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Calcium, Hypertension and Target Organ Damage: from prevention to regression

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Abnormalities in the metabolism of the electrolytes, magnesium, potassium, and calcium have been associated as etiologic factors in systemic hypertension, ischemic heart disease, congestive heart failure, atherosclerosis, diabetes mellitus and arrhythmia. An increasing body of evidence suggests a critical role of calcium metabolism in the pathogenesis of hypertensive disease.

Several studies have reported that long-acting calcium channel blockers can improve some elements of the continuum cardiovascular such as: glucose tolerance, lower insulin levels and potential effect in plaque-stabilization properties.

The propose of this article consist in review the alterations of metabolism of calcium and his role in the pathogenesis of hypertension. Also we will discuss on the potential beneficial role for a calcium antagonist in the treatment on atherosclerosis, beyond of the antihypertensive action.

Key Words: Calcium metabolism, primary hypertension, calcium channel blockers, atherosclerosis
Both deficiency states and abnormalities in the metabolism of the electrolytes, magnesium, potassium, and calcium have been associated as etiologic factors in systemic hypertension, ischemic heart disease, congestive heart failure, atherosclerosis, diabetes mellitus and arrhythmia. Replacement and supplementation of these substances in experimental animals have been shown to both prevent and treat these cardiovascular conditions.\(^1\)

Alterations in the metabolism of calcium (Ca\(^{2+}\)) and magnesium (Mg\(^{2+}\)) have been implicated in the pathogenesis of primary hypertension. Calcium influx across the external cellular membrane in smooth muscle cells and cardiomyocytes plays a crucial role in the control of cellular excitation contraction and impulse propagation. Intracellular calcium and magnesium concentrations are controlled by reversible binding to specific calcium-binding proteins.\(^2,3,4\)

Several studies have reported that long-acting calcium channel blockers (CCBs), can improve some elements of the continuum cardiovascular such as: glucose tolerance, lower insulin levels and potential effect in plaque-stabilization properties.\(^5\)

In this article, alterations of metabolism of calcium and his role in the pathogenesis of hypertension will be reviewed. Also we will discuss on the cellular and molecular mechanisms of action that may contribute to a beneficial role for a calcium antagonist in the treatment on atherosclerosis, beyond of the antihypertensive action.

An increasing body of evidence suggests a critical role of calcium metabolism in the pathogenesis of hypertensive disease. The calcium and magnesium flux across the external membrane is regulated by a calcium pump (calcium-magnesium-ATPase), calcium channels, and binding to the membrane. In cell membranes and in lymphocytes of essential hypertensives have been showed increased calcium and decreased magnesium and increased calcium/magnesium ratio in hypertensive cells.\(^4\)

Several investigators observed complex disturbances of Ca metabolism in animal models, cell cultures an patients with hypertension. The role of increased intracellular free Ca\(^{2+}\) concentrations in the development and pathogenesis of primary hypertension has been extensively studied.\(^5,6\) Increased concentrations of free calcium found within the cytosol of vascular smooth-muscle cells are thought to be responsible for the increased contractility of vessels in hypertension.

The role of calcium in hypertension may be approached in four ways:

- The relations between serum calcium levels and blood pressure
- The effect of dietary and supplemental calcium on blood pressure
- The renal excretion of calcium and serum parathyroid hormone (PTH) levels in patients with hypertension.
- The role of calcium ion in atherosclerosis

Hypertension is more common in the presence of hypercalcemia, and in many studies appears to be a direct relationship between the total serum calcium levels and blood pressure (BP). However, the relationship between the total serum ionized calcium and blood pressure does not appear to be as strong.

There are many data to suggest a vasoconstrictive effect of increasing extracellular calcium levels presumably by a stimulation of catecholamine release.\(^7\)

In vascular smooth muscle, plasma membrane depolarization - induced Ca\(^{2+}\) current and subsequent Ca\(^{2+}\) release from the sarcoplasmic reticulum elevates cytosolic free Ca\(^{2+}\) ([Ca\(^{2+}\)]) levels and triggers a cascade of molecular rearrangements, ultimately leading to myofilament shortening and vasoconstriction. Conversely, vasorelaxation restores basal [Ca\(^{2+}\)] levels via cellular Ca\(^{2+}\) egress and Ca\(^{2+}\) reuptake into sarcoplasmic reticulum stores.

BP remains relatively constant as long as steady-state [Ca\(^{2+}\)] levels remain unchanged. BP and cellular Ca\(^{2+}\) homeostasis are cooperatively regulated in a see-saw fashion. If extracellular Ca\(^{2+}\) increment during a high-salt diet is balanced by an suppression Ca\(^{2+}\) release and BP again remain constant. Contrarily, with a low dietary salt intake and the associated positive Ca\(^{2+}\) balance, there is a transient rise of extracellular Ca\(^{2+}\) and physiologic fall in Ca\(^{2+}\) regulating hormones. Generally, BP homeostasis remains intact.
unless an increase in extracellular Ca\(^{2+}\) entry or intracellular Ca\(^{2+}\) release exceeds the limits of physiologic compensation. In clinical conditions as primary aldosteronism, low-renin essential hypertension, unilateral renal artery stenosis, and rennin-secreting tumors, there is an imbalance favoring hypertension. Conversely, in such conditions as normal-high renin or nonmodulating hypertension, bilateral renal artery stenosis, preeclampsia or malignant tumors, there may be failure of reciprocal suppression of the counterregulatory mechanism.\(^8\)

Low renin hypertensive subjects exhibit significantly lower serum ionized Ca\(^{2+}\) and calcitonin levels and reciprocally higher serum Mg\(^{2+}\), parathyroid hormone, and 1,25-dihydroxyvitamin D concentrations when compared to normotensive or other hypertensive subjects. High-renin subjects exhibit oppositely skewed values. These deviations in both directions away from normotensive values suggest an extracellular Ca\(^{2+}\) deficiency in low-renin subjects and in high-renin subjects, a Ca\(^{2+}\) increase.\(^9\)

Voltage-dependent Ca\(^{2+}\) channels located in the plasma membrane are important for Ca\(^{2+}\) influx and VSM cell contraction; inhibition of these channels with antagonists such as dihydropiridines, phe-nilalkylamines, and benzotiazepines, also elicits or augments relaxation. This has clinical significance in controlling blood pressure and modulates the negative effects of calcium metabolism in the continuum cardiovascular.

Calcium and Insulin Resistance

The levels of glucose concentration may play an important role in intracellular ion regulations. Increase extracellular glucose raise ionic calcium and lower levels of magnesium and consequently may affect basal vascular tone. Subsequently, insulin also stimulates ion flux, raises ion free magnesium and calcium (under some circumstances) in vascular and other tissues. In hypertensive subjects, these ionic actions are blunted in direct proportion to the deviation of basal ionic values from normal. Insulin resistance is thus at least partly an ionic phenomenon that is part of a more generalized pattern of cell responses to different stimuli. This pattern is present in essential hypertension, insulin resistance, obesity, and type 2 Diabetes, clinical elements of metabolic syndrome.\(^10\)

Insulin resistance with hyperinsulinemia may place obese or hypertensive patients at an increased risk of developing atherosclerosis. Such patients may require therapy for insulin resistance and we should select antihypertensive agents that may have the added of the improving insulin resistance. CCBs have been generally reported to exert neutral or positive effects on insulin sensitivity. Amlodipine has been found to improve insulin sensitivity in essential hypertensive patients. Ueshiba\(^11\) showed improve insulin resistance a consequently increase serum levels of Dehydroepiandrosterone (an adrenal androgen with anti-atherogenic, anti-obesity, and antidiabetic actions) in hypertensive-obese patients treated with CCBs amlodipine, manidipine and cilnidipine.

There have been many reports on observational studies of calcium and hypertension, with the majority demonstrating an inverse relationship between calcium intake in the diet and level of blood pressure. However, clinical trials of calcium supplementation (1 to 2 g/day for up to 4 years) have been less consistent in this regard, with only approximately two-thirds of such studies demonstrating a beneficial effect of supplemental calcium on blood pressure. The rationale for supplemental calcium therapy is based on the assumption that PTH levels are elevated in response to low levels of ionized calcium, resulting from the hypercalcuria seen in some forms of volume-expanded hypertension.

Volume excess and high-salt diets transiently lower extracellular Ca\(^{2+}\) increasing levels of Ca\(^{2+}\) hormones such as PTH and 1,25-dihydroxyvitamin D (1,25SD), along with other factors such ouabain-like molecules and parathyroid hypertensive factor. Ca\(^{2+}\) active hor- mones stimulate extracellular Ca\(^{2+}\) an uptake, thereby promoting vasoconstriction and suppressing renal rennin release. In salt-sensitive subjects, salt loading reproduces the cellular ionic-hormonal profile of the low renin subject, with decreased extracellular Ca\(^{2+}\) levels owing to 1,25D, digitalis-like factors, and/or alpha adrenergic activity-mediated shifts of Ca\(^{2+}\) intracellularly, increased [Ca\(^{2+}\)]i and thus elevated BP\(^12\).

However, in unselected populations of hypertensive patients, most clinical studies have shown little or no effect of calcium supplementation on blood pressure. In contrast, studies in pregnant women have shown that calcium supplementation can provide important reductions in both systolic and diastolic blood pressures and can reduce the risk of preeclampsia.\(^13,14\)

In summary, based on the available data, calcium supplementation or an increased intake of calcium...
Hypertensive subjects excrete more calcium than normotensive individuals, both under basal circumstances and during a calcium infusion. This may be due to the increase to the increase in calcium excretion known to occur following intravascular volume expansion with the resulting rise in sodium excretion. Alternatively, it may be secondary to a decreased binding of calcium to kidney cells. Whatever the precise mechanism, it is known with volume-expansion forms of hypertension excrete calcium in excess.

Atherosclerosis is a systemic process, which is clinically manifested as coronary artery disease (CAD). The initial molecular and cellular events in atherogenesis are triggered by injury to the vascular endothelium, resulting in inflammation. This process is characterized by the widespread accumulation of mononuclear cells, migration and proliferation of smooth muscle cells, and formation of the mature atherosclerotic plaque. A number of these cellular processes, such as smooth muscle cell migration, are driven by a disruption in calcium homeostasis. Moreover, there is a marked change in transmembrane calcium transport in atherosclerotic vessels. It has been proposed that calcium antagonists may be effective in slowing the progression of CAD.

This hypothesis was tested in two trials: PREVENT and CAPARES, which evaluated the effects of the calcium antagonist amlodipine on the development and progression of atherosclerotic lesions in coronary and carotid arteries among patients with documented CAD. These results have led to the hypothesis that amlodipine may have direct antiatherogenic effects in CAD as a result of both calcium-dependent and independent actions: Antioxidant activity, remodeling of vascular smooth muscle cell membranes, inhibition of smooth muscle cell proliferation and migration, inhibition of endothelial apoptosis after cytokine treatment, enhancement of nitric oxide production and modulation of gene expression.

These results have led to an interest in potential plaque-stabilization properties of this lipophilic calcium antagonist.

References


