Benidipine Dilates Both Pre- and Post-Glomerular Arteriole in the Canine Kidney

Wang YUE, Shoji KIMURA, Yoshihide FUJISAWA*, Runxia TIAN, Fanzhu LI, Matlubur RAHMAN, Akira NISHIYAMA, Toshiki FUKUI, and Youichi ABE

The aim of the present study was to determine the effects of benidipine on renal function and whether benidipine may dilate the efferent arteriole as well as the afferent arteriole of the canine kidney. The effects of benidipine on the renal segmental vascular resistance were estimated using Gomez’s formula with some modification. The renal hemodynamic action of benidipine was also compared with that of amlodipine. Intrarenal arterial injection of benidipine at a dose of 3μg/kg resulted in a significant increase in renal blood flow (RBF), urine flow and urinary excretion of sodium, but not in glomerular filtration rate (GFR). Amlodipine at a dose of 300μg/kg also increased RBF, urine flow and urinary excretion of sodium to a significant degree equivalent to that by benidipine. However, in contrast to benidipine, amlodipine significantly increased GFR. After the administration of benidipine, autoregulation of RBF and GFR was relatively maintained and the renal perfusion pressure (RPP)–RBF relation shifted upward; that is, RBFs at 75 and 50 mmHg were maintained at a higher level than those of the control. In contrast to benidipine, amlodipine diminished the autoregulation of RBF and GFR. RBFs at 75 and 50 mmHg were not different from those of the control. The afferent and efferent arteriolar resistance (Ra and Re) were calculated based on the RPP–RBF and RPP–GFR relations. Benidipine reduced both Ra and Re, but amlodipine selectively reduced Re. Benidipine increased RBF but not GFR via the dilation of both afferent and efferent arterioles. Thus, benidipine has unique renal hemodynamic actions which differ from those by most calcium antagonists. (Hypertens Res 2001; 24: 429–436)

Key Words: amlodipine, renal function, afferent arteriole, efferent arteriole, autoregulation

Introduction
Calcium antagonists are the most widely used of the antihypertensive agents. The potent vasodilatory and natriuretic properties of calcium antagonists are generally recognized as their antihypertensive mechanisms (1). On the other hand, it has also been reported that calcium antagonists preferentially dilate preglomerular blood vessels and induce hyperfiltration (2–5). In fact, we have previously demonstrated that intrarenal infusion of nifedipine or nitrendipine concomitantly increase renal blood flow (RBF) and glomerular filtration rate (GFR) to the same degree, and as a result, the filtration fraction (FF) does not change during the infusion of these agents, indicating preferential dilation of preglomerular afferent arterioles (6, 7).

The preferential dilation of preglomerular afferent arterioles might induce the elevation of intraglomerular pressure and hyperfiltration, which have been recognized as important inducers of glomerular injury (8, 9). Brunner et al. (10) have reported that long-term administration of verapamil worsens glomerular injury in rats with reduced renal mass. Wenzel et al. (11) have also reported that nitrendipine worsens glomerular injury in rats with renovascular hypertension. However, it remains unclear whether all of the calcium antagonists preferentially dilate the preglomerular afferent
arterioles and induce hyperfiltration. Using hydropnephrotic kidneys, Hayashi et al. (12) recently demonstrated that efondipine dilated the afferent and efferent arterioles to the same degree. In addition, Kusada et al. (13) have also reported that benidipine, a 1,4-dihydropyridine calcium antagonist, increases p-aminohippuric acid clearance, but not creatinine clearance in anesthetized spontaneously hypertensive rats. The authors suggested that benidipine dilates the glomerular efferent arteriole as well as the afferent arteriole. It would be interesting to know whether benidipine, among the calcium antagonists, dilates both afferent and efferent arterioles of the kidney in normotensive animals.

The present study was designed to determine whether benidipine dilates the efferent arteriole as well as the afferent arteriole of the canine kidney. The effects of benidipine on the renal segmental vascular resistance were estimated using Gomez’s formula with some modification (14). In addition, the renal hemodynamic action of benidipine was also compared with that of amlopidine in anesthetized dogs.

**Materials and Methods**

**General Procedure**

Experiments were carried out on adult mongrel dogs weighing from 10 to 15 kg which had been maintained on standard laboratory chow for 1 week. All surgical and experimental procedures were performed according to the guidelines for the care and use of animals as established by the Kagawa Medical University. The animals were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and given additional doses as required. After tracheotomy, the animals were mechanically ventilated with room air. Catheters were inserted into the right brachial artery and vein for arterial blood sampling and infusion of isotonic saline or the administration of drugs. Isotonic saline was infused at a rate of 0.15 ml/(kg·min) throughout the experiment. A catheter was placed in the abdominal aorta at the level of the left renal artery bifurcation via the right femoral artery. The renal perfusion pressure (RPP) was considered equal to the aortic pressure and continuously recorded with a polygraph (Model 361; NEC-San-ei, Tokyo, Japan). The left kidney was exposed through a retroperitoneal flank incision. The kidney was carefully denervated by dissecting all visible nerve fibers as well as the tissue connecting the renal hilum cephalic to the renal artery. An electromagnetic flowmeter (MFV-1200; Nihon Kohden Co., Tokyo, Japan) was positioned around the renal artery and RBF was continuously monitored. An adjustable aortic clamp was placed on the aorta just above the bifurcation of the left renal artery. An additional catheter was introduced into the renal vein via the left spermatic or ovarian vein and renal venous blood was collected. A polyethylene catheter was inserted into the left ureter and urine was collected throughout the experiment. A no. 23 gauge needle was introduced into the left renal artery proximal to the flow probe for administration of saline or drug solution. A loading dose of creatinine (100 mg/kg) was given intravenously, followed by a maintenance dose of 50 mg/(kg·h). GFR was measured by creatinine clearance in the clearance experiment and by a renal extraction rate of creatinine in the autoregulation experiment.

After the surgery was completed, the dog was left for 60 to 90 min to allow for stabilization of RPP, RBF, and urine flow. Urine samples were then collected during 2 consecutive 10-min control clearance periods. At the midpoint of each period, systemic arterial and renal venous blood were collected from the right brachial artery and from the left renal vein. The blood and urine samples were tested for creatinine and electrolytes. After control periods, test drugs were administered. The experiments were carried out according to the following protocol.

**Experimental Protocols**

**Effects of Benidipine or Amlodipine on Renal Function**

After the second control clearance period, benidipine at a dose of 3 μg/kg (n=8) or amlopidine at a dose of 300 μg/kg (n=6) was injected into the renal artery and urine samples were collected during 3 consecutive 10-min clearance periods. At the midpoint of each period, blood samples were withdrawn for plasma analysis. The dose of benidipine or amlopidine was determined as the dose that did not affect RPP but increased RBF by 40–50%.

**Effects of Benidipine or Amlodipine on the Autoregulation of RBF and GFR and the Segmental Vascular Resistance**

During an intrarenal infusion of saline solution, the pressure–flow relation was obtained. RPP was altered in steps (RPPs of 125, 100, 75 and 50 mmHg) as shown in Fig. 1. In each step, systemic arterial and renal venous blood were collected. GFR was calculated as follows: GFR = (systemic arterial concentration of creatinine – renal venous concentration of creatinine) × renal plasma flow / systemic arterial concentration of creatinine. Sixty minutes after the release of the aortic clamp, benidipine at a dose of 3 μg/kg (n=7) or amlopidine at a dose of 300 μg/kg (n=6) was injected into the renal artery. Twenty minutes after the administration of drugs, the pressure–flow relations were obtained as described above.

**Analytical Procedures**

**Segmental Vascular Resistance**

The segmental renal vascular resistance was calculated by the following formula.

According to the concepts of glomerular dynamics:

\[
GFR = K_r (P_c - P_t - P_s) \quad (1)
\]

\(K_r\): glomerular permeability coefficient; \(P_c\): glomerular capillary pressure; \(P_t\): renal tissue pressure; \(P_s\): mean glomerular capillary plasma oncotic pressure (mean \(P_s = 25\))
Table 1. Effects of Benidipine on Renal Function in Anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>RBF (ml/g/min)</th>
<th>GFR (ml/g·min)</th>
<th>UF (μg/g·min)</th>
<th>UαV (μEq/g·min)</th>
<th>FEαα (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>138±4</td>
<td>2.98±0.33</td>
<td>0.71±0.06</td>
<td>20±4</td>
<td>2.1±0.4</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>Control 2</td>
<td>138±4</td>
<td>2.94±0.34</td>
<td>0.74±0.08</td>
<td>22±5</td>
<td>2.2±0.5</td>
<td>1.7±0.2</td>
</tr>
<tr>
<td>Benidipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>131±4</td>
<td>4.18±0.44*</td>
<td>0.79±0.08</td>
<td>98±12</td>
<td>8.2±2.1*</td>
<td>7.3±1.4*</td>
</tr>
<tr>
<td>20 min</td>
<td>130±4*</td>
<td>4.11±0.39*</td>
<td>0.77±0.06</td>
<td>105±18*</td>
<td>10.6±3.3*</td>
<td>9.1±2.0*</td>
</tr>
<tr>
<td>30 min</td>
<td>130±4*</td>
<td>4.02±0.40*</td>
<td>0.75±0.08</td>
<td>101±19*</td>
<td>11.9±3.1*</td>
<td>9.3±2.1*</td>
</tr>
</tbody>
</table>

All data are mean±SE. *Indicates significant difference from control 2 (p<0.05). MAP, mean arterial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; UF, urine flow; UαV and FEαα, urinary and fractional excretion of sodium.

Table 2. Effects of Amlodipine on Renal Function in Anesthetized Dogs

<table>
<thead>
<tr>
<th></th>
<th>MAP (mmHg)</th>
<th>RBF (ml/g·min)</th>
<th>GFR (ml/g·min)</th>
<th>UF (μg/g·min)</th>
<th>UαV (μEq/g·min)</th>
<th>FEαα (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control 1</td>
<td>127±3</td>
<td>2.84±0.26</td>
<td>0.66±0.07</td>
<td>15±3</td>
<td>2.4±0.5</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>Control 2</td>
<td>128±3</td>
<td>2.84±0.25</td>
<td>0.65±0.06</td>
<td>15±3</td>
<td>2.5±0.5</td>
<td>2.0±0.2</td>
</tr>
<tr>
<td>Amlodipine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td>123±2</td>
<td>4.12±0.40*</td>
<td>0.75±0.07</td>
<td>51±8</td>
<td>10.6±2.8*</td>
<td>8.0±1.1*</td>
</tr>
<tr>
<td>20 min</td>
<td>121±1*</td>
<td>4.05±0.41*</td>
<td>0.81±0.07*</td>
<td>76±17*</td>
<td>11.7±3.0*</td>
<td>9.3±1.5*</td>
</tr>
<tr>
<td>30 min</td>
<td>120±2*</td>
<td>4.20±0.50*</td>
<td>0.88±0.07*</td>
<td>84±20*</td>
<td>11.9±2.0*</td>
<td>10.1±1.7*</td>
</tr>
</tbody>
</table>

All data are mean±SE. *Indicates significant difference from control 2 (p<0.05). MAP, mean arterial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; UF, urine flow; UαV and FEαα, urinary and fractional excretion of sodium.

mmHg calculated from plasma protein concentration).

Then, the efferent arteriolar resistance (Rₑ) can be calculated as 
\[ Rₑ = \frac{(Pₛ - Pᵥ)}{RBF} \] (2)

A rearrangement of Eq. (2) yields:
\[ (Pₛ - Pᵥ) = Rₑ \times RBF \] (3)

Substituting Eq. (3) into Eq. (1), we obtain
\[ GFR = Kᵣ (Rₑ \times RBF - Pᵥ) \] (4)

In order to obtain the two unknown values (Kᵣ and Rₑ) in Eq.(4) we introduce the following two working assumptions. 1) The overall glomerular capillary permeability coefficient (Kᵣ) was assumed to be independent of perfusion pressure, and 2) Rₑ is assumed to be constant throughout the passive-flow range, since the total renal vascular resistance (Rₑ) was constant. The RBF and GFR values obtained at 75 and 50 mmHg of RPP were put into the Eq. (4).

\[ GFRₗ₃ₘ₄₉ₐₜₚ = Kᵣ (Rₑ \times RBFₗ₃ₘ₄₉ₐₜₚ - Pᵥ) \] (5)

\[ GFRₗ₃ₘ₄₉ₐₜₚ = Kᵣ (Rₑ \times RBFₗ₃ₘ₄₉ₐₜₚ - Pᵥ) \] (6)

We were then able to obtain Kᵣ and Rₑ values to solve Eqs. (5) and (6).

Rₑ is calculated from the following Eq.
\[ Rₑ = \frac{(RPP - Pᵥ)}{RBF} = Rᵣ + Rₑ \] (7)

Pᵥ, renal venous pressure; Rᵣ, afferent arteriolar resistance.

Thus, Rₑ is readily calculated with the above equation. Rᵣ, Rₑ and Kᵣ were calculated in each experiment using the above equations, and the mean value of each parameter was determined.

Autoregulation Factor

The autoregulation factor was calculated using the formula of Semple and De Wardener (15) as follows:

\[ \text{Autoregulation factor} = \frac{(\text{RBF}₂ - \text{RBF}₁)}{\text{RBF}₁/\text{RPP}₂ - \text{RPP}₁} \]

Statistical Analysis

All data were expressed as the means±SE. Statistical differences of data means were determined by Student’s t - and paired t-tests. Values of p less than 0.05 were considered to indicate statistical significance.

Results

Effects of Benidipine or Amlodipine on Renal Function

Intrarenal arterial administration of benidipine resulted in a significant increase in RBF, urine flow and urinary excretion of sodium, with a slight fall in systemic blood pressure (Table 1). GFR tended to increase immediately after the administration of benidipine, but returned to the control level 30 min after. The changes of GFR were not statistically significant. Amlodipine also increased RBF, urine flow and urinary excretion of sodium to a significant degree equivalent to that by benidipine (Table 2). However, in contrast to benidipine, amlodipine significantly increased GFR. As a
result, FF did not change with amlodipine (from 0.33±0.03 to 0.31±0.04) but decreased with benidipine (from 0.34±0.02 to 0.26±0.02; p<0.05).

**Effects of Benidipine or Amlodipine on the Autoregulation of RBF and GFR**

Figures 1 and 2 show the RPP–RBF and RPP–GFR relations before and after the administration of benidipine or amlodipine. All control dogs showed a complete autoregulation of RBF and GFR between 125 and 75 mmHg of RPP. Intrarenal arterial administration of benidipine increased RBF, but did not affect GFR. After the administration of benidipine, autoregulation of RBF and GFR was observed at between 125 and 100 mmHg of RPP. The reduction of RPP from 100 to 75 mmHg resulted in significant decreases of RBF and GFR. However, RBF at 75 mmHg was maintained at a higher level than that of the control RBF. In contrast to benidipine, amlodipine diminished the autoregulation of RBF and GFR. That is, both RBF and GFR decreased pres-
Table 3. Effects of Benidipine and Amlodipine on Autoregulation Factor

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Benidipine</th>
<th>Control</th>
<th>Amlodipine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step I (125–100 mmHg)</td>
<td>−0.04±0.05</td>
<td>0.07±0.03</td>
<td>−0.01±0.03</td>
<td>0.81±0.10*</td>
</tr>
<tr>
<td>Step II (100–75 mmHg)</td>
<td>−0.08±0.07</td>
<td>0.55±0.12*</td>
<td>0.04±0.05</td>
<td>0.92±0.17*</td>
</tr>
<tr>
<td>Step III (75–50 mmHg)</td>
<td>1.07±0.14</td>
<td>1.03±0.20</td>
<td>1.05±0.11</td>
<td>1.02±0.10</td>
</tr>
</tbody>
</table>

All Values are mean±SE. * Indicates significant difference from each control (p<0.05).

Table 4. Effects of Benidipine and Amlodipine on Renal Segmental Vascular Resistance and Permeability Coefficient

<table>
<thead>
<tr>
<th></th>
<th>$R_l$ (mmHg·g·min/ml)</th>
<th>$R_a$ (mmHg·g·min/ml)</th>
<th>$R_e$ (mmHg·g·min/ml)</th>
<th>$K_t$ (ml/mmHg·g·min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>47.3±6.2</td>
<td>27.7±4.4</td>
<td>19.6±3.1</td>
<td>0.0210±0.0051</td>
</tr>
<tr>
<td>Benidipine</td>
<td>28.6±4.0*</td>
<td>15.5±2.9*</td>
<td>13.1±2.1*</td>
<td>0.0250±0.0065</td>
</tr>
<tr>
<td>Control</td>
<td>44.7±5.3</td>
<td>25.6±4.2</td>
<td>19.1±3.0</td>
<td>0.0232±0.0042</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>27.2±3.8*</td>
<td>8.6±2.5*</td>
<td>18.6±2.6</td>
<td>0.0217±0.0090</td>
</tr>
</tbody>
</table>

All data are mean±SE. * Indicates significant difference from each control value (p<0.05). $R_l$, total renal vascular resistance; $R_a$, afferent arteriolar resistance; $R_e$, efferent arteriolar resistance; $K_t$, glomerular permeability coefficient.

sure dependently. RBF at 75 mmHg of RPP, which is the lower limit of the autoregulatory pressure range, was not changed from that of the control.

The data shown in Figs. 1 and 2 do not allow for a precise evaluation of the degree of autoregulation impairment by either drug. The efficiency of autoregulation was analyzed by a paired comparison of the autoregulation factor between the control and drug administration at the same pressure level (Table 3). The factor value is inversely related to autoregulatory efficiency: a value of 1 indicates no autoregulation, whereas values near 0 indicate a high efficiency of autoregulation. In the control, the autoregulation factors at steps I (125–100 mmHg) and II (100–75 mmHg) were practically 0, thereby indicating complete autoregulation of RBF. After the administration of benidipine, the autoregulation factor at step I stayed at nearly 0. However, in step II it was around 0.5, indicating partial abolishment of autoregulation. In contrast to benidipine, the autoregulation factor in step I was near 1 after the administration of amlodipine, indicating that the latter impaired autoregulation (Table 3).

Effects of Benidipine or Amlodipine on the Segmental Vascular Resistance and the Glomerular Capillary Permeability Coefficient

Benidipine decreased $R_l$ by 41%. $R_a$ and $R_e$ were significantly decreased by 43 and 34%, respectively (Table 4 and Fig. 3). There were no significant differences in changes of $R_a$ and $R_e$, indicating that benidipine dilated the afferent and efferent arterioles by the same magnitude. $K_t$ tended to increase, but this change was not statistically significant. Amlodipine also decreased $R_l$ significantly by 40%, and this reduction rate was not different from that by benidipine. In contrast to benidipine, amlodipine decreased $R_a$ by 67%, but did not affect $R_e$ or $K_t$.

Discussion

These experiments demonstrate that intrarenal arterial administration of benidipine resulted in a significant increase of RBF, urine flow and urinary excretion of sodium without any change in GFR. These results indicate that benidipine produced diuresis and natriuresis by inhibition of the sodium reabsorption at the tubular site, rather than by the increase of GFR. Amlodipine also increased RBF, urine flow and urinary excretion of sodium. The renal responses to benidipine or amlodipine in the canine kidney were identical to those obtained in other species (13, 16). The changes induced by amlodipine were not different from those by benidipine. Thus, benidipine and amlodipine increased RBF to a similar magnitude, but there were clear-cut differences in GFR. That is, benidipine did not affect GFR, but amlodipine sig-
significantly increased GFR and RBF with a similar degree. As a result, the calculated FF after the administration of amlo-
dipine did not change. We have previously reported that nicardipine or nitrendipine increase RBF as well as GFR in
anesthetized dogs (6, 7). On the other hand, Kusada et al.
(13) and Yokoyama et al. (17) have reported that benidipine
or NZ105 (a new calcium antagonist) increase RBF but not
GFR in anesthetized SHR. Thus, the differing effects of cal-
cium antagonists on GFR suggest a variation of vasodilating
action on the preglomerular and postglomerular resistance
vessels among drugs.

As shown in Figs.1 and 2, there were significant differ-
ences between RPP–RBF relations obtained after the admin-
istration of benidipine and amlodipine. Amlodipine markedly
impaired the autoregulatory efficiency of RBF or GFR and
changed the nature of the pressure–flow relationship so that
it nearly approached a passive linear system. Thus, the va-
sodilatory response to amlodipine was highly dependent on
the RPP within the autoregulatory pressure range. The RBF
value at 75 mmHg, which is the lower limit of the autoregu-
latory pressure range, was identical to the control RBF, and
the RBF values at RPPs lower than 75 mmHg were the same
between the control and amlodipine. In contrast to the effects
of amlodipine, we demonstrated that with benidipine, the au-
toregulation of RBF was maintained between 125 and 100
mmHg of RPP, and partially abolished between 100 and 75
mmHg. Thus, the autoregulatory capability was well-pres-
erved, but at a higher plateau and with an upward shift in
the passive portion of the relation. These findings indicate
that benidipine has a vasodilatory ability even at an RPP be-
low the lower limit of the autoregulatory pressure range, but
amlodipine does not. That is, the benidipine-induced renal
vasodilation at 100 mmHg of RPP was almost of the same
magnitude as that at normal RPP, whereas the renal vasodi-
lation induced by amlodipine was significantly weakened at
100 mmHg and completely abolished at 75 mmHg. The
RPP–GFR relations obtained after the administration of both
drugs were almost identical to the RPP–RBF relations. In
the benidipine-treated dogs, the RPP–GFR relation showed a
downward shift in the passive portion of the relation.

We have previously reported that autoregulation-induced
resistance alteration occurs predominantly at the afferent
arteriole (14, 18). Therefore, the observation that amlodipine
abolished the autoregulation of RBF and GFR indicates that
amlodipine primarily dilates the afferent arteriole. In contrast
to the action of amlodipine, benidipine increased RBF even
at an RPP of 75 mmHg, having a minimum value of afferent
arteriolar resistance (14, 18). These findings suggest that
benidipine may dilate the efferent arteriole as well as the a-
fferent arteriole. To define the action sites of benidipine and
amlodipine, we next calculated the segmental renal vascular
resistance using the formula presented in the Methods sec-
tion. In the benidipine’s control, the Rs and Re at a normal
RPP were 27.7 ± 4.4 and 19.6 ± 3.1 mmHg·g·min/ml, re-
spectively. When RPP was reduced to 75 mmHg, Rs was re-
duced to 5.7 ± 3.0 mmHg·g·min/ml, but Re remained at the
control value, indicating that the afferent arteriole dilated
maximally but the efferent arteriole maintained the basal
tone. As shown in Table 4 and Fig. 3, benidipine reduced the
Rs, Rs, and Re by 41%, 43% and 34%, respectively. Amlodi-
pine also reduced Rs by 40%, to a value identical to that in-
duced by benidipine. However, Re was reduced by 67%, but
Re was unchanged. Thus, the present results clearly dem-
strate that benidipine dilated both the afferent and efferent
arterioles, but amlodipine preferentially dilated the afferent
arteriole. We further examined the effects of nicardipine on
the renal autoregulation and arterioles. An intrarenal infu-
sion of nicardipine at a rate of 10 µg/min resulted in an impair-
ment of autoregulation of RBF and GFR, and a preferential
dilation of the afferent arteriole (unpublished observation).
These renal actions of nicardipine were identical to those by
amlodipine. However, the present experiments were per-
formed in anesthetized normotensive animals. These acute
results might not be suitable for prediction of the long-term
effects of these calcium antagonists on glomerular hemody-
namics.

Selective vasodilation of the afferent arteriole would be
expected to increase GFR to a greater extent than would oc-
cur with vasodilators that dilate both the afferent and effe-
rent arterioles. In fact, amlodipine increased GFR significa-
tively at a normal pressure but benidipine did not. Our results
confirm the data obtained in previous in vivo studies (18). These
GFR responses might have been induced by the changes in
Kf as well as changes in vessel resistance. Many studies have
evaluated the regulation of cytosolic Ca++ in mesangial cells
whose contraction or relaxation may affect Kf. While some
earlier studies have suggested that cultured mesangial cells
do not have voltage-dependent Ca++ channels (19), more re-
cent studies have shown that such cells are present (20). In
addition, Yue et al. (21) reported that more than one type of
calcium channel may exist in the mesangial cells, since the
effects of high KCl and Ca++ activators are additive. Thus,
at present, the effects of calcium antagonist on Kf are contro-
versial. However, our present experiments clearly show that
neither benidipine nor amlodipine affected Kf. Therefore,
GFR responses may depend predominantly on the differ-
ences of hydraulic pressure across the glomerular capil-
lary wall, which is determined by the relative tone of the two
resistance vessels.

A question arises as to why these differences can be ob-
served in the action of benidipine and amlodipine on arteri-
oles. It has been reported that calcium antagonists stimulate
the renin release which causes endorenal liberation of an-
giotensin II (7, 22). This may lead to a postglomerular vaso-
constriction which masks the vasodilatory effect of the cal-
cium antagonist at the postglomerular level. In addition, Carmines
and Navar (23) reported that angiotensin II-mediated afferent
arteriolar vasoconstriction is abolished in the presence of
calcium antagonist, but the vasoconstrictor effect of an-
giotensin II on efferent arterioles is preserved. Thus, the
rein-angiotensin system may contribute to the selective vascular action of calcium antagonists. We do not have any information about the differences between the effects of benidipine and amiodipine on renin release in dogs. However, it is generally recognized that voltage-dependent calcium channels play a major role in the control of cytosolic calcium in the afferent arterioles. In contrast, the efferent arterioles appear to rely primarily on other mechanisms for calcium entry and/or intracellular calcium mobilization (24–26). Therefore, benidipine might have additional direct or indirect vasodilatory actions as well as the calcium channel blocking action. Concerning the additional actions of calcium antagonists, Hayashi et al. (27) recently reported that calcium antagonists have an inhibitory effect on nuclear factor kappa B activation in human mesangial cells via the independent pathway of an L-type calcium channel and that the potency of this effect is variable among calcium antagonists.

Intraglomerular hypertension and hyperfiltration have been recognized as important accelerating factors of glomerular injury (28, 29). Angiotensin converting enzyme inhibitors (ACEI) ameliorate glomerular injury in a variety of experimental renal diseases, due to a reduction in intraglomerular pressure (29). In contrast to ACEIs, treatment with calcium antagonists in the renal disease state was originally thought to have adverse effects by preferentially dilating the afferent arteriole and increasing glomerular pressure. In the present study, we show that benidipine dilated both the afferent and efferent arterioles, but amiodipine and most of the other calcium antagonists preferentially dilated the afferent arteriole. The reason why benidipine dilated the efferent arteriole could not be defined based on the present experiments and awaits further investigation. Nevertheless, it is expected that benidipine will not produce glomerular hypertension and hyperfiltration in patients with renal diseases.

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References


