Divergent natriuretic action of calcium channel antagonists in mongrel dogs: renal haemodynamics as a determinant of natriuresis

Masanori HONDA, Koichi HAYASHI, Hiroto MATSUDA, Eiji KUBOTA, Hirobumi TOKUYAMA, Ken OKUBO, Yuri OZAWA and Takao SARUTA
Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan

ABSTRACT

This study examined the effects of different types of calcium channel antagonists on renal haemodynamics and natriuresis. The intravenous infusion of nifedipine (L-type blocker), efonidipine (L/T-type blocker) or mibefradil (predominant T-type blocker) into anaesthetized dogs elicited similar, albeit modest, reductions in blood pressure. Nifedipine (1 µg·min⁻¹·kg⁻¹) increased renal plasma flow (RPF) (23 ± 6%; P < 0.05) and glomerular filtration rate (GFR) (25 ± 5%; P < 0.05) (all values are means ± S.E.M., n = 7). Efonidipine (0.33 µg·min⁻¹·kg⁻¹) also elevated RPF (18 ± 6%; P < 0.05), and tended to increase GFR (17 ± 8%; P = 0.08). These antagonists exerted contrasting actions on the filtration fraction (FF), with an increase being elicited by nifedipine, whereas efonidipine had no effect. Furthermore, mibefradil (0.01–1 µg·min⁻¹·kg⁻¹) slightly elevated RPF (between 5 ± 3% and 8 ± 3%), but failed to alter GFR, resulting in a decrease in FF. Nifedipine slightly increased urinary sodium excretion (U NaV) (29 ± 16% increase at 1 µg·min⁻¹·kg⁻¹) and fractional sodium excretion (FE Na) (18 ± 14%), whereas efonidipine (0.33 µg·min⁻¹·kg⁻¹) elicited marked elevations in U NaV (110 ± 38%; P < 0.05) and FE Na (102 ± 44%; P < 0.05). Mibefradil (1 µg·min⁻¹·kg⁻¹) exerted a moderate natriuretic action [U NaV, +60 ± 32% (P = 0.1); FE Na, +67 ± 20% (P < 0.05)]. Furthermore, although a positive correlation was observed between U NaV and urinary nitrate/nitrite excretion, no differences were noted between the various calcium channel antagonists.

Collectively, this study demonstrates that the glomerular haemodynamic and natriuretic actions of these calcium channel antagonists, which possess diverse blocking activities on L/T-type channels, vary. Based on the divergent actions on FF (i.e. increase, no change and decrease by nifedipine, efonidipine and mibefradil respectively), the natriuretic action of calcium channel antagonists is possibly attributed to the inhibition of tubular sodium reabsorption associated with increased post-glomerular blood flow, rather than increased GFR.

INTRODUCTION

Calcium channel antagonists have been used widely in the treatment of hypertension and angina pectoris. Although they are potent vasodilators, calcium channel antagonists do not cause sodium retention [1], an undesired effect that is observed with the use of other vasodilators, including hydralazine and minoxidil. Indeed, long-term therapy with calcium channel antagonists produces no alterations in circulating blood pressure; t-NAME, Nω-nitro- l-arginine methyl ester; NO, nitrate + nitrite; PG, prostaglandin; RPF, renal plasma flow; U NaV, urinary sodium excretion.

Correspondence: Dr Takao Saruta (e-mail saruta@mc.med.keio.ac.jp).
volume [2]. Rather, calcium channel antagonists increase sodium excretion in the face of hypotension when administered acutely to patients [3] and experimental animals with hypertension [2]. It has been postulated that the natriuretic mechanisms of calcium channel antagonists are associated with changes in renal haemodynamics [4], direct effects on renal tubules [1] and activation/suppression of vasoactive substances [5–7]. The precise mechanism of the natriuretic effect of calcium channel antagonists, however, has not been fully characterized. Furthermore, a number of novel calcium channel antagonists have recently been developed, with different actions on renal afferent and efferent arterioles [8–10]. It has not yet been examined, however, whether these calcium channel antagonists exert divergent actions on natriuresis.

Although calcium channel antagonists exert their action mainly through the blockade of L-type voltage-dependent calcium channels in vascular smooth muscles, several lines of evidence suggest that the calcium channel antagonists possess multiple actions independent of this channel inhibition. Thus recent investigations have indicated that calcium channel antagonists increase nitric oxide (NO) production both in vitro [11] and in vivo [12]. Given that NO contributes to renal sodium handling [13–17], it is reasonable to speculate that natriuresis induced by calcium channel antagonists is associated with NO [18,19]. Furthermore, some newly developed calcium channel antagonists, including efonidipine, are reported to block T-type, as well as L-type, calcium channels [20,21], whereas traditional types of calcium channel antagonists inhibit only L-type calcium channels. Although T-type calcium channels have been identified in cardiac and vascular smooth muscle cells [21,22], the role of T-type calcium channels in the renal circulation and tubular function has not been fully understood until recently, due to the lack of selective antagonists to specific calcium channel subtypes.

In the present study, we have examined the role of renal haemodynamics and vasoactive substances, including NO and prostaglandins (PGs), in mediating the acute natriuretic response to calcium channel antagonists. In addition, we have evaluated the renal effects of three different calcium channel antagonists, nifedipine, efonidipine and mibefradil, which have been shown to possess blocking activity for L-type, L-/T-type and T-type calcium channels respectively [20,21], and to have distinct actions on renal microvascular beds [9].

METHODS

Measurement of systemic and renal haemodynamics

All experimental procedures in this study were conducted in accordance with the guidelines of the Animal Care Committee of Keio University. A total of 21 adult male mongrel dogs (10–15 kg) were fed on a standard diet (Oriental Yeast Co., Tokyo, Japan), and were anaesthetized with sodium pentobarbital (30 mg/kg). After intratracheal intubation, each animal was ventilated with an artificial respirator and placed on a heating blanket to maintain body temperature at 37 °C. A 7-Fr catheter was inserted through the right femoral artery to measure mean arterial pressure (MAP) and heart rate (HR), and the left radial vein was catheterized for drug infusion. The right radial vein was catheterized for blood sampling. A 7-Fr catheter was placed in the bladder for clearance studies.

Data on systemic (MAP and HR) and renal (see below) haemodynamics were analysed with a Macintosh laboratory system (Mac Lab; Analog-Digital Instruments, Castle Hill, NSW, Australia) [23–25].

Experimental protocol

After surgical preparation, the animals were allowed to equilibrate for 120 min before initiating experimental protocols. After a 30 min period of observation of basal haemodynamics, nifedipine (Bayer Yakuhin Ltd., Osaka, Japan), efonidipine (Nissan Chemical Industries, Ltd., Tokyo, Japan) or mibefradil (Nippon Roche Ltd., Tokyo, Japan) was infused intravenously at doses of 0.01, 0.1 and 1 μg min⁻¹·kg⁻¹ for nifedipine, 0.033, 0.16 and 0.33 μg min⁻¹·kg⁻¹ for efonidipine, and 0.01, 0.1 and 1 μg min⁻¹·kg⁻¹ for mibefradil. The doses were selected based on our preliminary results that these calcium channel antagonists exerted hypotensive actions of similar magnitude (up to 5%) at each dose, but that higher doses caused variable increases in HR, suggestive of different degrees of sympathetic nerve activation. To eliminate such confounding factors that would modify direct renal actions of calcium channel antagonists, we compared the renal actions of these antagonists at doses whereby MAP was reduced similarly in magnitude and HR was unaltered.

A 30 min period was allowed for equilibration of the action of the calcium channel antagonists on the renal circulation. Thereafter, two 15-min clearance studies were conducted for each dose of the calcium channel antagonists, and the effects of these agents on whole-kidney haemodynamics and the renal natriuretic response were assessed. Renal plasma flow (RPF) and glomerular filtration rate (GFR) were assessed by clearance of p-aminohippurate and inulin respectively. The filtration fraction (FF) was calculated as GFR/RPF. After completion of the experimental procedures, the dogs were humanely killed with an intravenous injection of a large amount of pentobarbital.

Urinary nitrate + nitrite (NO₃⁻) and PG excretion

For NO₃⁻ measurements, collected urine was kept in a
freezer at −20 °C. Nitrite and nitrate concentrations were evaluated using the Griess reaction [23,26], and the sum of these constituents was considered as a marker of NOx levels. PGE₂ and 6-oxo-PGF₁α concentrations in the urine were measured by RIA [27].

**Statistical analysis**
Data are expressed as means ± S.E.M. (n = 7). Data were analysed by two-way ANOVA followed by Fisher’s post hoc test or Student’s t-test, as appropriate. P < 0.05 was considered statistically significant.

**RESULTS**

**Systemic haemodynamics**
Systemic haemodynamic data are presented in Table 1. The doses of calcium channel antagonists used in the present study had only a modest vasodepresser action, with a slight decrease in MAP at the maximal dose of each antagonist. Similarly, the calcium channel antagonists had no effect on HR.

**Renal haemodynamics**
Basal values prior to administration of calcium channel antagonists are shown in Table 2. There was no significant difference between the groups for any of the basal parameters.

The effects of calcium channel antagonists on renal haemodynamics are illustrated in Figures 1–3. To facilitate comparisons, changes in renal function are expressed as percentage changes from the baseline (i.e. control) values. After the administration of 0.1 μg·min⁻¹·kg⁻¹ nifedipine, RPF was increased by 15 ± 4% (mean ± S.E.M., n = 7) (P < 0.05) (Figure 1). At a dose of 1 μg·min⁻¹·kg⁻¹, nifedipine elicited a 23 ± 6% increase in RPF (P < 0.01). Similarly, efonidipine caused marked rises in RPF, with increments of 20 ± 8% (P < 0.05) and 18 ± 6% (P < 0.05) at doses of 0.16 and 0.33 μg·min⁻¹·kg⁻¹ respectively. In contrast, mibefradil elicited modest increments in RPF at 0.1 μg·min⁻¹·kg⁻¹ (6 ± 3% ; P < 0.05) and 1 μg·min⁻¹·kg⁻¹ (8 ± 3%; P < 0.05).

As shown in Figure 2, nifedipine elevated GFR, with increments of 21 ± 7%, 18 ± 3% and 25 ± 5% (all P < 0.05) at doses of 0.01, 0.1 and 1 μg·min⁻¹·kg⁻¹ respectively. Efonidipine also augmented GFR; increments of 20 ± 8% (P < 0.05) and 17 ± 8% (P = 0.08) were observed at doses of 0.16 and 0.33 μg·min⁻¹·kg⁻¹ respectively. Mibefradil had no effect on GFR at the doses used in the present study.

Nifedipine significantly elevated FF at a dose of 0.01 μg·min⁻¹·kg⁻¹ (7 ± 2%; P < 0.05), and this tend-

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**Table 1** Effects of calcium channel antagonists on systemic haemodynamics in anaesthetized dogs

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Dose (μg·min⁻¹·kg⁻¹)</th>
<th>MAP (mmHg)</th>
<th>HR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine</td>
<td>Control</td>
<td>123 ± 4</td>
<td>117 ± 5</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>123 ± 5</td>
<td>117 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>121 ± 5</td>
<td>119 ± 5</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>118 ± 4*</td>
<td>123 ± 7</td>
</tr>
<tr>
<td>Efonidipine</td>
<td>Control</td>
<td>125 ± 2</td>
<td>112 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.033</td>
<td>123 ± 2</td>
<td>111 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.16</td>
<td>122 ± 2</td>
<td>110 ± 6</td>
</tr>
<tr>
<td></td>
<td>0.33</td>
<td>117 ± 3*</td>
<td>113 ± 5</td>
</tr>
<tr>
<td>Mibefradil</td>
<td>Control</td>
<td>127 ± 3</td>
<td>110 ± 8</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
<td>127 ± 3</td>
<td>109 ± 9</td>
</tr>
<tr>
<td></td>
<td>0.1</td>
<td>125 ± 3</td>
<td>108 ± 8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>123 ± 2*</td>
<td>108 ± 8</td>
</tr>
</tbody>
</table>

**Table 2** Baseline values prior to administration of calcium channel antagonists in anaesthetized dogs

Values are means ± S.E.M. (n = 7).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Nifedipine group</th>
<th>Efonidipine group</th>
<th>Mibefradil group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPF (ml/min)</td>
<td>113 ± 7</td>
<td>121 ± 14</td>
<td>119 ± 11</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>32.5 ± 2.3</td>
<td>31.0 ± 3.1</td>
<td>38.5 ± 3.6</td>
</tr>
<tr>
<td>FF</td>
<td>0.29 ± 0.02</td>
<td>0.26 ± 0.02</td>
<td>0.33 ± 0.02</td>
</tr>
<tr>
<td>U₀X (μmol/min)</td>
<td>3.0 ± 1.4</td>
<td>2.5 ± 0.7</td>
<td>3.0 ± 1.6</td>
</tr>
<tr>
<td>FS₉0 (%)</td>
<td>0.10 ± 0.04</td>
<td>0.10 ± 0.04</td>
<td>0.11 ± 0.06</td>
</tr>
<tr>
<td>Urinary NOx excretion</td>
<td>14.9 ± 5.3</td>
<td>17.7 ± 4.7</td>
<td>15.2 ± 4.3</td>
</tr>
<tr>
<td>(μmol/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary PGE₂ (pg/min)</td>
<td>328 ± 113</td>
<td>281 ± 44</td>
<td>325 ± 68</td>
</tr>
<tr>
<td>Urinary 6-oxo-PGF₁α excretion (pg/min)</td>
<td>681 ± 201</td>
<td>792 ± 260</td>
<td>807 ± 130</td>
</tr>
</tbody>
</table>

**Figure 1** Effects of calcium channel antagonists on RPF in anaesthetized dogs

Results are expressed as percentage changes from control. Significance of differences: *P < 0.05 compared with control; †P < 0.05 compared with nifedipine.
Figure 2 Effects of calcium channel antagonists on GFR in anaesthetized dogs
Results are expressed as percentage changes from control. Significance of differences: *P < 0.05, †P = 0.08 compared with control; ‡P < 0.05 compared with nifedipine.

Figure 3 Effects of calcium channel antagonists on FF in anaesthetized dogs
Results are expressed as percentage changes from control. Significance of differences: *P < 0.05, †P = 0.05 compared with control; ‡P < 0.05 compared with nifedipine.

Urinary sodium excretion (U_{Na}V) and fractional sodium excretion (F{E}_{Na})
Natriuretic responses to each calcium channel antagonist are illustrated in Figure 4. Nifedipine caused slight increases in U_{Na}V (increments of 25 ± 7% and 32 ± 8% at 0.01 and 0.1 µg·min^{-1}·kg^{-1} respectively; P < 0.05) (Figure 4, upper panel). In striking contrast, efonidipine markedly enhanced natriuresis. Thus U_{Na}V was increased by 108 ± 31% and 110 ± 38% at doses of 0.16 and 0.33 µg·min^{-1}·kg^{-1} respectively (P < 0.05 compared with nifedipine). Mibefradil exerted a mild natriuretic action [27 ± 15% at 0.1 µg·min^{-1}·kg^{-1} (P < 0.05); 60 ± 32% at 1 µg·min^{-1}·kg^{-1} (P = 0.1)], similar to that seen with nifedipine (P > 0.5).

In nifedipine-treated dogs, F{E}_{Na} paralleled the increases in U_{Na}V, with increments of 13 ± 4% (P = 0.05) and 21 ± 6% (P = 0.05) in F{E}_{Na} at doses of 0.01 and 0.1 µg·min^{-1}·kg^{-1} respectively (Figure 4, lower panel). As with its effects on U_{Na}V, efonidipine was very potent in enhancing F{E}_{Na}; 79 ± 29% and 102 ± 44% increments in F{E}_{Na} were observed at doses of 0.16 and 0.33 µg·min^{-1}·kg^{-1} respectively (P < 0.05 compared with nifedipine). Mibefradil also produced moderate increases in F{E}_{Na}, with increments of 51 ± 19% (P = 0.05) and 67 ± 20% (P < 0.05) observed at doses of 0.1 and 1 µg·min^{-1}·kg^{-1} respectively. The mibefradil-induced increases in F{E}_{Na} were greater than those with nifedipine at both 0.1 µg·min^{-1}·kg^{-1} (P = 0.05) and 1 µg·min^{-1}·kg^{-1} (P < 0.05).

Urinary NO and PG excretion
In contrast with their divergent actions on natriuresis, the calcium channel antagonists elicited similar effects on
urinary NO$_x$ excretion (Figure 5). Thus nifedipine caused slight increases in NO$_x$, although the increments did not attain statistical significance ($P > 0.1$). Mibefradil also elicited moderate increases in urinary NO$_x$ excretion, with increments of $26 \pm 11\%$ ($P < 0.05$) and $30 \pm 19\%$ ($P = 0.05$) observed at doses of 0.1 and 1 $\mu $g min$^{-1}$.$kg^{-1}$ respectively. Efonidipine augmented urinary NO$_x$ excretion; an increment of $48 \pm 30\%$ was attained at $0.16 \mu $g min$^{-1}$.$kg^{-1}$ efonidipine ($P < 0.02$). No differences in urinary NO$_x$ excretion were noted among these calcium channel antagonists ($P > 0.1$). Significant positive correlations were noted between $U_{Na,V}$ and urinary NO$_x$ excretion with nifedipine ($r = 0.65$, $P < 0.05$), efonidipine ($r = 0.57$, $P < 0.05$) and mibefradil ($r = 0.55$, $P < 0.05$).

In contrast, the calcium channel antagonists used had no effect on the urinary excretion of PGE$_2$ and 6-oxo-PGF$_{1\alpha}$ ($P > 0.5$; results not shown).

**DISCUSSION**

In the present study, we have demonstrated that calcium channel antagonists elicit increases in urinary sodium excretion. Thus the potency of the antagonists with regard to the magnitude of the natriuresis induced was efonidipine > nifedipine ~ mibefradil. Efonidipine-induced natriuresis was most marked ($U_{Na,V}$, $110 \pm 38\%$ increment; $FE_{Na}$, $102 \pm 44\%$ increment). In mibefradil-treated animals, although $U_{Na,V}$ was similar to that with nifedipine, the increment in $FE_{Na}$ ($60 \pm 32\%$) was greater than that observed with nifedipine. Since the doses of the calcium channel antagonists used in the present study resulted in only modest changes in blood pressure or HR, it appears that alterations in systemic parameters do not contribute substantially to the renal response to calcium channel antagonists. The heterogeneity in the natriuresis induced by these calcium channel antagonists therefore represents the divergent action of these agents on the intrarenal milieu.

Although the mechanisms behind calcium channel antagonist-induced natriuresis are not fully understood, it is likely that changes occur in both renal haemodynamics and tubular action. In the present study, we have demonstrated that nifedipine and efonidipine elevate GFR. The increased GFR therefore appears to be a factor facilitating natriuresis during treatment with these calcium channel antagonists. On the basis of the fact that efonidipine elicited greater natriuresis than nifedipine, however, the alteration in GFR cannot totally explain the natriuretic action of the calcium channel antagonists. Rather, the fact that mibefradil increases sodium excretion without changing GFR argues against a pivotal role for GFR in mediating calcium channel antagonist-induced natriuresis. The latter observations are consistent with previous reports that calcium channel antagonists augment natriuresis even when RPF and GFR are unchanged [8,28], and further suggest that an important site of action in mediating the calcium channel antagonist-induced natriuresis is the renal tubule. Indeed, the present study demonstrates that both efonidipine and mibefradil caused marked increases in $FE_{Na}$ ($102 \pm 44\%$ and $67 \pm 20\%$ respectively). In this regard, Dibona and Sawin [29] demonstrated that, in a micropuncture study, felodipine inhibited sodium reabsorption at the distal and collecting duct. Other investigators also suggested proximal tubules as a site for calcium channel antagonist-induced natriuresis [30,31]. Regardless of the exact tubular site of action, it is tubular rather than glomerular action that is the major determinant of calcium channel antagonist-induced natriuresis.

The heterogeneity in the natriuretic action of calcium channel antagonists has not been investigated hitherto. Based on their blocking activity on calcium channel subtypes, nifedipine, efonidipine and mibefradil are characterized as blockers of L-type, L-/T-type and predominantly T-type channels respectively [20,21]. The present study demonstrates a tendency for FF to increase with nifedipine, to remain constant with efonidipine and to decrease with mibefradil. Of note is our previous report which revealed that efonidipine resulted in dilation of efferent as well as afferent arterioles, while nifedipine caused predominantly afferent arteriolar dilation in isolated perfused rat hydronephrotic kidneys [9]. Furthermore, we have shown recently that mibefradil dilates efferent as well as afferent arterioles in canine kidneys, using the intravital CCD (charge-coupled-device) camera technique [32]. The latter observation is consistent with that by Nakamura et al. [33] demonstrating a decrease in efferent arteriolar resistance induced by mibefradil, which could be associated with the inhibitory action of mibefradil on T-type calcium channels. The renal micro-

**Figure 5  Effects of calcium channel antagonists on urinary NO$_x$ excretion in anaesthetized dogs**

Results are expressed as percentage changes from control. Significance of differences: *$P < 0.05$, †$P = 0.05$ compared with control; ‡$P < 0.05$ compared with nifedipine.

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vascular action of these calcium channel antagonists therefore accounts for their effects on FF. Furthermore, in the situation where efferent arterioles are dilated, the elevated RPF will increase vasa recta blood flow, and subsequently inhibit tubular sodium reabsorption [34–36]. Thus the greater natriuresis observed with verapamil may be attributable to increased vasa recta flow caused by the efferent arteriolar dilation. The link between the natriuretic action and the blocking activity on L- and T-type channels, however, requires further investigations.

In addition to changes in renal haemodynamics as a factor in calcium channel antagonist-induced natriuresis, several other factors may contribute to the enhancement of sodium excretion [13–17]. It has been reported that verapamil prevented the anti-natriuretic action of the NO synthase inhibitor N^ω-nitro-L-arginine methyl ester (L-NAME) [19], and partially reversed the attenuation of pressure natriuresis by L-NAME [18]. Furthermore, Ni et al. [12] reported that felodipine increased urinary NO\textsubscript{x} excretion in 5/6-nephrectomized rats. In contrast, verapamil is reported to exert a natriuretic action even in the presence of L-NAME [37]. Thus the role of NO in mediating calcium channel antagonist-induced natriuresis remains unclear. In the present study, we have demonstrated that calcium channel antagonists increase urinary NO\textsubscript{x} excretion; urinary excretion of NO\textsubscript{x} parallels that of sodium, but not GFR. Ostensibly, renal NO contributes in part to the augmentation of natriuresis by calcium channel antagonists, and this NO-induced renal response is most likely to be mediated by a tubular, but not a glomerular, action of these agents. On the other hand, the disproportionately greater increase in urinary sodium excretion compared with urinary NO\textsubscript{x} excretion suggests that renal NO plays a permissive role, rather than exerting a controlling action, in mediating calcium channel antagonist-induced natriuresis. Furthermore, the present study fails to demonstrate a difference in urinary NO\textsubscript{x} excretion for these three calcium channel antagonists, despite marked differences in urinary sodium excretion. Although calcium channel antagonists enhance NO production in vascular endothelial cells [11,12], urinary NO\textsubscript{x} excretion does not necessarily reflect alterations in the renal NO system, but may be attributed to the tubular handling of NO\textsubscript{x} [38]. Thus further investigations are required to clarify the role of NO in calcium channel antagonist-induced natriuresis.

In the present study, we found that calcium channel antagonists failed to affect the urinary excretion of PGE\textsubscript{2} or PGI\textsubscript{2} metabolites. Previous studies have not supported the premise that renal PGs contribute to calcium channel antagonist-induced natriuresis. For example, Seino et al. [39] reported that pretreatment with indomethacin failed to affect diltiazem-induced natriuresis in anaesthetized rabbits. Furthermore, Jenkins et al. [28] examined the natriuretic action of calcium channel antagonists in normal humans, and compared the effects of these antagonists with that during blockade of PGs. They observed the same degree of natriuresis even though urinary PG excretion was inhibited by indomethacin. Thus we conclude that PGs do not participate in calcium channel antagonist-induced natriuresis.

In summary, the present study has demonstrated that the ability of the calcium channel antagonists nifedipine, efedipine and mibefradil to induce natriuresis differs depending on the agent used. Based on our recent demonstration that these calcium channel antagonists exert differential actions on renal afferent and efferent arterioles, the difference in the natriuretic action appears to depend on alterations in FF and GFR. Finally, calcium channel antagonists can augment urinary NO\textsubscript{x} excretion. Whether the increased renal NO participates in the modulation of calcium channel antagonist-induced natriuresis requires additional investigation.

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