# ORIGINAL ARTICLE

## **Role of protein kinase C in Ca channel blocker-induced renal arteriolar dilation in spontaneously hypertensive rats** – Studies in the isolated perfused hydronephrotic kidney –

Koichi Hayashi, Shu Wakino, Yuri Ozawa, Koichiro Homma, Takeshi Kanda, Ken Okubo, Ichiro Takamatsu, Satoru Tatematsu, Hiroo Kumagai and Takao Saruta

Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

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Abstract. The present study examined the role of L-/T-type Ca channels and the interaction between these channels and protein kinase C (PKC) in hypertension. The isolated perfused hydronephrotic rat kidney model was used to visualize directly the renal microvascular effects of L-/T-type Ca channel blockers (nifedipine and mibefradil, respectively). Nifedipine reversed the angiotensin II-induced constriction of afferent, but not efferent, arterioles in kidneys from Wistar-Kyoto rats (WKY), and similar magnitude in dilation was observed in spontaneously hypertensive rats (SHR). Although mibefradil elicited dilation of both arterioles, the afferent arteriolar dilation was less in SHR than in WKY  $(57 \pm 5\%$  vs.  $80 \pm 4\%$  reversal at 1 µmol/L). The pretreatment with staurosporine did not alter the angiotensin II-induced afferent arteriolar constriction in WKY, but attenuated this response in SHR. Furthermore, staurosporine enhanced the nifedipine-induced afferent arteriolar dilation ( $62 \pm 3\%$  vs.  $50 \pm 3\%$  reversal at 10 nmol/L), and restored the attenuated afferent arteriolar response to mibefradil in SHR. The pretreatment with thapsigargin (a blocker of IP3-mediated intracellular calcium release) prevented the angiotensin II-induced afferent arteriolar constriction in WKY, but caused a significant constriction of afferent arterioles in SHR and efferent arterioles in WKY and SHR; in this setting, mibefradil did not alter efferent arteriolar tone. In conclusion, although both L-type (nifedipine) and T-type Ca channel blockers (mibefradil) exerted potent vasodilation of rat renal microvessels, these actions were modified by PKC, which determined the afferent arteriolar sensitivity to these blockers in SHR. Furthermore, the enhancement in nifedipine-induced afferent arteriolar dilation by staurosporine in SHR suggests that L-type Ca channel activity is augmented in hypertensive animals. (Keio J Med 54 (2): 102-108, June 2005)

Key words: hypertension, protein kinase C, mibefradil, afferent arterioles, efferent arterioles

### Introduction

It has been proposed that multiple mechanisms are responsible for the augmented vascular tone in hypertension. In previous studies, protein kinase C (PKC) is demonstrated to be augmented in vascular smooth muscle cells from spontaneously hypertensive rats (SHR), compared with that in normotensive littermates.<sup>1,2</sup> Furthermore, the activity of voltage-dependent Ca channels is altered in hypertensive animals.<sup>3</sup> Among the voltagedependent Ca channels, the role of L-type Ca channels has been extensively investigated, and has been reported to be enhanced in hypertensive animals.<sup>3,4</sup> Recently, a growing body of evidence has accrued that T-type Ca channels plays an important role in the cardiovascular system, and is rendered teleologically active in the tissues where the electrical function is periodically fluctuated, including cardiac pacemaker cells.<sup>5</sup> Furthermore, several lines of studies have demonstrated that the blockade of T-type Ca channels causes sustained vasodilation of renal arterioles<sup>6,7</sup> and mesenteric arteries.<sup>8</sup> Despite widespread distribution of

Reprint requests to: Dr. Koichi Hayashi, Department of Internal Medicine, School of Medicine, Keio University, 35 Shinanomachi, Shinjukuku, Tokyo 160-8582, Japan, e-mail: khayashi@sc.itc.keio.ac.jp T-type Ca channels in the vascular tissue, the role of these Ca channels remains undetermined in hypertensive animals.

The renal vasculature possesses unique characteristics with regard to the distinct microvascular property of afferent and efferent arterioles. Previous studies revealed that vascular smooth muscle cells of afferent arterioles manifest spindle-shaped morphology and contain both SM1 and SM2 myosine heavy chain isoforms, whereas those of efferent arterioles exhibit starlike shape and possess only a SM1 isoform.<sup>9,10</sup> Consistently, L-type Ca channels are distributed at the afferent, but not efferent, arteriole.<sup>11-13</sup> In contrast, T-type Ca channels are present in both afferent and efferent arterioles, and actually contribute substantially to the regulation of renal microvascular tone.<sup>6,7</sup> Additionally, several lines of studies have clarified differing mechanisms for intracellular signal transduction in afferent and efferent arterioles.<sup>14,15</sup> In the afferent arteriole, inositol 1,4,5-trisphosphate (IP3) stimulates sarcoplasmic reticulum, and elicits the intracellular Ca release, which finally gates L-type Ca channels.14,15 In contrast, in the efferent arteriole, both IP3 and diacylglycerol participate in the efferent arteriolar constrictor mechanism.<sup>14,15</sup> The IP3-mediated stimulation of sarcoplasmic reticulum is suggested to induce the Ca entry, possibly through store-operated Ca channels.<sup>14,16,17</sup> Furthermore, diacylglycerol and PKC are reported to activate transient receptor potential (TRP) channels<sup>18</sup> or nonselective cation channels,<sup>19</sup> which subsequently accelerate the Ca entry from the extracellular space. Of note, both mibefradil<sup>20</sup> and nickel, relatively selective inhibitors for T-type Ca channels, potently dilate efferent arterioles, thus suggesting that T-type Ca channels participate in the vasomotor mechanisms of the efferent arteriole, including IP3- and PKC-associated pathways. Although the divergent responsiveness of afferent and efferent arterioles controls glomerular capillary pressure, the alteration in the vascular tone of these arterioles in hypertension is not fully elucidated.

In the present study, we examined the effect of Ltype and T-type Ca channel blockers on angiotensin (ANG) II-induced constriction of afferent and efferent arterioles in hypertensive animals, and compared the role of L- and T-type Ca channels in mediating the renal microvascular tone in the normotensive control.

## Methods

Six-week-old male Wistar-Kyoto rats (WKY; n = 18) and spontaneously hypertensive rats (SHR; n = 18) were used for renal perfusion study. Under ether anesthesia, chronic hydronephrosis was established by ligation of the right ureter through a small mid-abdominal incision;<sup>6,14,21</sup> this model facilitates direct visualization of the renal microcirculation, with qualitatively parallel responses of renal microvessels with those expected from renal hemodynamic responses in normal kidneys.<sup>22,23</sup> Furthermore, lack of tubuloglomerular feedback<sup>24</sup> or systemic influence of neural and hormonal factors would allow direct assessment of renal microvascular responses. After 8–10 weeks, at which time renal tubular atrophy had progressed to a stage that

allowed direct microscopic visualization of renal microvessels, the kidneys were harvested for perfusion study. All procedures involving this study were conducted following the guidelines of the Animal Care Committee of Keio University. The animals had free access to water and chows throughout the study. The rats were anesthetized with ether, and the abdominal cavity was exposed by midline incision. The

dominal cavity was exposed by midline incision. The renal artery of the hydronephrotic kidney was cannulated *in situ* through the superior mesenteric artery across the aorta. The hydronephrotic kidney was placed on the stage of an inverted microscope (IMT-2, Olympus, Tokyo, Japan) modified to accommodate a heated chamber equipped with a thin glass viewing port on the bottom surface. Kidneys were allowed to equilibrate for 30 min before initiating experimental procedures.

Kidneys were perfused with medium consisting of a Krebs-Ringer bicarbonate buffer containing 5 mmol/L D-glucose, 7.5% bovine serum albumin (Sigma, St. Louis, MO), and a complement of amino acids.<sup>25</sup> The perfusion apparatus is illustrated in our previous publication.<sup>22</sup> The perfusion medium was saturated with a gas mixture of  $95\% O_2/5\% CO_2$  within a pressurized reservoir. The perfusion pressure, monitored at the level of the renal artery, was maintained constant at 80 mmHg by adjusting the back-pressure-type regulator (Model 10BP, Fairchild Industrial products Co., Winston-Salem, NC).

Vessel diameters were measured as detailed previously.<sup>21,22</sup> In brief, video images from a video camera (model XC-77, Sony, Tokyo) were recorded with a videocassette recorder and transmitted to a computer (PS55/Model 5551, IBM Japan, Tokyo) equipped with a video acquisition board (Targa 16+, Truevision Inc., Indianapolis, IN). Segments of afferent and efferent arterioles approximately 50  $\mu$ m in length, near the glomerulus, were evaluated at 0.5–1.0 second intervals. Mean vessel diameter was determined by averaging all measurements obtained during the plateau of the response.

## Experimental protocols

1) Effect of nifedipine and mibefradil on ANG IIinduced renal vasoconstriction

Following the observation of ANG II (0.3 nmol/L)-

induced vasoconstrictor responses, the vasodilator effect of nifedipine (0.01, 0.1, and 1  $\mu$ mol/L) and mibefradil (0.01, 0.1, and 1  $\mu$ mol/L) was assessed in kidneys from both WKY and SHR. Thereafter, losartan (10  $\mu$ mol/L) was added directly into the perfusate to eliminate the remaining vasoconstrictor tone of these arterioles.

2) Effects of staurosporine on nifedipine/mibefradilinduced changes in renal microvascular tone

The ANG II-induced vasoconstriction of renal arterioles involves both PKC- and IP3-mediated pathways as intracellular signaling mechanisms.<sup>14,15</sup> Initially, 50 nmol/L staurosporine was administered into the perfusate. Following the induction of ANG II (0.3 nmol/L)-induced renal vasoconstriction, nifedipine (0.01, 0.1 and 1  $\mu$ mol/L) or mibefradil (0.01, 0.1 and 1  $\mu$ mol/L) was added to the perfusate, and the vasodilator effect of these agents was evaluated in WKY and SHR.

3) Effects of thapsigargin on nifedipine/mibefradilinduced changes in renal microvascular tone

The effect of nifedipine and mibefradil on the ANG II-induced constriction of renal arterioles was evaluated during the inhibition of the IP3 pathway by thapsigargin. In the presence of thapsigargin (1  $\mu$ mol/L), which depleted sarcoplasmic Ca store by inhibiting sarcoplasmic Ca-ATPase<sup>26</sup> and thus mainly blocked the IP3-mediated vascular tone, ANG II (0.3 nmol/L) was added to establish the basal vascular tone. Subsequently, the effect of nifedipine (0.01, 0.1 and 1  $\mu$ mol/L) or mibefradil (0.01, 0.1 and 1  $\mu$ mol/L) on the ANG II-induced renal vascular tone was evaluated in WKY and SHR.

## Analysis of data

Data are expressed as the means  $\pm$  SEM. Data were analyzed by 2-way ANOVA followed by Bonferroni's post hoc test. P values < 0.05 were considered statistically significant.

#### Results

## Comparison of nifedipine- and mibefradil-induced renal vasodilation in WKY and SHR

Renal arteriolar responses to nifedipine and mibefradil in kidneys from SHR were evaluated, and were compared with those in WKY kidneys (Table 1). In WKY, ANG II (0.3 nmol/L) elicited marked vasoconstriction of afferent ( $30 \pm 3\%$  decrement in diameter, n = 12) and efferent arterioles ( $31 \pm 4\%$  decrement in diameter, n = 12). In SHR kidneys, afferent arteriolar vasoconstrictor responses to ANG II ( $36 \pm 3\%$  dec-

**Table 1** Effects of Angiotensin II on Renal Afferent and Efferent Arteriolar Diameters

		Diameter (µm)	
		Baseline	Angiotensin II (0.3 nmol/L)
WKY	Afferent arterioles $(n = 12)$	$14.6 \pm 0.3$	$10.1 \pm 0.3*$
	Efferent arterioles $(n = 12)$	$13.0 \pm 0.3$	$9.0 \pm 0.4*$
SHR	Afferent arterioles $(n = 12)$	$14.2 \pm 0.2$	$9.0 \pm 0.3*$
	Efferent Arterioles $(n = 12)$	$12.8 \pm 0.3$	$9.1 \pm 0.3*$

WKY; Wistar-Kyoto rats, SHR; spontaneously hypertensive rats. \*, p < 0.01 vs. Baseline.



**Fig. 1** Effects of nifedipine and mibefradil on angiotensin II-induced constriction of renal arterioles in kidneys from WKY and SHR. Nifedipine caused similar dilation of afferent arterioles in WKY and SHR, whereas mibefradil-induced dilation of the afferent arteriole was attenuated in SHR. Efferent arterioles did not respond to nifedipine, or exhibited nearly identical dilator response to mibefradil in WKY and SHR. Results are means  $\pm$  SEM.  $\dagger$ , p < 0.05 vs. WKY.

rement in diameter, n = 12) tended to be greater than those in WKY (p = 0.1). Efferent arteriolar responses (29 ± 5% decrement in diameter, n = 12) did not differ from those from WKY kidneys (p > 0.5).

Nifedipine caused a dose-dependent vasodilation of the ANG II-constricted afferent arteriole, with nearly identical responses observed in WKY (n = 6) and SHR (n = 6; Fig. 1, upper). Nifedipine however failed to relax the efferent arteriolar constriction in either WKY or SHR. Mibefradil also inhibited the afferent arteriolar responses to ANG II in a dose-dependent manner (n = 6; Fig. 1, lower left). Of note, the vasodilator



Fig. 2 Role of protein kinase C and intracellular Ca release in angiotensin II-induced constriction of renal arterioles from WKY and SHR kidneys. In WKY, angiotensin (ANG, 0.3 nmol/L) II-induced constriction of afferent arterioles was unaffected by the pretreatment with staurosporine (50 nmol/L, filled bars), but completely abolished by thapsigargin (1  $\mu$ mol/L, hatched bars). In SHR kidneys, however, staurosporine blunted the constrictor responses to ANG II of both afferent arterioles. Results are means  $\pm$  SEM. \*, p < 0.05 vs. ANG II (open bars); \*\*, p < 0.01 vs. ANG II.

action of mibefradil on the afferent arteriole was blunted in SHR, compared with that in WKY (100 nmol/L,  $30 \pm 3\%$  vs.  $48 \pm 4\%$ , p < 0.05; 1 µmol/L,  $57 \pm 5\%$  vs.  $80 \pm 4\%$ , p < 0.05; n = 6). In contrast, efferent arterioles manifested similar responsiveness to mibefradil in WKY (n = 6) and SHR kidneys (n = 6).

# Effects of staurosporine/thapsigargin on nifedipine- and mibefradil-induced changes in renal microvascular tone

The pretreatment with staurosporine (50 nmol/L) had no effect on basal arteriolar diameters in WKY (n = 6) or SHR kidneys (n = 6). In the presence of staurosporine, ANG II (0.3 nmol/L) caused vasoconstriction of both afferent and efferent arterioles in WKY and SHR (Fig. 2, filled bars). Of note, in WKY the ANG II-induced change in afferent arteriolar diameter did not differ from that in the absence of staurosporine (open bars, p > 0.5), whereas blunted responses were observed in efferent arterioles from WKY and in afferent and efferent arterioles from SHR (p < 0.05). In this setting, nifedipine dilated the ANG II-constricted afferent arterioles in a dose-dependent manner, with greater responsiveness observed in SHR kidneys at doses of 10 and 100 nmol/L (p < 0.5; Fig. 3, upper left). No vasodilator effect was observed in the efferent arteriole from WKY or SHR (Fig. 3, upper right).

In the presence of staurosporine, mibefradil potently reversed the ANG II-induced constriction of afferent arterioles in both WKY and SHR (Fig. 3, lower left). Thus, in the afferent arterioles from SHR, the pretreatment with staurosporine eliminated the attenuated vasodilator responses to mibefradil (see Fig. 1, lower left). No difference in the vasodilator response to mibefradil was noted in the efferent arteriole between WKY and



Fig. 3 Effect of nifedipine and mibefradil on angiotensin II-induced constriction of renal arterioles in the presence of staurosporine. In afferent arterioles from SHR kidneys, the pretreatment with staurosporine (50 nmol/L) enhanced the vasodilator responses to nifedipine (upper), and restored the blunted responsiveness to mibefradil, but had no effect on efferent arteriolar responses to mibefradil (lower). Results are means  $\pm$  SEM.  $\dagger$ , p < 0.05 vs. WKY.

## SHR (Fig. 3, lower right).

The administration of thapsigargin  $(1 \ \mu mol/L)$  did not alter the basal diameters of afferent or efferent arterioles. In this setting, the vasoconstrictor response to ANG II was totally abolished in the afferent arterioles from WKY kidneys  $(-1 \pm 4\%, n = 12;$  Fig. 2, hatched bars). In the efferent arteriole from WKY, thapsigargin markedly blunted, but did not eliminate completely, this response  $(-18 \pm 3\%, n = 12)$ . Similarly, the afferent and efferent arterioles from SHR kidneys exhibited diminished vasoconstrictor responses to ANG II (afferent,  $-9 \pm 4\%$ ; efferent,  $-22 \pm 4\%$ ; n = 12). In the presence of thapsigargin, nifedipine had no effect on arteriolar diameter in WKY or SHR kidneys (Fig. 4, upper). Similarly, mibefradil failed to alter the arteriolar tone of either vessel (Fig. 4, lower).

## Discussion

The present study has demonstrated that nifedipine causes marked vasodilation of the afferent arteriole, which is nearly identical in magnitude in WKY and SHR kidneys (Fig. 1). In contrast, the ability of mibe-fradil to dilate this arteriole differs, with blunted responsiveness observed in SHR. Since mibefradil elicits relatively selective inhibition on T-type Ca channels,<sup>20</sup> the diminished responsiveness of the afferent



**Fig. 4** Effect of nifedipine and mibefradil on angiotensin II-induced constriction of renal arterioles in the presence of thapsigargin (1  $\mu$ mol/L). In WKY, angiotensin (ANG) II failed to constrict the afferent arterioles. In SHR, ANG II exerted a diminished constrictor action on afferent/efferent arterioles. Neither nifedipine (upper) or mibefradil (lower) had any vasodilator effect on renal arteriolar tone in the presence of thapsigargin. Results are means  $\pm$  SEM.

arteriole to mibefradil would be associated with altered function of T-type Ca channels in this vessel in hypertension.<sup>4,27</sup> Of interest, in SHR kidneys the mibefradilinduced vasodilation is greater in efferent than in afferent arterioles, whereas nifedipine produces a relatively selective vasodilation of the afferent arteriole (Fig. 1).<sup>11,12,14,21</sup> Since systemic hypertension and elevated renal perfusion pressure would elevate myogenic afferent, but not efferent, arteriolar tone through the Ltype Ca channel-dependent mechanism,<sup>21</sup> the blockade of T-type Ca channels is expected to cause greater dilation of efferent than afferent arterioles in hypertensive animals. The difference in renal arteriolar action of these channel blockers therefore could influence the renal protective action of L-type and T-type Ca channel blockers in SHR.28

Renal microvessels possess unique characteristics with regard to their vasoconstrictor mechanisms. It is well established that L-type Ca channels prevail predominantly in the afferent arteriole.<sup>12–14</sup> Furthermore, the mechanisms for ANG II-induced vasoconstriction differ in afferent and efferent arterioles.<sup>14</sup> Thus, in WKY kidneys the effects of staurosporine and thapsigargin on the renal microvessels (i.e., Fig. 2) strongly suggest that the IP3 production constitutes a major determinant of the afferent arteriolar tone induced by ANG II in kidneys from normotensive rats, whereas the efferent arteriole requires both IP3- and PKC- mediated pathways for the ANG II-induced constrictor response.<sup>14</sup> Moreover, the present study shows that the ability of staurosporine to inhibit the ANG II-induced afferent arteriolar constriction is augmented in SHR (Fig. 2). These observations indicate that relative activity of PKC and IP3 pathways is altered in afferent arterioles of SHR, with greater activation of PKC in SHR, which is consistent with the previous reports by other investigators indicating enhanced PKC activity in aorta<sup>29,30</sup> and mesenteric artery<sup>30</sup> of hypertensive animals. Of interest, PKC is reported to activate various biological signaling, including free radical formation<sup>31</sup> and Rho-kinase activation.<sup>32</sup> Indeed, both free radicals<sup>33</sup> and Rho-kinase are demonstrated to be upregulated in SHR.<sup>34</sup> These effects of PKC as well as direct effects on vascular smooth muscles would serve to modify vascular tone in renal arterioles.

Alterations in PKC activity in hypertension would modify the responsiveness to Ca channel blockers. In the present study, we have found that during the treatment with staurosporine, in which PKC is blocked while the IP3 pathway ostensibly remains intact, nifedipine exerts greater vasodilator action on the afferent arteriole in SHR than in WKY (Fig. 3). This observation suggests, although indirectly, that the IP3-mediated vasoconstrictor component is more sensitive to the vasodilator action of nifedipine in SHR, and therefore may bear on the issue that L-type Ca channel activity is enhanced in hypertensive animals.<sup>3,35</sup> In this regard, we previously demonstrated that the PKC-mediated constrictor tone of the afferent arteriole is relatively refractory to the blocking action of the L-type Ca channel blocker.<sup>14,15</sup> It might be that the apparently identical responsiveness of the afferent arteriole to nifedipine (i.e., Fig. 1, upper left) is the overall consequences originating from the attenuated action of nifedipine on PKC-mediated tone and the enhanced sensitivity to the L-type Ca channel blockade. Clearly, it requires further investigations to establish this formulation.

In analogy with the action of nifedipine, the present study demonstrates that the pretreatment with staurosporine restores the diminished responsiveness to mibefradil observed in afferent arterioles from SHR kidneys (Figs. 1 and 3). Since staurosporine prevents the PKC-mediated constrictor mechanism, a substantial component of the remaining vasoconstrictor tone during ANG II and staurosporine treatment should be an IP3-mediated Ca release pathway.<sup>14,15</sup> Consequently, it is conjectured that the T-type Ca channel blockade by mibefradil causes similar degrees of the inhibition on the IP3-mediated vasoconstrictor tone in WKY and SHR. Alternatively, to the extent that mibefradil potently inhibits the IP3-mediated constrictor mechanism but fails to reverse the PKC-mediated vasoconstriction [36; see below], the attenuated vasodilation observed in SHR kidneys (i.e., Fig. 1) may reflect the reminiscence of the enhanced PKC activity in SHR. Again, these observed results are consistent with the formulation that hypertension alters the PKC activity,<sup>29,30</sup> which would contribute to the enhanced vascular responsiveness in hypertensive animals. Although it remains undetermined how mibefradil modifies intracellular vasoconstrictor mechanisms, recent investigations suggest an intimate communication between the plasma membrane and the endoplasmic reticulum.<sup>37</sup> Thus, T-type Ca channels within the plasma membrane might affect the sarcoplasmic Ca release. Indeed, T-type channel activation is reported to facilitate Ca<sup>2+</sup> release from sarcoplasmic reticulum in cardiac myocytes.<sup>38</sup>

In contrast to the potent vasodilator action of Ca channel blockers on the arteriolar tone during the PKC inhibition, these blockers exert less vasodilator action on renal arteriolar tone induced by PKC activation. Thus, in the presence of thapsigargin, nifedipine failed to alter the afferent arteriolar tone induced by ANG II in SHR (Fig. 4, upper right). Furthermore, mibefradil had no effect on the ANG II-induced constriction of renal arterioles in either WKY or SHR. In this regard, we have recently demonstrated that the PKC-induced tone of renal arterioles is resistant to the vasodilator action of nifedipine<sup>14</sup> and mibefradil.<sup>36</sup> Collectively, the differing responsiveness to Ca channel blockers of PKC and IP3 pathways would determine the vasodilator of these agents in hypertensive animals.

Finally, whether the difference in the experimental setting affect the renal microvascular responsiveness warrants comment. Since our results are obtained in the isolated perfused hydronephrotic kidney model, renal microvascular responsiveness might differ from that in the normal kidney. In this regard, we previously demonstrated that the renal microvascular response to ANP,<sup>22</sup> pressure,<sup>23</sup> and endothelin<sup>39</sup> is qualitatively identical in isolated normal and hydronephrotic rat kidneys. Furthermore, the renal microvascular effects of nifedipine and mibefradil in the isolated perfused hydronephrotic kidney are similar to those observed in canine renal microvessels using the intravital CCD videomicroscopic technique.<sup>40</sup> Of course, caveat is in order in interpreting our current observations because some intrarenal mechanisms indirectly affecting renal hemodynamics (i.e., tubuloglomerular feedback) are lacking in the hydronephrotic kidney model.

In conclusion, the present study demonstrates that L-type (nifedipine) and T-type Ca channel blockers (mibefradil) exert potent vasodilator action on rat renal microvessels. In SHR, however, these actions are modifies by a PKC-mediated component of the vascular tone on which either T-type or L-type Ca channel blockers are ineffective. Furthermore, the greater sensitivity to nifedipine of the afferent arteriole of SHR kidneys during the treatment with staurosporine suggests that L-type Ca channel activity is augmented in hypertensive animals. These alterations in renal arteriolar responsiveness in hypertensive animals therefore would affect the sensitivity of renal arterioles to Ca channel blockers, and may determine the renal microvascular hemodynamics in hypertension.

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