

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Received 28 March 2006

Abstract

Magnesium affects blood pressure by modulating vascular tone and reactivity. It acts as a calcium channel antagonist, it stimulates production of vasodilator prostacyclins and nitric oxide and it alters vascular responses to vasoactive agonists. Magnesium deficiency has been implicated in the pathogenesis of hypertension with epidemiological and experimental studies demonstrating an inverse correlation between blood pressure and serum magnesium levels. Magnesium also influences glucose and insulin homeostasis, and hypomagnesemia is associated with metabolic syndrome. Although most epidemiological and experimental studies support a role for low magnesium in the pathophysiology of hypertension, data from clinical studies have been less convincing. Furthermore, the therapeutic value of magnesium in the management of hypertension is unclear. The present review addresses the role of magnesium in the regulation of vascular function and blood pressure and discusses the implications of magnesium deficiency in experimental and clinical hypertension, in metabolic syndrome and in pre-eclampsia.

Keywords: Calcium cations; Minerals; Blood pressure; Vascular smooth muscle; Metabolic syndrome; Pre-eclampsia; Magnesium sulfate

Magnesium is an essential element critically involved in cardiac and vascular function. At the subcellular level, magnesium regulates contractile proteins, modulates transmembrane transport of calcium (Ca^{2+}), sodium (Na^{+}) and potassium (K^{+}), acts as an essential cofactor in the activation of ATPase, controls metabolic regulation of energy-dependent cytoplasmic and mitochondrial pathways and influences DNA and protein synthesis [1,2]. Small changes in extracellular Mg^{2+} levels ($[Mg^{2+}]_e$) and/or intracellular free Mg^{2+} concentration ($[Mg^{2+}]_i$) have significant effects on cardiac excitability and on vascular tone, contractility, reactivity, and growth [3,4]. Thus, magnesium, through its cardiovascular actions, may be physiologically important in blood pressure regulation whereas changes in magnesium levels could contribute to the pathophysiology of hypertension.

Many studies support a role for magnesium deficiency in the development of hypertension, with reports demonstrating, for the most part, an inverse correlation between body magnesium levels and blood pressure, hypotensive actions of dietary magnesium supplementation and hypertensive effects of magnesium deficiency [5–8]. Mechanisms underlying these processes probably relate to magnesium effects on vascular tone and reactivity. However, the therapeutic value of magnesium in the management of hypertension is unclear, with results from clinical trials being heterogeneous and inconsistent [9]. The present review discusses the role of magnesium in the regulation of vascular function in relation to hypertension. In addition, alterations in magnesium homeostasis in the pathogenesis of hypertension and metabolic syndrome will be considered. Finally, the putative role of magnesium as a therapeutic modality in the management of hypertension will be discussed. Magnesium regulates many systems in the body, however, the present review focuses specifically on the vascular system and implications in hypertension.

Regulation of vascular function by magnesium

Magnesium influences blood pressure regulation by modulating vascular tone and reactivity. The direct

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doi:10.1016/j.abb.2006.05.005

vascular effect of magnesium was first suggested in the early 1900s when it was observed in clinical studies that magnesium salt infusion lowers blood pressure via a reduction in peripheral vascular resistance [10] in spite of a slight increase in myocardial contractility [11]. Experimental studies support these clinical observations and confirm that acute magnesium administration induces hypotension through vasodilatory actions [12,13]. Increased concentrations of extracellular magnesium cause vasodilation, improve blood flow, decrease vascular resistance, increase capacitance function of peripheral, coronary, renal, and cerebral arteries, and attenuate agonist-induced vasoconstriction, whereas, decreased concentrations cause contraction, potentiate agonist evoked vasoconstriction, and increase vascular tone [3,4,14,15]. Exact molecular mechanisms underlying magnesium vascular actions are unclear, but magnesium probably influences intracellular free Ca^{2+} concentration ($[Ca^{2+}]_i$), which is fundamental in myocardial regulation, endocrine and renal secretion, and smooth muscle contraction. In vascular smooth muscle cells, magnesium antagonizes Ca^{2+} by inhibiting transmembrane calcium transport and calcium entry. It also acts intracellularly as a calcium antagonist thereby modulating the vasoconstrictor actions of $[Ca^{2+}]_i$, a major determinant of vascular contraction [16–19]. Low magnesium causes an increase in $[Ca^{2+}]_i$ with associated vascular contraction and increased tone.

Since $[Mg^{2+}]_i$ influences many enzymes in the signal transduction pathways involved in vascular contraction, low $[Mg^{2+}]_i$ could have important implications in vascular smooth muscle cell function in hypertension. Intracellular magnesium depletion has been demonstrated in many tissues (heart, lungs, kidney, bone, and muscle) and cell types (vascular smooth muscle cells, fibroblasts, erythrocytes, platelets, and lymphocytes) in both human and experimental hypertension [5,20–24]. Underlying mechanisms for cellular magnesium changes in hypertension are unclear, but magnesium-deficient states, decreased membrane permeability, altered Na^+–Mg^{2+} exchange, defective membrane binding as well as altered cellular responsiveness have been implicated [24–27]. We recently suggested that altered activity of vascular TRPM6/7, the major transcellular magnesium transporter, may also play a role in cellular magnesium deficiency in hypertension [28,29].

Endothelial effects of magnesium

Magnesium influences vascular tone, in part, by modulating endothelial function [30]. The vascular endothelium plays a fundamental role in the regulation of vasomotor tone by releasing nitric oxide (NO),[1] endothelin-1 (ET-1), cyclo-oxygenase-derived prostanoid(s) such as prostacyclin (PGI_2), and endothelial-derived hyperpolarizing factor. Magnesium stimulates prostacyclin production and NO formation and it modulates endothelium-dependent and endothelium-independent vasodilation [31–33]. An acute reduction of extracellular magnesium leads to a transient vasorelaxation followed by a sustained constriction. In the presence of endothelial damage, low magnesium induces a sustained contraction without the transient vasorelaxation phase [34,35], suggesting that magnesium could have a dual effect in the regulation of vascular reactivity, depending on the integrity of the endothelium. An intact endothelium prevents against the detrimental effects of acute hypomagnesemia, whereas in the presence of an injured endothelium, as is the case in many cardiovascular diseases, the compensatory vasodilatory effect is absent and low magnesium promotes constriction [36]. The endothelium-dependent relaxation observed after acute magnesium withdrawal seems to be related to Ca^{2+}-dependent release of NO [36–38]. In streptozotocin-induced diabetic rats, magnesium modulates endothelial function through NO-independent mechanisms [33,39]. Landau et al. recently demonstrated that magnesium induces dose-dependent endothelium-dependent venodilation in healthy women independent of systemic hemodynamic effects [32].

Magnesium and vasoactive agents

Magnesium also modulates vascular tone and reactivity by altering responses to vasoconstrictor and vasodilator agents. Increased extracellular magnesium concentration attenuates vasoconstrictor actions and potentiates vasorelaxant properties of many vasoactive agents [39]. These effects may be related to altered binding of agonists to their specific cell membrane receptors and/or to production of vasoactive agents such as ET-1 and angiotensin II (Ang II), potent vasoconstrictors, and prostacyclin (PGI_2), a vasodilator [31,40,41]. In magnesium-deficient rats, plasma ET-1 levels are elevated, whereas in magnesium-supplemented rats, plasma ET-1 levels are reduced [42,43]. Increased magnesium attenuates ET-1-induced contraction whereas reduced magnesium levels augment ET-1-stimulated contraction [44]. Increased magnesium levels stimulate endothelial release of vasodilator PGI_2 from human umbilical arteries and cultured umbilical vein endothelial cells [45,46]. These effects may be particularly relevant in $MgSO_4$ treatment of eclampsia and pre-eclampsia [47]. Interactions between magnesium and neural function could also impact on blood pressure regulation. Shimosawa et al. recently reported that magnesium inhibits norepinephrine release from nerve endings, which decreases blood pressure independent of its direct vasodilating action [48].

Another possible mechanism whereby magnesium could modulate vascular function is via its antioxidant and anti-inflammatory actions [49,50]. There is increasing evidence that the vasculature is a rich source of reactive oxygen species, which directly alters vascular smooth muscle cell contraction and growth [51,52]. Magnesium has antioxidant/anti-inflammatory properties that could attenuate damag-

[1] *Abbreviations used:* NO, nitric oxide; ET-1, endothelin-1; PGI_2, prostacyclin; Ang II, angiotensin II ARIC, atherosclerosis risk in communities PRA, plasma renin activity TOHP, trial of hypertension prevention.

ing actions of oxidative stress on the vasculature, thereby preventing vascular injury. These effects may be important in hypertension, where generation of reactive oxygen species is increased and $[Mg^{2+}]_i$ is reduced [53].

Magnesium and experimental hypertension

Hypomagnesemia and decreased tissue content of magnesium have been demonstrated in various experimental models of hypertension [54–57]. $[Mg^{2+}]_i$ is lower in isolated cardiomyocytes, striated and vascular smooth muscle cells, as well as in circulating cells from SHR and DOCA-salt hypertensive rats compared to normotensive controls [58,59]. In experimental models with severe hypertension, such as stroke-prone SHR and DOCA-treated SHR, $[Mg^{2+}]_i$ is negatively and $[Ca^{2+}]_i$ is positively correlated with systolic blood pressure, while $[Mg^{2+}]_i$ and $[Ca^{2+}]_i$ are inversely associated [60,61] suggesting that $[Mg^{2+}]_i$ may be involved in blood pressure regulation by competing with calcium effects. Mechanisms underlying magnesium deficiency in experimental hypertension are unclear, but could relate to altered intestinal magnesium absorption [62], defective cellular magnesium handling and increased renal magnesium loss [63–65].

Long-term magnesium deficiency in experimental animals potentiates responses to vasoconstrictor agents, attenuates responses to vasodilator agents, increases vascular tone and elevates blood pressure [66,67]. Some of these effects may be due to endothelial dysfunction, as reported in DOCA-salt hypertensive rats [68]. Magnesium deficiency is associated with vascular structural changes, including decreased lumen diameter and increased media-to-lumen ratio, indicative of medial hypertrophy and vascular remodeling, which are characteristic features of vascular changes in hypertension [69]. Hypomagnesemia also promotes vascular inflammation and oxidative stress in hypertension, which are ameliorated by antioxidant treatment [70].

Blood pressure lowering effects of magnesium supplementation have been shown in some, but not all, models of hypertension. In DOCA-salt hypertension and in cyclosporin-induced hypertension, magnesium supplementation attenuates the development of hypertension [71,72] whereas in adult SHR with established hypertension, magnesium supplementation has little blood pressure-lowering effect [73,74]. However, dietary magnesium loading during the prehypertensive and the developing stages of hypertension in SHR prevents the rise in blood pressure [75,76]. These data suggest that oral magnesium may be beneficial in preventing further blood pressure elevation if magnesium is given at a critical period during the development of hypertension.

Magnesium and human hypertension

Epidemiologic studies have linked hypertension and cardiac disease with ‘soft water’, low in magnesium, and protection against cardiovascular disease with ‘hard water’, high in magnesium. The relationship between dietary magnesium intake and blood pressure in humans was first demonstrated in the Honululu Heart study [77], and later by many epidemiological and clinical investigations that supported the hypothesis that increased magnesium intake contributes to prevention of hypertension and cardiovascular disease [77–80]. Data from well conducted, large, prospective studies on nutrition and blood pressure in US and Dutch populations, reported that magnesium-rich diets may reduce blood pressure levels, especially in older individuals [81,82]. A large retrospective study which assessed magnesium and calcium content in drinking water in subjects who died from hypertension (2336) compared with those who died from other causes (2336) demonstrated that magnesium levels in drinking water were inversely related to the risk of death from hypertension [83]. Results from the large cross-sectional Atherosclerosis Risk in Communities (ARIC) study on 15,000 middle-aged Americans demonstrated a negative correlation of dietary and serum magnesium levels to both systolic and diastolic blood pressure [84]. These epidemiologic studies together with experimental evidence suggest physiological relationships between Mg^{2+} and blood pressure and pathophysiological associations between Mg^{2+} deficiency and hypertension.

Clinical studies have shown, for the most part, some form of hypomagnesemia (serum and/or tissue) in hypertensive patients, with significant inverse correlations between magnesium concentration and blood pressure. A relationship has also been described between the renin–angiotensin system, magnesium and blood pressure. High renin hypertensive patients have significantly lower serum magnesium levels than normotensive subjects [85] and serum magnesium is inversely associated with plasma renin activity (PRA) [85]. Since increased PRA indicates activation of the renin–angiotensin system, it may be possible that Ang II-dependent hypertension is associated, at least in part, with vascular and cardiac effects of hypomagnesemia. Recent studies have also reported a negative dependency between $[Mg^{2+}]_i$ and arterial compliance in humans, the lower the $[Mg^{2+}]_i$, the stiffer the blood vessels and the greater the blood pressure [86]. Underlying causes for altered magnesium metabolism in hypertension are unclear, but genetic, dietary, hormonal factors or drugs could play a role.

Not all clinical investigations reported magnesium depletion in hypertension. Some studies found no differences in serum magnesium levels or in $[Mg^{2+}]_i$ in hypertensive patients [87,88], while others reported increased erythrocyte $[Mg^{2+}]_i$ in patients with essential hypertension [89,90]. Furthermore, a few epidemiological studies failed to show an association between magnesium intake and blood pressure or cardiovascular disease [78,91]. It is evident that not all hypertensive patients are hypomagnesaemic, and not all patients with magnesium deficiency are hypertensive.

Despite the inconsistencies in the literature regarding magnesium status in hypertension, there are subgroups of hypertensive patients who consistently demonstrate altered

magnesium metabolism. These include, individuals of African descent, obese patients, patients with severe or malignant forms of hypertension and those with metabolic syndrome [92–94]. These patients may be magnesium-sensitive and potentially could benefit from magnesium supplementation.

Magnesium and metabolic syndrome

Metabolic syndrome is an atherogenic cardiovascular risk factor, defined by the co-occurrence of at least two of the following characteristics: hyperglycemia, hypertension, dyslipidemia, and obesity [95]. Hypomagnesemia is a common feature in subjects with hyperlipidemia, hypertension, and type 2 diabetes mellitus [96,97]. Patients with metabolic syndrome have low serum magnesium levels [98] and intracellular magnesium deficiency [97,99]. Song et al. reported that magnesium intake is inversely associated with systemic inflammation and the prevalence of metabolic syndrome in middle-aged and older women [100]. In line with this, Lifton and colleagues recently identified a group of patients who have a cluster of metabolic defects, including hypertension, dyslipidemia, and severe hypomagnesemia. This syndrome has been attributed to a mutation in a mitochondrial tRNA [101]. To further support a relationship between magnesium and metabolic syndrome, findings from the CARDIA study showed that a magnesium rich-diet may help reduce the risk of metabolic syndrome and, perhaps, a heart attack or diabetes [102].

Magnesium and pre-eclampsia

Pre-eclampsia, defined as hypertension after 20 weeks of gestation, with proteinuria, has been treated with magnesium salts since the turn of the century. The cause of pre-eclampsia remains unclear but it is thought that endothelial dysfunction or damage could be important [103]. Magnesium has been shown to improve endothelial function in pre-eclampsia. This may be due to the direct vasodilatory properties of magnesium and/or to the ability of magnesium to stimulate release of the endothelial vasodilator prostacyclin, which induces vasodilation as well as inhibits platelet adherence and aggregation [104,105].

Data relating to serum magnesium concentrations in pre-eclampsia are conflicting, with some studies failing to demonstrate any differences between pre-eclampsia and uncomplicated pregnancy [106,107] and others reporting decreased serum and intracellular magnesium levels [108]. Some investigations found total magnesium levels to be higher in pre-eclamptic women [109]. Reasons for these differences are unclear, but heterogeneity of populations studied may be important. Although the exact role of magnesium in the pathogenesis of pre-eclampsia remains obscure, it has been suggested that magnesium can be used as a predictive tool for pre-eclampsia. Standley et al. [110] studied the magnesium levels at different gestational ages. They found that magnesium decreases in both preclamptic and uncomplicated pregnancies, but that the magnesium concentration was lowered earlier in women with pre-eclampsia. This difference has been proposed as a marker of severity of the condition.

Magnesium is the most frequently used treatment in the management of pre-eclampsia and eclampsia in the USA [111–113]. In fact with the recent findings of the Magpie trial, which demonstrated that magnesium sulfate halves the risk of eclampsia, and probably reduces the risk of maternal death, magnesium sulfate is now considered the therapy of choice in the management of pre-eclampsia and eclampsia [114].

The therapeutic role of magnesium in hypertension

The therapeutic value of magnesium in the treatment of clinical hypertension was suggested in 1925 when magnesium infusion was found to improve malignant hypertension [10]. Since then many investigations have supported a putative role for magnesium in the treatment of hypertension. Considering the inexpensive nature of the agent, and the fact that it is easy to handle, magnesium is theoretically an excellent agent in the routine management of hypertension. However, this is not so in clinical medicine. In general, data from clinical trials of magnesium therapy in hypertension have been disappointing. Some studies reported significant blood pressure-lowering effects of oral or intravenous magnesium treatment [115–117] and magnesium supplementation to patients already receiving diuretics or other antihypertensive agents appears to reduce blood pressure further [118,119]. However, other trials failed to demonstrate any hypotensive action of magnesium supplementation [87,88] and results from the Trial of Hypertension Prevention (TOHP) showed no benefit of magnesium therapy in 698 patients followed for 6 months [120]. The inconsistency in results may be due to the number of studies that were small or of short duration, differing treatment protocols, variable forms of magnesium salts used, different concentrations of magnesium supplemented and the heterogeneity of the population of hypertensives investigated. Studies that have consistently shown a beneficial effect of magnesium treatment were performed in black patients, those with established hypomagnesemia, those with diuretic-associated hypertension, and in patients where magnesium was supplemented long term [121,122]. Also, in many forms of secondary hypertension as well as in pre-eclampsia, magnesium is therapeutically effective in lowering blood pressure [123,124]. Thus, although this cation may not be a universally effective antihypertensive agent, it does seem to benefit a subgroup of patients with hypertension.

Conclusions

Increasing evidence indicates that low magnesium may play a pathophysiological role in the development of hypertension. Recent studies demonstrate that magnesium defi-

ciency is also associated with the metabolic syndrome. Magnesium normally regulates vascular tone and reactivity by modulating intracellular Ca^{2+}, Na^{+}, K^{+}, and pH_i, important in the processes that regulate vascular smooth muscle contraction and relaxation. At the vascular level, reduced magnesium concentrations are associated with endothelial dysfunction, increased vascular reactivity, increased vascular tone, and elevated blood pressure, whereas increased magnesium levels are associated with opposite effects. Despite sound epidemiological and experimental data supporting a role for low magnesium in the pathogenesis of hypertension, clinical observations, and clinical trials have provided controversial and often conflicting results. Moreover, the therapeutic value of magnesium in the management of hypertension is still unclear. Before making definitive therapeutic recommendations on the use of magnesium in the management of hypertension, well controlled, long-term therapeutic trials, in carefully characterized hypertensive patients are need. However, the potential benefits of magnesium are recognized and the current European, American, Canadian, and International guidelines have included maintenance of adequate dietary magnesium intake as a recommendation for life-style modifications for hypertension prevention management [125,126]. With new methodologies to accurately measure extracellular and intracellular magnesium concentrations and the growing interest in the biology of magnesium, the time is now ripe for the progression of experimental magnesium research to extend to the clinical milieu where the exact role of magnesium in the pathophysiology of cardiovascular diseases, such as hypertension, can be studied in human patients.

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