Multiple Effects of Calcium Entry Blockers on Renal Function in Hypertension

J. CARLOS ROMERO, LEOPOLDO RAIJ, 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 CA²⁺ CELLULAR INFUX 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 SUBLIME 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 • renal blood flow • glomerular mesangium

CALCIUM ENTRY BLOCKERS ARE RELATIVELY NEW DRUGS THAT ARE ACCEP TING RAPID ACCEPTANCE FOR THE TREATMENT OF HYPERTENSION.² In fact, their potent properties for relaxing smooth muscle³ could well account for their efficacy in lowering the increase of total peripheral resistance in patients with hypertension.⁴ However, a fundamental concept implicit in the evaluation of any antihypertensive drug is related to its effect on renal function⁵ because a decrease in renal perfusion pressure induces several compensatory reac-

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### 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 vasoconstrictor 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. The characteristics of the pressure-natriuresis curve to the left without changing RBF or GFR; in the second instance, the increase in U_{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_{Na}. In seven of these studies, the intrarenal administration of various calcium blockers produced a marked increase in RBF and U_{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_{Na}, can be dissociated from elevations in GFR.

In three studies, the administration of a calcium blocker into the renal artery was accompanied by arterial and poor modulation of angiotensin II. 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 vasodilation. In the first instance, the increase of U_{Na} shifts the natriuresis curve to the left without changing RBF or GFR; in the second instance, the increase in U_{Na} is accompanied by a proportional elevation of RBF and GFR.

### 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 II&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Greater vasodilatation than in normotensive subjects&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Are calcium blockers the drug of choice for treatment of hypertension with increase in renal resistance and poor modulation of angiotensin II?&lt;sup&gt;16-20&lt;/sup&gt;</td>
</tr>
<tr>
<td>GFR</td>
<td>Increase in GFR by increasing glomerular capillary pressure or area of filtration&lt;sup&gt;15, 21-28&lt;/sup&gt;</td>
<td>Selective increase of GFR in essential hypertension with GFR&lt;80 ml/min&lt;sup&gt;19&lt;/sup&gt;</td>
<td>Do calcium blockers restore GFR without inducing glomerular damage?&lt;sup&gt;29-32&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glomerular mesangial function</td>
<td>Decrease in mesangial uptake of macromolecules&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Do calcium blockers protect against macromolecular uptake by the mesangium in hypertensive subjects?&lt;sup&gt;23&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peritubular capillary circulation</td>
<td>Redistribution of RBF to juxtamedullary nephrons?&lt;sup&gt;34, 35&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Are calcium blockers the drug of choice to correct a deficient medullary flow associated with salt-sensitive hypertension?&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tubuloglomerular feedback</td>
<td>Inhibition of tubuloglomerular feedback response&lt;sup&gt;37, 38&lt;/sup&gt;</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&lt;sup&gt;39-43&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Are there Ca&lt;sup&gt;2+&lt;/sup&gt; channels in epithelial cells? How could calcium blockers increase cytosolic Ca&lt;sup&gt;2+&lt;/sup&gt; so as to decrease Na transport?&lt;sup&gt;26&lt;/sup&gt;</td>
</tr>
<tr>
<td>Renin secretion and prostaglandin synthesis</td>
<td>In vitro studies, calcium blockers increased renin release and decreased prostaglandin synthesis&lt;sup&gt;44-46&lt;/sup&gt;</td>
<td>Only transient increments in plasma renin activity; no alterations during chronic administration&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Could the acute increase in intrarenal renin and simultaneous decrease in prostaglandins precipitate aggravation of renal insufficiency?&lt;sup&gt;47&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aldosterone secretion</td>
<td>Decrease in release of aldosterone directly in adrenal gland&lt;sup&gt;48&lt;/sup&gt;</td>
<td>No alteration in plasma levels of aldosterone during chronic treatment&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Do calcium blockers impair aldosterone secretion during a low sodium diet?&lt;sup&gt;48&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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 UNa 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 UNa 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, UNa 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 renal 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 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. 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>5 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/kg/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>20</td>
<td>NS</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.

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. 66 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). UNa 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. 64, 66-68 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 diltiazem 62 or nifedipine 60 or administration of nicardipine 67 for 1 week produced a reduction in blood pressure in hypertensive subjects comparable to that induced by identical doses in normotensive subjects (see Table 3). However, the increases in RBF, GFR, and UNa 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 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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sakurai et al.</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></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leonetti et al.</td>
<td>Verapamil</td>
<td>160 mg, single dose</td>
<td>NS</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</td>
<td>NS</td>
<td>—</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>—</td>
<td>NS</td>
<td>2.71</td>
<td>1 wk</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>3 hr</td>
</tr>
</tbody>
</table>

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 UN 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 four-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 UN 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 (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**

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 efferent glomerular vascular tone and the glomerular permeability coefficient are affected heterogeneously by vasoconstrictor substances. For instance, in isolated perfused kidney, diltiazem completely 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 of these effects 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.
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).23-25 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 arterioles.85

**FIGURE 2.** Top panel: Average cumulative rates of urinary sodium excretion (UNa) in five normotensive subjects and five subjects with hypertension during infusion of isotonic saline before (○) and after (●) administration of a single 20-mg oral dose of nifedipine. Vertical bars represent SEM. Bottom panel: UNa secretory rates during each of the 5 hours of sodium overload plotted against averages of mean arterial pressure recorded during the same hour. Horizontal bars represent SEM.
preglomerular vascular resistance, which protects glomerular function from hypertensive injury. Under these circumstances, a predominant afferent versus efferent vascular response is expected. Studies of the effect of calcium blockers on glomerular function 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 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.96–98 Evidence has also been provided that increased deposition of macromolecules in the mesangium can lead to alterations in mesangial architecture and function.96–98

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...
from the mesangium. The administration of verapamil or an angiotensin II antagonist significantly reduces the mesangial uptake of macromolecules without improving the velocity of removal (see Table 1).33

The important implications emerging from these studies are that naturally occurring vasoactive factors can influence glomerular dynamics as well as mesangial circulation and that concomitant alterations of these two functions may be closely related during the progression of glomerular injuries (see Table 1).

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 interstitial pressure, 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, renal blood flow redistribution, papillary plasma flow, or interstitial pressure.

However, this could be the case if the increase in glomerular filtration pressure is large enough to induce a shift in blood flow similar to that induced by acetylcholine or bradykinin. It remains to be determined whether this effect corrects the defect in medullary circulation seen in salt-sensitive Dahl rats.

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 and efferent vasoconstriction mediated by tubuloglomerular feedback. Subsequently, Bell and Navar showed that the addition of a calcium ionophore (which facilitates the entry of Ca++ 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 Ca++.

These observations indicate that an increase in cytosolic Ca++ 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 Ca++ 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.

Recent concepts about transepithelial sodium transport are based on the model of Koeboe-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⁺-K⁺ pump and Na⁺-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,115 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.116 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, Figuiredo 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).46

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.47 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).48 Early studies indicate that, in most experimental circumstances, renin release is mediated by a concomitant increase in prostaglandin synthesis.49 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.15 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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