Multiple Effects of Calcium Entry Blockers on Renal Function in Hypertension

J. CARLOS ROMERO, LEOPOLDO RAJI, JOEY P. GRANGER, LUIS M. RUILOPE, AND JOSE LUIS RODICIO

SUMMARY Characterization of the renal effects of calcium entry blockers has not been easy because the inhibition of Ca$^{2+}$ 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. In fact, their potent properties for relaxing smooth muscle could well account for their efficacy in lowering the increase of total peripheral resistance in patients with hypertension. However, a fundamental concept implicit in the evaluation of any antihypertensive drug is related to its effect on renal function because a decrease in renal perfusion pressure induces several compensatory reactions that tend to limit any blood pressure-lowering effect.

Initial attempts to elucidate the renal effects of calcium blockers encountered many difficulties because the elicited responses are spread to many interrelated functions that are seemingly regulated by the entry of Ca$^{2+}$ into the cell, such as vascular tone, hormonal secretion, and to a large extent, epithelial transport. 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 vasodilator autoregulatory response that prevents changes in renal blood flow (RBF) and GFR. These autoregulatory characteristics of RBF and GFR are not shared by systemic 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_N increases renal clearance of sodium; in the second instance, the increase in U_N 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_N. In seven of these studies, the intrarenal administration of various calcium blockers produced a marked increase in RBF and U_N 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_N, can be dissociated from elevations in GFR.

In three studies, the administration of a calcium blocker into the renal artery was accompanied by

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**Table 1. Summary of Major Effects of Calcium Blockers on Renal Function in Normotensive and Hypertensive Subjects and the Corresponding Questions That Remain Unanswered**

<table>
<thead>
<tr>
<th>Function affected</th>
<th>In normotensive subjects</th>
<th>In hypertensive subjects</th>
<th>Remaining questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBF</td>
<td>Vasodilatation, depending on preexisting vascular tone when set mainly by angiotensin</td>
<td>Greater vasodilatation than in normotensive subjects</td>
<td>Are calcium blockers the drug of choice for treatment of hypertension with increase in renal resistance and poor modulation of angiotensin?</td>
</tr>
<tr>
<td>GFR</td>
<td>Increase in GFR by increasing glomerular capillary pressure or area of filtration</td>
<td>Selective increase of GFR in essential hypertension with GFR&lt;80 ml/min</td>
<td>Do calcium blockers induce global renal damage?</td>
</tr>
<tr>
<td>Glomerular mesangial function</td>
<td>Decrease in mesangial uptake of macromolecules</td>
<td>Unknown</td>
<td>Do calcium blockers protect against macromolecular uptake by the mesangium in hypertensive subjects?</td>
</tr>
<tr>
<td>Peritubular capillary circulation</td>
<td>Redistribution of RBF to juxtamedullary nephrons</td>
<td>Unknown</td>
<td>Are calcium blockers the drug of choice to correct a deficient medullary flow associated with salt-sensitive hypertension?</td>
</tr>
<tr>
<td>Tubuloglomerular feedback</td>
<td>Inhibition of tubuloglomerular feedback response</td>
<td>Unknown</td>
<td>Do calcium blockers normalize Na load--induced natriuresis by inhibiting tubuloglomerular feedback?</td>
</tr>
<tr>
<td>Tubular Na transport</td>
<td>Decreased tubular Na reabsorption by altering other enzyme mechanism, such as cyclic AMP</td>
<td>Unknown</td>
<td>Are there Ca^2+ channels in epithelial cells? How could calcium blockers increase cytosolic Ca^2+ so as to decrease Na transport?</td>
</tr>
<tr>
<td>Renin secretion and prostaglandin synthesis</td>
<td>In vitro studies, calcium blockers increased renin release and decreased prostaglandin synthesis</td>
<td>Only transient increments in plasma renin activity; no alterations during chronic administration</td>
<td>Could the acute increase in intra--renal renin and simultaneous decrease in prostaglandins precipitate aggravation of renal insufficiency?</td>
</tr>
<tr>
<td>Aldosterone secretion</td>
<td>Decrease in release of aldosterone directly in adrenal gland</td>
<td>No alteration in plasma levels of aldosterone during chronic treatment</td>
<td>Do calcium blockers impair aldosterone secretion during a low sodium diet?</td>
</tr>
</tbody>
</table>

**Summary of Major Effects of Calcium Blockers on Renal Function in Normotensive and Hypertensive Subjects**

GFR = glomerular filtration rate; RBF = renal blood flow.
a variable, although significant, decrement in systemic blood pressure (see Table 2). In one of these studies, the increments in RBF, GFR, and UrNa were similar to those in the aforementioned studies in which blood pressure remained constant. However, in the two other studies, 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 UrNa 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.

Because the effects of calcium blockers are largely determined by the resting vascular tone, 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., 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 abolished by previously decreasing the renal perfusion pressure to the lowest limit of RBF autoregulation. However, UrNa 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., 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. These observations do not detract from the view that blockade of Ca2+ 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. Under this circumstance, the increase in circulating levels of catecholamines and angiotensin may favor influx of Ca2+ into smooth muscle and restore the vasodilator effect of calcium blockers. This view is supported by the study of Ishikawa et al., 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 pentolintan 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. 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. However, there seems to be uniform agreement that calcium blockers effectively increase RBF and GFR 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.

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-
Table 2. Reported Effects of Calcium Blockers on Renal Hemodynamics and Renal Excretory Function When Administered into the Renal Artery

<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 UNa above control (fold)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abe et al.</td>
<td>Nicardipine</td>
<td>5 μg/min</td>
<td>NS</td>
<td>29</td>
<td>17</td>
<td>5.9</td>
</tr>
<tr>
<td>Roy et al.</td>
<td>Verapamil</td>
<td>4 μg/kg/min</td>
<td>NS</td>
<td>16</td>
<td>42</td>
<td>4.31</td>
</tr>
<tr>
<td>Bell and Lindner</td>
<td>Verapamil</td>
<td>5 μg/kg/min</td>
<td>NS</td>
<td>11</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>Bell and Lindner</td>
<td>Nifedipine</td>
<td>0.32 μg/kg/min</td>
<td>12</td>
<td>29</td>
<td>50</td>
<td>24</td>
</tr>
<tr>
<td>Yamaguchi et al.</td>
<td>Diltiazem</td>
<td>10 μg/kg/min</td>
<td>NS</td>
<td>11</td>
<td>17</td>
<td>2.6</td>
</tr>
<tr>
<td>Abe et al.</td>
<td>Verapamil</td>
<td>50 μg/kg/min</td>
<td>NS</td>
<td>39</td>
<td>NS</td>
<td>4.42</td>
</tr>
<tr>
<td>Dietz et al.</td>
<td>Verapamil</td>
<td>50 μg/min</td>
<td>NS</td>
<td>10</td>
<td>NS</td>
<td>5.90</td>
</tr>
<tr>
<td>Dietz et al.</td>
<td>Nifedipine</td>
<td>5 μg/min</td>
<td>NS</td>
<td>20</td>
<td>NS</td>
<td>2.8</td>
</tr>
<tr>
<td>Burke et al.</td>
<td>Verapamil</td>
<td>5 μg/kg/min</td>
<td>NS</td>
<td>45</td>
<td>NS</td>
<td>3.60</td>
</tr>
<tr>
<td>DiBona and Sawin</td>
<td>Felodipine</td>
<td>2.7 mmol/kg/min</td>
<td>10</td>
<td>NS</td>
<td>NS</td>
<td>2.4</td>
</tr>
</tbody>
</table>

All studies were performed on anesthetized dogs, except for the study by DiBona and Sawin, which was performed on anesthetized rats.

GFR = glomerular filtration rate; NS = not significant; RBF = renal blood flow; SBP = systemic blood pressure; UNa = urinary sodium excretion.

Table 3. Reported Effects of Systemically Administered Calcium Blockers on Renal Hemodynamics and Renal Excretory Function

<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 UNa above control (fold)</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>Diltiazem</td>
<td>60 mg</td>
<td>5</td>
<td>11</td>
<td>15</td>
<td>2.6</td>
<td>Acute</td>
</tr>
<tr>
<td>Leonetti et al.</td>
<td>Verapamil</td>
<td>160 mg, single dose</td>
<td>20</td>
<td>—</td>
<td>NS</td>
<td>NS</td>
<td>6 hr</td>
</tr>
<tr>
<td>Leonetti et al.</td>
<td>Nifedipine</td>
<td>10 mg, single dose</td>
<td>30</td>
<td>—</td>
<td>NS</td>
<td>1.9</td>
<td>6 hr</td>
</tr>
<tr>
<td>Yokoyama and Kaburagi</td>
<td>Nifedipine</td>
<td>13.3 μg/min</td>
<td>3.1</td>
<td>44.8</td>
<td>45.6</td>
<td>0.83</td>
<td>1.V., 45 min</td>
</tr>
<tr>
<td>Van Schaik et al.</td>
<td>Nicardipine</td>
<td>60 mg/day</td>
<td>4.6</td>
<td>—</td>
<td>11</td>
<td>3.28</td>
<td>1 wk</td>
</tr>
<tr>
<td>Normotension</td>
<td>Verapamil</td>
<td>160 mg, single dose</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>6 hr</td>
</tr>
<tr>
<td>Leonetti et al.</td>
<td>Nifedipine</td>
<td>10 mg</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>6 hr</td>
</tr>
<tr>
<td>Yokoyama and Kaburagi</td>
<td>Nifedipine</td>
<td>13.3 μg/min</td>
<td>4.2</td>
<td>2.2</td>
<td>6.2</td>
<td>0.10</td>
<td>1.V., 45 min</td>
</tr>
<tr>
<td>Van Schaik et al.</td>
<td>Nicardipine</td>
<td>60 mg/day</td>
<td>4.6</td>
<td>NS</td>
<td>2.71</td>
<td>1 wk</td>
<td>3 hr</td>
</tr>
<tr>
<td>Wallia et al.</td>
<td>Nitrendipine</td>
<td>5–10 mg</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>2.23</td>
<td></td>
</tr>
</tbody>
</table>

See Table 2 for key to abbreviations.
ly two thirds of patients with essential hypertension \[69\] is associated with a lack of modulation of renin release and renal vascular tone during changes in sodium balance. \[10, 17\]

Alternatively, Resnick and Laragh\(^1\) 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\[70\]; however, volume-dependent hypertension exhibits an increased responsiveness to calcium blockers. \[20\]

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. \[18, 69\]

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 \(U_{Na}\) 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 \(U_{Na}\) 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\[6\] after the decrease in blood pressure has been appropriately compensated. \[6, 64\] 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, \[82, 71-73\] Sunderrajan et al.\[19\] 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. \[74, 75\]

Verapamil was also found not to alter serum electrolytes, \[76\] plasma volume, \[76\] or body weight\[70, 76, 77\] during long-term administration. Similar results were obtained with the administration of 10 to 40 mg of nifedipine.\[78\] The beneficial effects of diltiazem, verapamil, and nifedipine were also noted with nifedipine.\[1, 20, 76, 78-82\] Diamond et al.,\[47\] however, reported that the administration of nifedipine could produce significant renal dysfunction in patients with decreased GFR. In contrast, Sunderrajan et al.\[19\] 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\[15\] 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 efferent glomerular vascular tone and the glomerular permeability coefficient are affected heterogeneously by vasoconstrictor substances. For instance, in isolated perfused kidney, diltiazem\[23-25\] completely reversed renal vasoconstriction induced by potassium chloride and U-44069, an endoperoxide analogue that mimics the actions of thromboxane \(A_2\) (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\[25\] or the removal of calcium from the perfusion media\[27\] 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.\textsuperscript{15}

In isolated kidneys perfused with norepinephrine, however, calcium blockers produced a more effective reversal in GFR than in renal fluid flow (Figure 4).\textsuperscript{23-28} This action was suggested to be produced by a greater antagonism of calcium blockers against norepinephrine on the afferent arterioles.\textsuperscript{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,\textsuperscript{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
and efferent arteriolar resistance (see Table 1). Further studies of the extent to which calcium blockers could differentially affect the dynamics of glomerular filtration and mesangial function are warranted.

Studies of the effect of calcium blockers on glomerular dynamics may prove useful for interpreting their corresponding effects in hypertension. In fact, the development of hypertension in some experimental models and the occurrence of hypertension in humans are known to be attended by a marked increment in preglomerular vascular resistance, which protects glomeruli from hypertensive injury. Under these circumstances, a predominant afferent versus efferent vascular dynamics may prove useful for interpreting their corresponding effects in hypertension. In fact, the administration of triple drug therapy, consisting of reserpine, hydralazine, and hydrochlorothiazide, produced a significant aggravation of glomerular lesions in spontaneous hypertensive rats even when blood pressure was reduced to normal. This unwanted effect, however, is not exerted by all antihypertensive agents because administration of a converting enzyme inhibitor was followed by a similar normalization of blood pressure but no glomerular damage.

The results of these studies in rats were interpreted as indicating that converting enzyme inhibitors produced a predominant decrease of efferent arteriolar resistance with maintenance of the transcapillary hydraulic pressure gradient at near normal levels. The triple combination therapy may produce a more pronounced decrease of afferent arteriolar resistance, leading to a higher glomerular capillary pressure. These assumptions were recently confirmed by Anderson et al. in micropuncture studies of Munich-Wistar rats rendered hypertensive by subtotal nephrectomy and treated with either triple drug therapy or converting enzyme inhibitors.

The effects of calcium blockers on glomerular function in hypertension have not been studied extensively (see Table 1). Harris et al. showed that verapamil exerts a protective effect on glomeruli of rats with reduced renal mass. Moreover, in a preliminary report, the converting enzyme inhibitor enalapril and felodipine were equally effective in normalizing hypertension in rats that had subtotal nephrectomy. However, felodipine did not prevent glomerular damage as effectively as did enalapril. Aguas and Nickerson showed that verapamil added to drinking water (1% sodium chloride containing verapamil hydrochloride, 3.6 mg/dl) prevented the development of deoxycorticosterone-induced hypertension and significantly ameliorated 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 hypertension (see Table 1).

**Glomerular Mesangium**

Studies of the effect of calcium blockers on glomerular 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 macromolecules through the mesangial channels has been well demonstrated. Evidence has also been provided that increased deposition of macromolecules in the mesangium can lead to alterations in mesangial architecture and function.

The systemic administration of angiotensin II induces a significant increase in mesangial macromolecular trapping and a considerable reduction of the velocity at which these macromolecules are cleared.

**Figure 3.** Dose-response curves comparing diltiazem-induced vasodilation of isolated perfused rat kidneys during vasoconstriction 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 Epstein by permission of the American Physiological Society.)

**Figure 4.** Comparison of reversal by Ca²⁺ 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 Ca²⁺ antagonist. As indicated by open symbols, diltiazem (△), nitrendipine (○), and nisoldipine (●) exerted a selective effect on norepinephrine-induced decrement in GFR. In contrast to these organic Ca²⁺ antagonists, manganese (●) exhibited no selectivity and increased both RPF and GFR. (Reprinted from Loutzenhiser and Epstein 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, an increase in papillary plasma flow, and an elevation of renal interstitial pressure. In contrast, vasodilatation induced by secretin and by prostaglandin E2 synthetic analogue is not accompanied by any change in sodium excretion. Conversely, a decrease in medullary circulation would lead to sodium retention, volume expansion, and hypertension. Such a sequence of events has been postulated to occur during the development of hypertension.

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 by increasing distal delivery of tubular fluid as a result of the washout of papillary osmotic gradient or by increasing interstitial pressure, which diminishes sodium reabsorption preferentially in juxtamedullary nephrons. Conversely, a decrease in medullary circulation would lead to sodium retention, volume expansion, and hypertension. Such a sequence of events has been postulated to occur during the development of hypertension.

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.

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 UNa above the level that should correspond to a given intrarenal perfusion pressure.

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 UNa 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.
calcium ionophores, or low peritubular sodium concentration, decreases sodium reabsorption. On the basis of these observations, changes in cytosolic Ca++ were suggested to be a major factor in regulating the entry of these cations on the apical border. In this scheme, an increase in intracellular Ca++ 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 Ca++. In tubular epithelial cells. Nevertheless, in a microperfusion experiment, MacLaughlin et al. 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. 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 studies 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. 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. and Jacobson 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. 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., 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. 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. 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. However, as mentioned, the enhancement of calcium influx suppresses renin release. 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. 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.

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