Effects of Calcium Channel Blockade on Renal Vascular Resistance Responses to Changes in Perfusion Pressure and Angiotensin-Converting Enzyme Inhibition in Dogs

L. Gabriel Navar, W. Jackson Champion, and Charles E. Thomas

SUMMARY We conducted these experiments to evaluate the selectivity of calcium channel blockade on the renal autoregulatory mechanism and on angiotensin II-mediated renal vasoconstriction. Experiments were performed in anesthetized dogs in which renal arterial pressure, renal blood flow, and glomerular filtration rate were measured at normal and reduced renal arterial pressure. At control arterial pressures, renal arterial infusions of verapamil increased renal blood flow and glomerular filtration rate significantly. The decreases in renal vascular resistance elicited with verapamil (n = 13) and nifedipine (n = 4) occurred only at renal arterial pressure levels within the normal autoregulatory range. Renal blood flow autoregulatory efficiency was markedly attenuated, and the pressure-flow relationship obtained during calcium channel blockade approached that of a passive system. Systemic infusions of an angiotensin-converting enzyme inhibitor (captopril) during continued verapamil infusion caused further vasodilation at all renal arterial pressure values, as evidenced by an increase in slope of 27% of the pressure-blood flow relationship. This response was reversed by angiotensin II infusions. This shift indicates a reduction in minimal vascular resistance elicited by captopril, not obtainable with verapamil alone, and sensitive to angiotensin II. The effects of verapamil and nifedipine on renal blood flow autoregulation suggest a specific effect at preglomerular sites of potential operated membrane calcium channels in the autoregulatory phenomenon. The additional vasodilation elicited with captopril and reversed by angiotensin II indicates the presence of an angiotensin-sensitive postglomerular resistance component which is not influenced by calcium entry blockers (Circ Res 58: 874-881, 1986).

IT is generally agreed that the increases in cystolic calcium concentration essential to initiate the contractile process can be achieved in different ways (Greenberg et al., 1983; Sperelakis, 1984). In some smooth muscle cells, contraction occurs primarily in response to an increase in calcium influx, whereas, in others, it appears that the increase is due primarily to the mobilization of intracellular calcium (Deth and Van Breeman, 1977; Cauvin et al., 1983; Loutzenhiser and Van Breeman, 1983). The specific means by which the contractile mechanisms are activated in the renal vasculature have not been adequately delineated; however, studies on isolated perfused kidneys have suggested that renal vascular resistance is highly dependent on transmembrane calcium flux (Baker et al., 1981; Cohen and Fray, 1982; Loutzenhiser and Epstein, 1985). In addition, it has been reported that calcium channel-blocking agents are effective in blocking renal autoregulatory capability in isolated perfused kidneys (Ono et al., 1974; Cohen and Fray, 1982). To our knowledge, the effects of calcium channel blockers on renal autoregulatory behavior in vivo have not been assessed.

The data available suggest that the effects of calcium channel blockers on renal hemodynamics are unique, compared to the effects of other vasodilators (Ono et al., 1974; Ichikawa et al., 1979; Abe et al., 1983; Bell and Lindner, 1984). In particular, calcium channel blockers reportedly elicit substantive increases in glomerular filtration rate, as well as increases in renal blood flow; indeed, filtration fraction has increased in some studies or remained unchanged (Dietz et al., 1983; Roy et al., 1983; Bell and Lindner, 1984; Arend et al., 1984). This response is different from that ordinarily observed with other vasodilators which generally reduce filtration fraction (Baer and Navar, 1973; Baylis et al., 1976; Thomas et al., 1983). It has also been shown that verapamil, unlike several other vasodilators, does not reduce the glomerular filtration coefficient (Ichikawa et al., 1979). An additional important finding is that the tubuloglomerular feedback mechanism can be rendered nonresponsive by verapamil (Muller-Suur et al., 1976). The interactions between calcium channel blockers and angiotensin II have also been of interest.
Ichikawa et al. (1979) reported that reduction of the glomerular filtration coefficient by angiotensin II could be prevented by verapamil. Also, responses to bolus doses of angiotensin II have been markedly diminished by calcium channel blockers (Bell and Lindner, 1984; Goldberg and Schrier, 1984). In apparent contrast, Ogawa et al. (1984) pointed out that verapamil reduced, but did not abolish, the effects of angiotensin II on renal vascular resistance.

From these previous studies, it remained uncertain whether some or all of the active renal vascular resistance component(s) are dependent on contractile processes which are activated primarily by cell membrane calcium influx. Also, the quantitative extent to which calcium channel blockers diminish renal autoregulatory efficiency in intact dogs was not apparent. Finally, since some of the studies have suggested that calcium channel blockers can completely antagonize the vascular effects of angiotensin, it seemed important to compare the similarity between the effects of calcium channel blockade and the effects of inhibition of the renin angiotensin system on renal vascular resistance responses to reductions in renal arterial pressure.

**Methods**

Experiments were performed on 20 mongrel dogs of both sexes, weighing 13–19 kg, which were maintained on standard diet. Anesthesia was induced with 30 mg/kg sodium pentobarbital, iv, and maintenance doses were given as necessary. A tracheotomy was performed, and a left flank incision, and the renal artery and vein, the ureter, and the gonadal vein were dissected free from surrounding fascia. To minimize the effects of neurogenic vasoconstriction, visible renal nerves were isolated and severed. A 22-gauge bent needle was inserted retrograde into the renal artery near the kidney, this was attached to a Statham pressure transducer and Sage syringe pump by a Statham pressure transducer and Sage syringe pump by a perfusion. After collection of an arterial blood sample, a flow probe was calibrated "in situ" by catheterizing the renal artery near the aorta. An adjustable plastic clamp was placed on the renal artery between the needle and the right femoral artery and left jugular vein were catheterized for measurement of systemic blood pressure, sampling of arterial blood, and infusion of solutions.

As previously described (Rosivall and Navar, 1983), retroperitoneal access to the kidney was obtained through a left flank incision, and the renal artery and vein, the ureter, and the gonadal vein were dissected free from surrounding fascia. To minimize the effects of neurogenic vasodilation, visible renal nerves were isolated and severed. A 22-gauge bent needle was inserted retrograde into the renal artery near the kidney, this was attached to a Statham pressure transducer and Sage syringe pump by PE 50 polyethylene tubing for measurement of renal arterial pressure and infusion of drugs. The needle was prevented from clotting by continuous infusion of a heparinized saline solution at 0.1 ml/min. To collect renal venous blood samples, another bent 22-gauge needle attached to a 10-ml syringe by PE 50 tubing was inserted retrograde into the renal vein. This was maintained patent by filling with heparinized saline between samples. Renal blood flow was measured with an electromagnetic flow probe attached to a square wave electromagnetic flowmeter (Carolina Medical Electronics, Inc.) placed on the renal artery near the aorta. An adjustable plastic clamp was placed on the renal artery between the needle and the flow probe for control of renal arterial pressure. The ureter was catheterized with PE 50 tubing for collection of timed urine samples in graduated test tubes. A polygraph (Grass model 7D, Grass Instrument Co.) was used to record the output of the pressure transducers and the flowmeter. After collection of an arterial blood sample, a priming dose of a 2.5% inulin solution (Sigma Chemical Co.) was given (16 ml/kg), followed by a continuous infusion (0.03 ml/kg per min) to maintain appropriate plasma levels for clearance measurements. A 45-minute equilibration period was allowed after priming before collection of samples.

For control measurements, three or more timed urine samples were collected, and at the midpoint of each collection period, arterial and renal venous blood samples were collected. To ascertain renal blood flow and glomerular filtration rate (GFR) autoregulatory capability, we obtained pressure-flow relationships by reducing renal arterial pressure in steps of 10–20 mm Hg, using the adjustable plastic clamp. Each pressure was maintained for several minutes to allow a complete autoregulatory response. Before control arterial pressures were restored, the renal artery was occluded for 10 seconds or less to determine the zero blood flow reference level. In the series in which GFR autoregulation was evaluated (n = 7), systemic arterial and renal venous blood samples were collected at three to four levels of renal arterial pressure. These samples were used to determine GFR using arterovenous inulin concentration differences in order to minimize delays that are inherent with the clearance approach.

Following control measurements, the heparinized saline solution being infused into the renal artery was replaced with a solution containing verapamil-HCl (Searle Pharmaceuticals Inc.; 0.3 mg/ml in heparinized saline) and the pump was adjusted to deliver 5 μg/min per kg body weight as a starting dose. Dosage was adjusted to obtain the maximal degree of renal vasodilation possible without excessive effects on systemic arterial pressure and was usually in the range of 5–7 μg/min per kg. After a stabilization period of about 15 minutes, clearance measurements, pressure-flow relationships, and arterial and renal venous blood samples were repeated. In addition, a group of four dogs was subjected to a similar protocol except that a different calcium channel blocker was used. For these experiments, nifedipine (Pfizer Laboratories) was infused into the renal artery instead of verapamil (0.36 μg/min per kg).

In 10 of the dogs subjected to verapamil infusions, angiotensin-converting enzyme blockade was induced by intravenous administration of 1 mg/kg captopril (SQ 14225 E R. Squibb & Sons, Inc.) followed by continuous infusion (1 mg/kg per hr.) (Navar et al., 1982). All previous measurements were repeated. For comparison purposes, one group of dogs (n = 7) was subjected only to captopril administration without the superimposed verapamil infusion.

In eight of the dogs that were infused with captopril and verapamil, angiotensin II (Vega Biochemicals) then was infused iv in order to restore arterial pressure back to values seen before captopril infusion. The dose was adjusted until systemic blood pressure returned close to the pre-captopril level and averaged 0.1–0.5 μg/min per kg. All measurements were again repeated.

At the end of each experiment, the electromagnetic flow probe was calibrated "in situ" by catheterizing the renal artery, and collecting timed volumetric blood samples. The kidney was then removed, stripped of all surrounding tissue, blotted dry, and weighed in order to express hemodynamic data per gram of kidney weight. Inulin concentrations in plasma and urine samples were determined by the anthractone technique. GFR was calculated by the standard clearance formula for the values obtained at control arterial pressures. GFR at the reduced arterial pressures was calculated on the basis of the arterovenous inulin
differences in conjunction with renal plasma flow values obtained from the electromagnetic flow measurements and arterial hematocrits (Navar, 1970). These two methods were compared during control clearance periods. GFR measured by the inulin extraction technique was 0.76 ± 0.06 ml/min per g and was not significantly different from the GFR calculated on the basis of standard clearance measurements. Filtration fraction was determined from GFR, renal blood flow, and arterial hematocrit. Plasma and urine sodium and potassium levels were determined by flame photometry (model 443, Instrumentation Laboratory).

Statistical evaluation of differences between the means of control measurements and experimental values was conducted using Student's paired t-test. Paired analysis was utilized for each subset in order to achieve maximum discrimination of the specific hemodynamic responses to verapamil alone (n = 13), captopril in the presence of verapamil (n = 10), and angiotensin II superimposition (n = 8). To assess autoregulatory efficiency, each pressure-flow relationship was linearized by regression analysis into two components, one within the autoregulatory range, and one at the pressures below the autoregulatory range. This allowed direct comparison of the slopes for these relationships obtained during the different experimental periods and also allowed the paired comparison of the slopes within and below the autoregulatory range. Autoregulation of GFR was analyzed by averaging all the GFR values obtained during each experimental period and then expressing each value as a percent of the mean. This normalization allowed more rigorous analysis of the renal arterial pressure (RAP)-GFR relationships by reducing interference due to animal-to-animal variance. Probability values of less than 5% were accepted as indicating statistically significant differences (Freund, 1984).

**Results**

The hemodynamic data obtained at the spontaneous arterial pressures in the absence of renal arterial constriction are shown in Table 1. To allow paired comparison, the control data for each phase of the experimental protocol include only those experiments which were successful through the experimental period. As shown for the first phase, intraarterial infusion of verapamil vasodilated the kidney consistently and also caused slight decreases in systemic arterial pressure. The average decrease in renal vascular resistance was 33%. There were significant increases in both renal blood flow (RBF) and GFR; in relative terms; these changes were approximately the same, so that the filtration fraction was not altered significantly, although a downward trend was noted. In addition, sodium excretion and urine flow increased markedly during verapamil infusion.

The administration of captopril caused further reductions in systemic arterial pressure and renal vascular resistance. RBF and GFR were not altered significantly. Under these conditions of uncontrolled renal perfusion pressure, urine flow and sodium excretion decreased from the values observed with verapamil alone. When angiotensin was superimposed, systemic arterial pressure increased to control levels and there was also an associated increase in renal vascular resistance. No significant changes were observed in RBF and GFR during angiotensin II infusion; however, the increased arterial pressure induced a diuresis and an impressive natriuresis.

In the seven dogs infused with captopril alone, systemic arterial pressures decreased from 132 ± 5 to 117 ± 5 mm Hg, and RBF increased slightly from 4.2 ± 0.5 to 4.6 ± 0.5 ml/min per g. Renal vascular resistance decreased by 27%. There were no statistically significant changes in GFR, filtration fraction, or urinary sodium excretion rate.

To obtain a more comprehensive characterization of the changes in renal vascular resistance induced by verapamil, the responses of RBF and renal vascular resistance to reductions in renal arterial pressure were evaluated. In Figure 1, panels A and B compare the respective effects of verapamil alone and captopril alone on these relationships. Although both of these agents elicited vasodilation, the effects on the overall relationships were quite distinct. Verapamil vasodilated the kidney such that there was a marked attenuation of autoregulatory efficiency. The slope of the relationship between RAP and RBF was increased from 1 × 10⁻⁵ to 0.036 ml/(g/min)/mmHg within the autoregulatory range. In addition, the vasodilation induced with verapamil was re-

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**Table 1**

**Renal Responses to Verapamil, Captopril, and Angiotensin II at Spontaneous Arterial Pressures**

<table>
<thead>
<tr>
<th></th>
<th>CONT</th>
<th>VERP</th>
<th>VERP + CAP</th>
<th>VERP + CAP + AII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AP (mm Hg)</strong></td>
<td>122 ± 4</td>
<td>115 ± 4</td>
<td>90 ± 4</td>
<td>89 ± 5</td>
</tr>
<tr>
<td><strong>RBF ml/(mm-g)</strong></td>
<td>3.75 ± 0.22</td>
<td>4.60 ± 0.25</td>
<td>4.32 ± 0.26</td>
<td>4.65 ± 0.31</td>
</tr>
<tr>
<td><strong>RVR mm Hg/ml/(min-g)</strong></td>
<td>391 ± 18</td>
<td>26 ± 0.9</td>
<td>26 ± 1.3</td>
<td>18 ± 1.5</td>
</tr>
<tr>
<td><strong>GFR ml/(min-g)</strong></td>
<td>0.77 ± 0.02</td>
<td>0.87 ± 0.03</td>
<td>0.84 ± 0.05</td>
<td>0.83 ± 0.08</td>
</tr>
<tr>
<td><strong>FF</strong></td>
<td>0.35 ± 0.02</td>
<td>0.32 ± 0.02</td>
<td>0.33 ± 0.02</td>
<td>0.31 ± 0.02</td>
</tr>
<tr>
<td><strong>UF (ml/min)</strong></td>
<td>0.60 ± 0.15</td>
<td>2.0 ± 0.3</td>
<td>2.2 ± 0.3</td>
<td>1.3 ± 0.36</td>
</tr>
<tr>
<td><strong>FE Na %</strong></td>
<td>1.19 ± 0.29</td>
<td>4.36 ± 0.49</td>
<td>4.68 ± 0.48</td>
<td>1.84 ± 0.55</td>
</tr>
<tr>
<td><strong>FE K %</strong></td>
<td>22.9 ± 1.57</td>
<td>33.6 ± 2.1</td>
<td>34.5 ± 2.4</td>
<td>29.8 ± 3.9</td>
</tr>
</tbody>
</table>

Values for each period for each phase are given as the average ± SEM. Only paired comparisons were made, and significant differences are indicated by *P < 0.001, †P < 0.05. NS indicates that the mean values are not statistically different. Abbreviations used in Table 1 are defined as follows: arterial pressure (AP), renal blood flow (RBF), renal vascular resistance (RVR), filtration fraction (FF), urine flow (UF), fractional excretion (FE), control (CONT), verapamil (VERP), captopril (CAP), angiotensin II (AII).
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FIGURE 1. Effects of verapamil alone (panel A) n = 13, and captopril (CEI) alone (panel B) n = 7, on the relationships between RAP and RVR (panels A and B, top) and RAP and RBF (panels A and B, bottom). Values indicated by asterisks are statistically different from their respective values during control conditions. These are shown only for the RBF data, but apply also to the RVR data. Slope comparisons were carried out by linear regression of the curves in two segments, one within the autoregulatory range (80-140 mm Hg) and one below (20-80 mm Hg). For the verapamil data, the slopes in the higher pressure range were significantly altered for both RVR and RBF. No differences were noted in the lower pressure range. For the CEI data, only the RBF slope at the lower pressure range was increased significantly.

To determine whether a chemically dissimilar calcium channel blocker would elicit similar responses, experiments were also conducted with nifedipine. The results from these experiments (shown in Figure 3) compare favorably with those from the verapamil experiments. Nifedipine caused marked impairment of autoregulatory capability without inducing vasodilation at arterial pressures below the autoregulatory range. Superimposed converting enzyme inhibition induced further vasodilation that was characterized by a leftward shift in the arterial pressure-RBF relationship. This was reversed by the angiotensin II infusions.

In the seven experiments in which both arterial and renal venous blood samples were collected, GFR values were determined from the arteriovenous inulin extraction data collected at 3-4 levels of renal arterial pressure. The changes observed in response to verapamil infusions are shown in Figure 4. For the analysis of each relationship, GFR values were averaged, and then each value was expressed as a percent of this mean value. This approach allows a more rigorous evaluation of the relative responses to changes in RAP. GFR averaged 0.61 ml/min per g during control measurements and varied by only 10% over the autoregulatory arterial pressure range from 130 mm Hg to 85 mm Hg. During the infusion...
of verapamil, there was a significant increase in the mean GFR to 0.84 ml/min per g. There also was a marked increase in the sensitivity of GFR to reductions in RAP. During control conditions there was a 0.2% change in GFR per mm Hg change in RAP which was not statistically significant; in contrast, this slope increased to 1.22% change in GFR per mm Hg during verapamil infusion. Thus, GFR autoregulatory capability was markedly impaired during verapamil infusion.

Discussion

The results of the present series of experiments extend previous observations by Cohen and Fray (1982) and Ono et al. (1974) and clearly demonstrate that intrarenal infusions of verapamil or nifedipine increase RBF at RAP levels within the autoregulatory range. In contrast to the effects of several other vasodilators (Baer and Navar, 1973; Gross et al., 1976), renal vascular resistance was not significantly reduced at the lower arterial pressures below the autoregulatory range by calcium channel blockade. It should be emphasized that further vasodilation at this pressure range is quite possible. In the present series of experiments, captopril elicited vasodilation at these lower pressures, whether it was given alone or during verapamil infusion. It has also been documented that several other vasodilators including acetylcholine, dopamine, and PGE2 can induce further vasodilation at these arterial pressures below the normal autoregulatory range (Baer and Navar, 1970; Gross et al., 1976). Thus, these data indicate that at least one component of the renal vascular contractile system is relatively insensitive to calcium channel blockers.

Although both verapamil and captopril vasodilated the kidney at normal arterial pressures, there were clear-cut differences between the renal arterial pressure-renal blood flow relationships obtained with these two agents. In contrast to the effects of captopril, verapamil and nifedipine markedly impaired autoregulatory efficiency and changed the nature of the pressure-flow relationship to one more nearly approaching a passive linear system. Consequently, the magnitude of the vasodilatory response induced by calcium channel blockers was highly dependent on the arterial pressure. These findings help explain the considerable variability in the literature regarding the degree of renal vasodilation that occurs with calcium channel blockers. Further, these results support the concept that the smooth muscle cells that are specifically responsible for autoregulatory mediated adjustments in vascular resistance operate in a selective manner predominantly by altering the rate of transmembrane calcium flux through voltage-dependent calcium channels.

The responses obtained with captopril alone agree with those previously reported (Navar et al., 1982; Navar and Rosivall, 1984) and demonstrate that autoregulatory capability was well preserved, but at a higher plateau and with a shift in the linear portion of the relationship. These effects presumably were due to reductions in the circulating and intrarenal angiotensin II levels and also to enhanced kinin levels (Scicli and Carretero, 1986). It is likely that the contribution of enhanced kinin levels was relatively modest, since it has been shown that the RBF responses obtained with receptor blockers such as saralasin (Hall et al., 1977) are very similar to those obtained with captopril. The most significant point, however, is that the vasodilation obtained with captopril during coincident verapamil infusion could be reversed by angiotensin II. This indicates the presence of an angiotensin II-sensitive component not dependent on intact voltage-dependent calcium channels.

Studies in cultured rat aortic smooth muscle cells have also shown that responsiveness to angiotensin II is not substantively blocked by verapamil (Zelcher and Sperelakis, 1981). This indicates that these smooth muscle cells have different activation mechanisms not highly dependent on calcium entry. Presumably, they respond to various stimuli by increased mobilization of intracellular bound calcium.
Such an effect of angiotensin II is known to occur in various tissues (Peach, 1981; Kojima et al., 1984) and has been recently demonstrated in cultured aortic smooth muscle cells (Smith et al., 1984; Brock et al., 1985). The pathway for this mechanism is thought to involve an increase in phospholipase C with subsequent generation of inositol triphosphate and intracellular calcium mobilization. It is possible that such a mechanism mediated the responses to angiotensin II that occurred in the presence of calcium channel blockade.

Since autoregulation-induced resistance alterations generally are considered to be predominantly preglomerular (Thurau, 1966; Navar, 1970; Robertson et al., 1972), the observation that calcium channel blockade interferes selectively with the autoreg-
ulatory component suggests that calcium antagonists primarily vasodilate preglomerular arterioles. Selective vasodilation of these vessels would be expected to increase GFR to a greater extent than would occur with vasodilators which reduce both preglomerular and postglomerular blood vessels such as acetylcholine (Baylis et al., 1976; Thomas et al., 1982, 1983). The GFR responses were intriguing not only because of the increased GFR values occurring during verapamil infusion but also because of the concomitant loss of autoregulatory capability. During control conditions, the relationship between GFR and RAP within the autoregulatory range was relatively flat with a slope of only 2% change in GFR per 10 mm Hg change in arterial pressure. In contrast, GFR responses to reductions in RAP during verapamil infusion were much steeper and approached that of a passive relationship between RAP and GFR. The predicted intercept for zero GFR on the abscissa at an RAP of 20 mm Hg is compatible with a passive relationship.

In the presence of afferent arteriolar vasodilation, one would have expected a decrease in GFR in response to captopril and an increase upon superimposition of angiotensin II. As shown in Table 1, this did not occur. It is not clear why GFR values were so unresponsive during these procedures, but it is possible that the overall variability in the GFR measurements prevented the demonstration of these effects. It is also possible that verapamil did not completely block the angiotensin II effects on the glomerular filtration coefficient (Ichikawa et al., 1979). Alternatively, it is possible that verapamil and captopril exerted variable effects on different regions of the kidney and induced different patterns of blood flow and GFR distribution. It has been demonstrated that calcium antagonists produce a redistribution of renal blood flow eliciting greater increases in deep nephrons (Abe et al., 1983), but it remains unclear to what extent such effects could be responsible for differences observed between the responses to captopril and to verapamil.

The mechanisms responsible for the striking natriuresis observed with verapamil remain incompletely understood (Bell and Lindner, 1984; McCrorey et al., 1980). Since GFR was increased, part or all of the natriuresis could be due to the increased filtered sodium load. In addition, the nonspecific effects of vasodilators to alter peritubular capillary dynamics (Baylis et al., 1976) could have contributed to the reductions in fractional sodium reabsorption. Nevertheless, it remains possible that verapamil had a direct effect on tubular sodium reabsorption. This has yet to be definitively established; however, it was demonstrated that proximal tubular reabsorption rate decreased even when arterial pressure was maintained low enough to avoid increases in GFR or renal plasma flow (McCrorey et al., 1980).

The present results should not be interpreted as indicating that calcium channel blockers do not interfere with part of the vascular effects of angiotensin II. In several other studies, it has been demonstrated that calcium antagonists almost abolish the sensitivity of the renal vasculature to vasoconstrictors (Goldberg and Schrier, 1984; Bell and Lindner, 1984; Steele and Challoner-Hue, 1984; Loutzenhiser and Epstein, 1985). In addition, Ichikawa et al. (1979) demonstrated that verapamil could nullify the effects of angiotensin II on the glomerular filtration coefficient and glomerular dynamics. More recently, Huelsemann et al. (1985) evaluated the renal hemodynamic responses in rats to prolonged angiotensin II infusion for up to 10 days. This led to increases in renal vascular resistance, and decreases in both renal plasma flow and GFR. These effects were largely blocked by the calcium entry blocker, nitrendipine. In the present experiments, angiotensin II infusion restored the pressure-flow relationship only to that observed with verapamil alone, which is a much lesser response than can be observed without calcium channel blockers (Rosivall and Navar, 1983). These studies make it clear that only part of the vascular responsiveness to angiotensin II was preserved during calcium channel blockade, and therefore indirectly support an important angiotensin II-sensitive contractile response which is dependent on cell calcium entry.

The presence of an angiotensin-sensitive component of the renal vascular resistance that was not blocked by calcium entry antagonists would seem to be at variance with several previous studies (Ichikawa et al., 1979; Bell and Lindner, 1984; Goldberg and Schrier, 1984). However, it should be recognized that the effect of angiotensin II was manifested in the presence of reduced endogenous angiotensin II levels subsequent to converting enzyme inhibition. Only very modest renal vascular resistance responses could be obtained in animals not treated with captopril. Thus, it is possible that this angiotensin II component is already fully stimulated by the endogenous levels of angiotensin II existing in anesthetized animals not treated with converting enzyme inhibitors. Since renin release may be increased during infusions of calcium channel blockers (Abe et al., 1983; Arend et al., 1984), it is possible that angiotensin II levels are sufficiently high to exert the maximal effects possible on the component not dependent on cell calcium entry. Under such conditions, administration of angiotensin II would not exert any substantive constrictor effects in the presence of calcium channel blockade.

Collectively, the results indicate that angiotensin may elicit renal vasoconstrictor responses by at least two receptor-activated mechanisms: one that operates by increasing calcium entry and can be blocked by the calcium antagonists; and one that is relatively insensitive to calcium blockers. One interpretation compatible with the hemodynamic results is that the angiotensin-sensitive component of the efferent arteriolar resistance (Ichikawa et al., 1979; Edwards, 1983), is unresponsive to calcium channel blockers and is regulated primarily by mechanisms capable of mobilizing intracellular calcium in response to angiotensin II (Smith et al., 1984; Brock et al., 1985).
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