Multiple Effects of Calcium Entry Blockers on Renal Function in Hypertension

J. CARLOS ROMERO, LEOPOLDO RAJ, JOEY P. GRANGER, LUIS M. RUIMIN, AND JOSE LUIS RODICIO

SUMMARY Characterization of the renal effects of calcium entry blockers has not been easy because the inhibition of Ca\textsuperscript{2+} cellular influx alters several regulatory functions. The ability of calcium blockers to dilate renal vasculature and to increase glomerular filtration rate is largely determined by the preexisting vascular tone. However, the increments in sodium excretion could occur without alterations in renal hemodynamics. Calcium blockers could increase sodium excretion by inducing a redistribution of renal blood flow toward juxtamedullary nephrons, by inhibiting tubuloglomerular feedback responses, or by a direct action on the tubular transport of sodium. These effects are poorly understood at present. In vitro studies show that the blockade of calcium entry enhances renin secretion and decreases prostaglandin synthesis. This dissociation has not been found during long-term administration, which has been proved to be effective for the treatment of essential hypertension with normal maintenance of renal function. In this respect, there are reports indicating that calcium blockers are particularly effective in a subgroup of patients with essential hypertension who exhibit subtle but detectable alterations in calcium metabolism. Further studies are needed to determine whether this significant response to calcium blockers is due to correction of an early defect of calcium cellular kinetics that initiated the increase in blood pressure. (Hypertension 10: 140–151, 1987)

KEY WORDS • glomerular filtration rate • renin-angiotensin-prostaglandin system • renal blood flow • glomerular mesangium

CALCIUM entry blockers are relatively new drugs that are gaining rapid acceptance for the treatment of hypertension.\textsuperscript{1,2} In fact, their potent properties for relaxing smooth muscle\textsuperscript{3} could well account for their efficacy in lowering the increase of total peripheral resistance in patients with hypertension.\textsuperscript{3} However, a fundamental concept implicit in the evaluation of any antihypertensive drug is related to its effect on renal function\textsuperscript{5} because a decrease in renal perfusion pressure induces several compensatory reactions that tend to limit any blood pressure-lowering effect.\textsuperscript{7}

Initial attempts to elucidate the renal effects of calcium blockers\textsuperscript{4,11} encountered many difficulties because the elicited responses are spread to many interrelated functions that are seemingly regulated by the entry of Ca\textsuperscript{2+} into the cell, such as vascular tone,\textsuperscript{12} hormonal secretion,\textsuperscript{13} and to a large extent, epithelial transport.\textsuperscript{14} These ubiquitous effects have precluded the postulation of a coherent scheme to predict the effect of calcium blockers on renal function in hypertension. Therefore, in the present article we review recent advances regarding the effects of calcium blockers on renal hemodynamics and on renal tubular function with the hope of producing a more integrated view of their therapeutic applications in hypertension. In doing so, we do not intend to be inclusive but rather to focus on the studies that, in our opinion, specifically address the critical issues. A summary of the major effects of calcium blockers on renal function in hypertensive patients and in normotensive persons along with the central questions that remain to be answered are presented in Table 1.
Effects of Calcium Blockers on Renal Hemodynamics and Renal Excretory Function When Administered into the Renal Artery

Guyton et al. fostered the concept that the development of hypertension is critically dependent on the ability of the kidney to excrete sodium at a given perfusion pressure. The characteristics of the pressure-natriuresis curve with respect to changes in renal plasma flow and glomerular filtration rate (GFR) under normal conditions are shown in Figure 1. A decrease in renal perfusion pressure to 75 mm Hg evokes a prompt vasoconstriction that prevents changes in renal blood flow (RBF) and GFR. These autoregulatory characteristics of RBF and GFR are not shared by the excretion of sodium in the urine (U\textsubscript{Na}), which varies in direct proportion to changes in renal perfusion pressure. This relationship must be considered when examining the renal effects of antihypertensive agents because their natriuretic effects can be offset and even reversed by the concomitant decrease of blood pressure. Hence, the renal effects of a drug should be established first by direct infusion into the renal artery at constant renal perfusion pressure; subsequently, it should be determined how these local effects are modified when systemic pressure is allowed to change.

Furthermore, the administration of a drug into the renal artery will allow determination of whether the natriuretic effect is produced by direct tubular action or whether it is the result of renal vasodilatation. In the first instance, the increase of U\textsubscript{Na} shifts the natriuresis curve to the left without changing RBF or GFR; in the second instance, the increase in U\textsubscript{Na} is accompanied by a proportional elevation of RBF and GFR.

These conditions have not been systematically followed in studies on the renal effects of calcium blockers. However, Table 2 lists most of the studies in which the intrarenal administration of calcium blockers was performed simultaneously with recording of changes in blood pressure, RBF, GFR, and U\textsubscript{Na}. In seven of these studies, the intrarenal administration of various calcium blockers produced a marked increase in RBF and U\textsubscript{Na} in the absence of any significant changes in systemic blood pressure. The increment in GFR did not seem to be a universally reproducible finding; in three of the studies, the intrarenal administration of verapamil failed to induce significant changes in GFR. These findings indicate that the localized renal effects of calcium blockers, characterized by a systematic increment in RBF and U\textsubscript{Na}, can be dissociated from elevations in GFR.

In three studies, the administration of a calcium blocker into the renal artery was accompanied by...
a variable, although significant, decrement in systemic blood pressure (see Table 2). In one of these studies,49 the increments in RBF, GFR, and U\textsubscript{Na} were similar to those in the aforementioned studies in which blood pressure remained constant. However, in the two other studies,52,54 the decrease in systemic blood pressure was accompanied by natriuresis but no significant changes in RBF or GFR. Thus, within the constraints imposed by the limited number of observations, it can be concluded that the increments in RBF and GFR induced by calcium blockers occur in only 50% of the experimental animals when the systemic blood pressure is decreased, whereas the increments in U\textsubscript{Na} are always present. This feature strongly suggests that the natriuretic effects of calcium blockers are largely independent of the hemodynamic changes. Such a notion is further supported by the increase in the fractional excretion of sodium in the studies in which this factor was calculated.46,49,53,54

Because the effects of calcium blockers are largely determined by the resting vascular tone,13 their efficacy conceivably will be diminished during localized renal hypoperfusion because of the ongoing autoregulatory vasodilatation. This view is supported by the study of Yamaguchi et al.,50 who showed that the increments in the clearance of inulin (70%) and p-aminohippurate (14%) evoked by renal arterial infusion of diltiazem at a rate of 10 µg/kg/min were abolised by previously decreasing the renal perfusion pressure to the lowest limit of RBF autoregulation. However, U\textsubscript{Na} was not decreased to the level that would have been established by the decrease in perfusion pressure alone. In the same study, a direct tubular effect of diltiazem was suggested because a similar increase in RBF produced by the intrarenal administration of papaverine evoked a much lower natriuretic action. Similar results were obtained by Abe et al.,34 who observed that the increments in RBF and GFR induced by the intrarenal infusion of nicardipine, 5 µg/min, were significantly blunted when the infusion was repeated after renal perfusion pressure was controlled with artery clamping.

Some studies have shown that calcium blockers are capable of blocking the renal constrictor autoregulatory response induced by an increase in perfusion pressure to 150 mm Hg.55-56 These observations do not detract from the view that blockade of Ca\textsuperscript{2+} will have less of a vasodilator effect when the directional change toward vasodilatation has already been set in motion by the autoregulatory response. The responses induced by a local decrease in renal perfusion pressure differ from the responses elicited by a decrease in systemic blood pressure in that the latter are accompanied by marked stimulation of the sympathetic nervous system and an increase in the release of renin.55 Under this circumstance, the increase in circulating levels of catecolamines and angiotensin may favor influx of Ca\textsuperscript{2+} into smooth muscle and restore the vasodilator effect of calcium blockers. This view is supported by the study of Ishikawa et al.,58 in which renal perfusion pressure was controlled at a constant level by using an extracorporeal circuit. The administration of diltiazem, 3 µg/kg, into the renal arterial lines of the circuit evoked a 13% increase in RBF. However, a smaller increase in RBF (4.8%) was observed when diltiazem was given after the blockade of sympathetic activity with pentolinium tartrate.

The influence that renal compensatory mechanisms activated by changes in systemic pressure have on the response to calcium blockers may also explain the results of Bell and Lindner.49 They observed that extracellular volume expansion in dogs abolished the increments in RBF induced by the intrarenal infusion of verapamil.

Collectively, these observations stress the importance of endogenous vasoconstrictors in setting vascular tone and thereby determining the vascular responses to calcium blockers (see Table 1). This may account for the variability observed in different experimental settings, in which the levels of vasoconstrictors have been unintentionally increased by, for example, anesthesia or surgical stress.15 However, there seems to be uniform agreement that calcium blockers effectively increase RBF and GFR49,50,59-63 when the renal vasculature has been previously constricted with angiotensin II (see Table 1). In contrast, such an antagonistic effect has not been uniformly demonstrated for norepinephrine.21,50,53,59,60

**Effects of Calcium Blockers on Renal Hemodynamics and Renal Excretory Function When Administered Systemically to Hypertensive Subjects**

**Short-term Effects**

An analysis of the renal effects of calcium blockers in hypertensive subjects must differ from that in normotensive subjects because of the lack of data compar-
ing the local effects in the renal vasculature with the systemic effects. However, for clinicians, the major interest regarding antihypertensive agents is in determining the extent to which a decrease in blood pressure could hamper the natriuretic effect.66

The early studies by Leonetti et al.65 showed that the administration of nifedipine or verapamil produced decreases in blood pressure of 30 and 20%, respectively, in subjects with essential hypertension, whereas similar doses failed to change blood pressure in normotensive subjects (Table 3). UN increased only in the hypertensive group treated with nifedipine, and it was not affected by the administration of verapamil in either group. The lack of a natriuretic effect in normotensive subjects is difficult to interpret because it is at odds with the findings of other investigators, which show that natriuresis is the most conspicuous event in normotensive animals in the absence of changes in blood pressure.34, 48-50 Wallia et al.68 observed a marked natriuresis in normotensive humans with nitrendipine administration in the absence of any change in renal hemodynamics (see Table 3).

Other studies revealed that short-term treatment with diltiazem62 or nifedipine65 or administration of nicardipine67 for 1 week produced a reduction of blood pressure in hypertensive subjects comparable to that induced by identical doses in normotensive subjects (see Table 3). However, the increases in RBF,66, 67 GFR,6, 66 and UN were greater in hypertensive than in normotensive subjects. These findings could have important clinical implications. In fact, an exaggerated increase in intrarenal resistance found in approximate-

<table>
<thead>
<tr>
<th>Reference</th>
<th>Agent</th>
<th>Dose</th>
<th>Decrease in SBP (%)</th>
<th>Increase in RBF (%)</th>
<th>Increase in GFR (%)</th>
<th>Increase in UN above control (fold)</th>
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See Table 2 for key to abbreviations.
ly two thirds of patients with essential hypertension is associated with a lack of modulation of renin release and renal vascular tone during changes in sodium balance. Alternatively, Resnick and Laragh emphasized that volume-dependent hypertension is associated with low circulating levels of renin and ionic Ca^2+ and with specific alterations in the hormones that regulate Ca^2+ metabolism. The pathogenetic mechanism underlying these calcium disturbances has not been defined; however, volume-dependent hypertension exhibits an increased responsiveness to calcium blockers. From a speculative standpoint, it is tempting to postulate that subtle disturbances of Ca^2+ metabolism could be manifested more readily in the renal circulation because of its higher sensitivity to vasoactive principles. Therefore, it remains to be determined whether the disturbances of calcium metabolism in patients with volume-dependent hypertension constitute the same process that may account for the increase in renal vascular resistance and lack of modulation of renal function to sodium overload (see Table 1).

In an attempt to determine whether the decrease in blood pressure induced by calcium blockers impairs the ability of the kidney to correct volume expansion, we measured the excretory rate of U_k in five subjects with essential hypertension and in five normotensive volunteers during 4 hours of isotonic saline infusion (500 ml/hr) in the absence of any medication (unpublished data, 1986). The results were compared with the responses exhibited by both groups submitted to an identical volume expansion 1 hour after a single, 20-mg oral dose of nifedipine. The 4-hour cumulative increments of sodium excretion rates in untreated hypertensive subjects were similar to those in untreated normotensive subjects (Figure 2, top panel). Pretreatment with nifedipine enhanced the excretory rates of U_k during volume expansion by virtually the same magnitude in hypertensive and normotensive subjects. However, before volume expansion, nifedipine induced an 11.2% decrease in average systemic pressure in hypertensive subjects (from 116 ± 6 to 103 ± 3 mm Hg), whereas systemic pressure was unchanged in normotensive subjects (approximately 81 ± 4 mm Hg; Figure 2, bottom panel). This finding indicates that the nifedipine-induced potentiation of natriuresis during volume expansion in hypertensive subjects was not diminished by the observed decrease in renal perfusion pressure.

Long-term Effects

From the aforementioned considerations it follows that an ideal antihypertensive drug should be capable of resetting renal function as close as possible to normal after the decrease in blood pressure has been appropriately compensated. An evaluation of these characteristics requires assurances that 1) during long-term antihypertensive therapy the basal values of critical renal functions are comparable to those in normal subjects and 2) the renal efficacy to adapt to homeostatic changes, such as a high or low sodium diet, water overload, or water deprivation, is not disturbed. In this respect, most of the studies of long-term therapy with several calcium blockers show that renal function is preserved. Long-term therapy with diltiazem (in dosages ranging from 30 to 120 mg/day for 1 week to 3 months) resulted in a persistent increase in RBF, often accompanied by increments in GFR. Sunderrajan et al. found that the administration of 120 to 240 mg of diltiazem twice daily for 8 weeks was effective for normalizing blood pressure in essential hypertensive subjects while maintaining renal function within the normal range and a low intrarenal vascular resistance.

Preservation of renal function during 12 months of therapy with verapamil has also been reported. Verapamil was also found not to alter serum electrolytes, plasma volume, or body weight during long-term administration. Similar results were obtained with the administration of 10 to 40 mg of nifedipine. The beneficial effects of diltiazem, verapamil, and nifedipine were also noted with nifedipine. However, reported that the administration of nifedipine could produce significant renal dysfunction in patients with decreased GFR. In contrast, Sunderrajan et al. found that diltiazem increased GFR and the fractional excretion of sodium when given to hypertensive subjects whose basal GFR was 80 ml/min/1.73 m^2 or less.

Collectively, most of the studies of the long-term effects of calcium blockers indicate that high blood pressure can be reduced without impairing renal hemodynamics or renal excretory function. However, it is not known whether long-term treatment impairs renal ability to cope efficiently with acute homeostatic changes.

Effects of Calcium Blockers on Glomerular Function

Glomerular Filtration

As mentioned, the efficacy of calcium blockers in producing renal vasodilatation is largely determined by the preexisting vascular tone. This characteristic also seems to be true for GFR. Recently, Loutzenhiser and Epstein pointed out that calcium blockers increase GFR in anesthetized animals only when given during the infusion of a vasoconstrictor. However, the overall effects of calcium blockers on GFR are not easy to schematize because afferent and effluent glomerular vascular tone and the glomerular permeability coefficient are affected heterogeneously by vasoconstrictor substances. For instance, in isolated perfused kidney, diltiazem completely reversed renal vasoconstriction induced by potassium chloride and U-44069, an endoperoxide analogue that mimics the actions of thromboxane A2 (Figure 3). However, it reversed the vasoconstrictor effect of angiotensin II by only 80% and that of norepinephrine by 20%. The administration of nonspecific calcium antagonists such as manganese or the removal of calcium from the perfusion media completely reversed the vasoconstrictor effect of norepinephrine. The interpretation...
from these observations was that an important component of the calcium entry activated by norepinephrine is insensitive to calcium blockers.15

In isolated kidneys perfused with norepinephrine, however, calcium blockers produced a more effective reversal in GFR than in renal fluid flow (Figure 4).22-28 This action was suggested to be produced by a greater antagonism of calcium blockers against norepinephrine on the afferent arterioles.15 The specific effects of calcium blockers in antagonizing the effects of angiotensin on glomerular function have not been studied extensively. Because angiotensin II exerts a selective vasoconstriction on the efferent vasculature,83,84 one would expect that the antagonism of calcium blockers would be circumscribed to the same arteriolar segment. However, micropuncture studies have shown that verapamil reverses the decrease induced by angiotensin in the ultrafiltration coefficient and in afferent...
preglomerular vascular resistance, which protects glo-

cular dynamics may prove useful for interpreting their

differentiation of glomerular hydrostatic pressure and foster glomerular

efferent arteriolar resistance (see Table 1). Further

and efferent arteriolar resistance (see Table 1).22 Further

Studies of the effect of calcium blockers on glomer-

Hypertension in rats that had subtotal nephrectomy. How-

felodipine did not prevent glomerular damage as
effectively as did enalapril. Aguas and Nickerson95

Studies of the effect of calcium blockers on glomer-

Glomerular Mesangium

Studies of the effect of calcium blockers on glomer-

function should not be restricted to the effect that

these agents have on glomerular dynamics but should

consider their effects on the glomerular mesangium.

The existence of a plasma flow carrying macromole-

cules through the mesangial channels has been well

demonstrated.96-98 Evidence has also been provided

that increased deposition of macromolecules in the

mesangium can lead to alterations in mesangial archi-

tecture and function.96-98

The systemic administration of angiotensin II in-

duces a significant increase in mesangial macromo-

cular trapping and a considerable reduction of the

velocity at which these macromolecules are cleared

The results of these studies in rats were interpreted

as indicating that converting enzyme inhibitors pro-

duced a predominant decrease of efferent arteriolar

resistance with maintenance of the transcapillary hy-

draulic pressure gradient at near normal levels. The

triple combination therapy may produce a more pro-

ounced decrease of afferent arteriolar resistance,

leading to a higher glomerular capillary pressure.

These assumptions were recently confirmed by And-

erson et al.30 in micropuncture studies of Munich-Wistar

rats rendered hypertensive by subtotal nephrectomy

and treated with either triple drug therapy or conver-

ting enzyme inhibitors.

The effects of calcium blockers on glomerular func-

tion in hypertension have not been studied extensively

(see Table 1). Harris et al.31 showed that verapamil

exerts a protective effect on glomeruli of rats with

reduced renal mass. Moreover, in a preliminary re-

port,39 the converting enzyme inhibitor enalapril and

felodipine were equally effective in normalizing hy-

pertension in rats that had subtotal nephrectomy.

However, felodipine did not prevent glomerular damage as

effectively as did enalapril. Aguas and Nickerson95

showed that verapamil added to drinking water (1%

sodium chloride containing verapamil hydrochloride,

3.6 mg/dl) prevented the development of deoxycorti-

costerone-induced hypertension and significantly ame-

iorated the severity of cardiovascular and renal lesions

in rats. Hemodynamic data were not reported, and no

attempts were made to delineate whether verapamil

altered glomerular hemodynamics. More studies are

needed to define the impact of calcium blockers on

glomerular function during the treatment of hyperten-

sion (see Table 1).

and efferent arteriolar resistance is plotted as percentage of control value. Response to diltiazem varies depending on mode of action. All = angiotensin II; NE = norepinephrine. (Reprinted from Loutzenhiser and Ep-

stein15 by permission of the American Physiological Society.)

Figure 3. Dose-response curves comparing diltiazem-in-
duced vasodilation of isolated perfused rat kidneys during vaso-

constriction induced by different agonists. Renal perfusate flow

is plotted as percentage of control value. Response to diltiazem

varies depending on mode of action. All = angiotensin II; NE = norepinephrine. (Reprinted from Loutzenhiser and Ep-

stein15 by permission of the American Physiological Society.)

Figure 4. Comparison of reversal by Ca 2+ antagonists of

norepinephrine-induced decreases in glomerular filtration rate

(GFR) and renal perfusate flow (RPF) of isolated rat kidneys.

Each point is a single study in which norepinephrine infusion

was followed by administration of a Ca 2+ antagonist. As indi-
cated by open symbols, diltiazem (△), nitrendipine (O), and

nisoldipine (○) exerted a selective effect on norepinephrine-

induced decrement in GFR. In contrast to these organic Ca 2+

antagonists, manganese (●) exhibited no selectivity and in-

creased both RPF and GFR. (Reprinted from Loutzenhiser and Ep-

stein15 by permission of the American Physiological Society.)
Renal Interstitial Pressure and Medullary Circulation

The increase in sodium excretion induced by renal vasodilators such as bradykinin or acetylcholine is also attended by a redistribution of blood flow from the superficial to the deep cortex, and an elevation of renal interstitial pressure. In contrast, vasodilation induced by secretin and prostaglandin E2 synthetic analogue is not accompanied by any change in sodium excretion. In papillary plasma flow, and interstitial pressure.

The intrarenal process that links the distribution of blood flow to the renal medulla with an increase in renal interstitial pressure and natriuresis remains to be elucidated. It has been suggested that the diversion of blood toward the peritubular capillary circulation in the renal medulla may favor natriuresis 1) by increasing distal delivery of tubular fluid as a result of the washout of papillary osmotic gradient or 2) by increasing interstitial pressure.

Abe et al. reported 1) that the administration of nicardipine or diltiazem caused a shift in blood flow from the outer cortical region to the juxtamedullary zone in anesthetized dogs and 2) that diltiazem induced a similar response when administered during angiotensin II infusion. These results support the idea that part of the natriuretic effects of calcium blockers can be explained by a redistribution of blood flow similar to that induced by acetylcholine or bradykinin. It remains to be determined whether this effect corrects the deficiency in medullary circulation seen in salt-sensitive models of hypertension.

Tubuloglomerular Feedback Mechanism

A large body of evidence shows that changes in the volume or electrolyte composition of the tubular fluid coming out of the loop of Henle are detected by the macula densa, which in turn could regulate glomerular filtration by adjusting the tone of afferent glomerular arterioles. This tubuloglomerular feedback response is assessed by blocking proximal tubular segments with oil while simultaneously perfusing distal nephron segments beyond the oil block with artificial tubular fluid. Under these conditions, the single nephron GFR or the existing pressure (stop-flow pressure) in proximal segments of the blocked tubule is taken as an index of glomerular capillary pressure.

In 1976, Müller-Suur et al. reported that verapamil can induce a reversible inhibition of the afferent vasoconstriction mediated by tubuloglomerular feedback. Subsequently, Bell and Navar showed that the addition of a calcium ionophore (which facilitates the entry of Ca2+ into the cell) to the distal tubule perfusion fluid decreases stop-flow pressure. However, the tubuloglomerular feedback responses are not modified by varying the calcium concentrations or adding calcium blockers to the perfusion media. Tubuloglomerular feedback responses are also abolished in a dose-dependent manner by the administration of 8-(N,N-diethylamino)octyl 3,4,5-trimethoxybenzoate, which stabilizes intracellular-bound Ca2+.

These observations indicate that an increase in cytosolic Ca2+ at the level of the macula densa is an important mediator of tubuloglomerular feedback responses but that such an increment is unlikely to result from an increased influx of calcium from the distal tubular lumen (see Table 1).

It is premature to suggest that many of the renal effects of calcium blockers are the result of an effective inhibition of the tubuloglomerular feedback responses. However, this could be the case if the increase in afferent arteriolar resistance in hypertensive subjects is produced by altered regulation of cytosolic Ca2+ in the macula densa. Under these conditions, calcium blockers could reset UN above the level that should correspond to a given intrarenal perfusion pressure (see Table 1).

Effects of Calcium Blockers on Renal Tubular Function

As mentioned, the notion that calcium blockers have a direct renal tubular effect comes from the demonstration that the induced natriuresis cannot be accounted for by changes in RBF or GFR and that the acute increase in UN far outlasts the renal hemodynamic changes. However, the mechanism by which calcium blockers alter tubular sodium absorption is far from being understood.

Present concepts about transepithelial sodium transport are based on the model of Koefoed-Johnsen and Ussing, in which the entry of sodium in the apical (luminal) border of the cell activates a series of sodium extrusion mechanisms (for example, adenosine triphosphatase-driven Na+\textsuperscript{+}-K+\textsuperscript{+} pump and Na+\textsuperscript{+}-Ca2+ exchange system) in the basolateral side. However, this model does not explain how the rate of apical sodium transport is kept in proportion with a basolateral extrusion of sodium. Such an equilibrium between the amount of sodium coming in and going out of the tubular cell is essential to keep the intracellular ionic composition constant during changes of sodium reabsorption.

Taylor and Windhager emphasized that every maneuver that increases the intraepithelial concentration of calcium, such as that induced by quinidine,
calcium ionophores,113,114 or low peritubular sodium concentration,113 decreases sodium reabsorption. On the basis of these observations, changes in cytosolic Ca²⁺ were suggested to be a major factor in regulating the entry of these cations on the apical border.112 In this scheme, an increase in intracellular Ca²⁺ reduces sodium reabsorption and presumably produces natriuresis.

All these findings are difficult to reconcile with a preconceived notion that calcium blockers may produce natriuresis by decreasing the level of cytosolic Ca²⁺ in tubular epithelial cells. Nevertheless, in a micropuncture experiment, MacLaughlin et al.39 observed that 10⁻⁵ M verapamil added to the luminal fluid perfusate of normal Wistar rats produced a 36% decrease of sodium reabsorption and that a greater reduction (61%) of sodium reabsorption occurred when verapamil was infused into peritubular capillaries. Similarly, Figueiredo et al.40 found a significant decrease of sodium reabsorption in isolated perfused proximal tubules of rabbits when verapamil was added to the bathing solution in a concentration of 5 μmol/dl. The authors of these studies39,40 concurred that the inhibitory effect of verapamil on the tubular transport of sodium may not be explained by a decrease in cytosolic calcium but by an effect on other transport mechanisms (see Table 1).

Such nonspecific effects of calcium blockers have also been described by Levine et al.,41 who studied their influence on vasopressin. They found that the effect that three different calcium blockers exerted on vasopressin actions in the toad bladder could be explained by changes in cell enzymes involved in cyclic nucleotide metabolism. Consistent with this finding are the demonstrations of Baumann et al.42 and Jacobson43 that the increase in cellular cyclic adenosine 3',5'-monophosphate decreases net fluid proximal reabsorption. It will be important to determine whether renal tubular cells do have calcium channels and the precise mechanism by which calcium blockers can alter cytosolic levels of calcium (see Table 1).

Effects of Calcium Blockers on the Renin-Angiotensin-Aldosterone Axis and Renal Prostaglandins

The role of calcium on the release of renin was reviewed by Keeton and Campbell.44 According to these authors, renin release is markedly inhibited during maneuvers that increase the cytosolic levels of calcium in juxtaglomerular cells, and the opposite is observed during interventions that lead to a decrease of intracellular calcium levels. Hence, the administration of calcium blockers might be expected to stimulate renin secretion. However, the actual response in whole animals has been difficult to assess because renin release is also influenced by the concomitant decrease in blood pressure and by the increase in the amount of sodium flowing at the level of the macula densa during natriuresis. According to Bauer et al.,45 nifedipine, which is considered the most potent peripheral vasodilator of all calcium blockers, is the only calcium blocker that produces a consistent, but short-lived, increase in renin release after short-term administration. Other calcium blockers, such as diltiazem, verapamil, or nitrendipine, have no significant acute or chronic effects on the renin-angiotensin system (see Table 1).

Experimental evidence also indicates that calcium blockers produce a direct inhibition of aldosterone secretion that may be exerted independently of the existing levels of renin.46 However, the long-term administration of calcium blockers does not produce clinically significant alterations in any of the components of the angiotensin-aldosterone axis (see Table 1).

Early studies indicate that, in most experimental circumstances, renin release is mediated by a concomitant increase in prostaglandin synthesis.44 The entry of calcium into the cell and the binding of calcium to calmodulin are known to constitute the first step in the chain of reactions leading to an increase in prostaglandin synthesis.113 However, as mentioned, the enhancement of calcium influx suppresses renin release.44 These disparate facts are reconciled by the speculation that the cytosolic levels of calcium, which influence the synthesis of prostaglandins, may be compartmentalized in intracellular sites that are different from those affecting the release of renin. An alternative is that such a compartmentalization is not intracellular but refers to different populations of renin and prostaglandin secretory cells affected differently by alterations in calcium fluxes.44 Currently, no experimental studies distinguish between these possibilities (see Table 1). Furthermore, additional studies are needed to define whether the possible dissociating effect of calcium blockers, which may favor the release of renin with a simultaneous increase in prostaglandin synthesis, is common in whole animals. Such an effect may explain the deterioration of renal function that has been observed in patients with renal insufficiency who were treated with calcium blockers.47

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References

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17. Hollenberg NK, Merrill JP. Intrapelvic pressure in the young “essential” hypertensive; a subpopulation resistant to sodium restriction. Trans Am Phys 1970;83:93–100


42. Levine SD, Levin DN, Schonhordt D. Calcium flow-independent actions of calcium channel blockers in toad urinary bladder. Am J Physiol 1983;244:C243–C249


44. Bauer HJ, Sunderrajan S, Reams G. Effects of calcium entry blockers on renin and aldosterone in ischemic dogs. J Pharmacol Exp Ther 1983;244:C885–C889


82. Gattone VH II, Evan AP, Willis LR, Luft FC. Renal afferent arteriole in the spontaneously hypertensive rat. Hypertension 1983;5:8–16
96. Fadem SZ, Hernández-Llamas G, Pataki RV, Rosenblatt SG, Lifschitz MD, Stein JH. Studies on the mechanism of sodium
108. Schnermann J, Wright FS, Davis JM, Stackelberg Wv, Grill G. Regulation of superficial nephron filtration rate by tubuloglomerular feedback. Pflugers Arch 1970;318:147–175
111. Lorenzen M, Lee CO, Windhager EE. Effect of quinidine and ouabain on intracellular Ca (aq) and sodium (aq) ion activities in isolated perfused proximal tubules of Necturus kidney [Abstract]. Kidney Int 1982;21:281
Multiple effects of calcium entry blockers on renal function in hypertension.
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