Cilnidipine Attenuates Renal Nerve Stimulation-Induced Renal Vasoconstriction and Antinatriuresis in Anesthetized Dogs

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ABSTRACT—We examined the effects of cilnidipine, which is an L and N-type Ca2+ channel blocker, on adrenergically regulated renal functions in anesthetized dogs. Renal nerve stimulation (RNS) at high frequency (3–7 Hz) decreased renal blood flow (RBF) without changes in systemic blood pressure. The RBF response was inhibited by intrarenal arterial (i.r.a.) infusion of cilnidipine at 0.1–0.3 μg/kg/min. Low-frequency RNS (0.5–1 Hz) reduced absolute and fractional urinary sodium excretion. These responses were attenuated during i.r.a. infusion of cilnidipine at 0.3 μg/kg/min. An increase in norepinephrine secretion rate induced by low-frequency RNS was also attenuated during cilnidipine infusion. These results suggest that cilnidipine can suppress norepinephrine release from the renal nerve endings and thereby interfere with the neural control of renal functions.

Keywords: Cilnidipine, Renal nerve stimulation, Renal vasoconstriction, Antinatriuresis, Norepinephrine secretion rate

The kidney is densely innervated by adrenergic nerve fibers. The renal nerve stimulation (RNS) releases norepinephrine (NE) and induces renal vasoconstriction and antinatriuresis by activation of α1-adrenoceptors. There are observations that L-type Ca2+ channel blockers, such as verapamil (1, 2), nicardipine (3), felodipine (4), and nifedipine (1, 5), induce renal vasodilation and natriuresis in anesthetized dogs and rats. However, RNS-induced renal vasoconstriction or antinatriuresis can not be suppressed by Ca2+ channel blockers (6–9). Thus, L-type Ca2+ channel blockers do not seem to interfere with the adrenergic regulation of the renal vascular tone and the renal tubular reabsorption, including NE release from the renal nerve endings. The release of neurotransmitters from the sympathetic nerve endings has been considered to be dominantly regulated by N-type Ca2+ channels (10). The release of NE from the renal sympathetic nerve was also shown to be inhibited by an N-type Ca2+ channel blocker in perfused rat kidney (11).

Cilnidipine (FRC-8653, Fig. 1) is a 1,4-dihydropyridine-derived Ca2+ channel blocker that has long-lasting hypotensive action (12). Cilnidipine has also been shown to attenuate the pressor response to acute cold stress by reducing the sympathetic nerve activity in spontaneously hypertensive rats (13). Recently, it has been found that cilnidipine attenuates both L- and N-type Ca2+ currents in the rat dorsal root ganglion neurons (14). In acutely dissociated sympathetic neurons of the rat, we have also observed that cilnidipine can inhibit N-type Ca2+ currents (15). Cilnidipine may be able to interfere with the adrenergic regulation of the renal vascular tone and the renal tubular reabsorption by inhibition of sympathetic Ca2+ channels.

In the present study, we examined the effects of cilnidipine on the RNS-induced renal vascular and tubular responses to clarify the action of cilnidipine on adrenergically regulated renal function in vivo.
MATERIALS AND METHODS

Animal preparation

Male beagle dogs weighing 9.5–13 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and then intubated and artificially ventilated with room air. The cephalic veins were cannulated for drug administration. Anesthesia was maintained by a continuous i.v. infusion of sodium pentobarbital at a rate of 5 mg/kg/hr throughout the experiments. The right brachial artery was cannulated for collection of blood samples and measurement of mean arterial pressure (MAP) with a pressure transducer (TP-400T; Nihon Kohden, Tokyo). The left kidney was exposed by a retroperitoneal flank incision. The renal nerves were dissected away from the renal vessels and cut after ligation. Platinum electrodes were placed on the distal portion of the renal nerve bundle so that electrical stimulation evoked nerve impulses running to the kidney. An electromagnetic flow probe was attached to the renal artery to measure the renal blood flow (RBF) with a square-wave flowmeter (MFV-3200, Nihon Kohden). Two curved 25-gauge needles connected to a polyethylene tube were inserted to the left renal artery for drug administration.

Animals were divided into two groups. In the experiment of urine formation and NE release (group 2), a catheter for collection of urine samples was inserted into the ureter. A catheter was also inserted into the gonadal vein, and the tip of a catheter was placed in the renal vein to collect the renal venous blood samples.

Experimental protocol

Effects of cilnidipine on high-frequency RNS-, NE- and angiotensin II (ANG II)-induced renal vasoconstriction (group 1): The control RBF responses to high-frequency RNS (3–7 Hz, 1-msec duration, supramaximal voltage of 10–20 V) for 30 sec, and intrarenal arterial injections of NE (100 ng/kg) and ANG II (5 ng/kg) were obtained during intrarenal arterial infusion of vehicle at a rate of 0.1 ml/min. Renal vasoconstriction induced by each stimulus was expressed as the maximum changes in RBF. The frequency of RNS was adjusted to decrease the RBF to about one half of its initial level. After the control period, cilnidipine was infused into the renal artery at a dose of 0.1 μg/kg/min. Ten minutes later, RNS and injections of NE and ANG II were repeated during the infusion, followed by experiments using a sequentially higher dose of the drug (0.3 μg/kg/min) in a similar manner. One hour after stopping the infusion of cilnidipine, RNS and intrarenal injections of NE and ANG II were repeated.

Effects of cilnidipine on low-frequency RNS-induced antinatriuresis and NE release (group 2): After completion of surgery, creatinine, dissolved in 0.45% NaCl and 2.5% dextrose, was given i.v. at a prime dose of 50 mg/kg and at a maintenance dose of 1 mg/kg/min (0.1 ml/kg/min), and 60 to 90 min were allowed for stabilization. When RBF and urine flow rate (UV) reached constant levels for more than three consecutive monitoring periods (10 min each), urine and blood samples for basal values were obtained. Urine was collected over 10-min period, and the arterial and the renal venous blood were withdrawn simultaneously at the end of urine collection. Low-frequency RNS (0.5–1 Hz, 1-msec duration, supramaximal voltage of 10–20 V), which had little effect on RBF, was then started, and the 10-min urine collection and blood sampling were performed. When 10-min urine collection was terminated, RNS was stopped. About 20 min after the end of RNS, cilnidipine at a dose of 0.3 μg/kg/min was infused into the renal artery at a rate of 0.1 ml/min and urine volume was monitored every 2 min. When UV became constant, a series of RNS and urine and blood sampling were performed again. One hour after stopping the infusion of cilnidipine, a series of RNS and urine and blood sampling were performed.

Measurements

Plasma and urinary concentrations of creatinine were measured by a modified version of Jaffe's test with an automatic analyzer (Type 7250; Hitachi, Ltd., Tokyo). Plasma and urinary concentrations of sodium were measured by an ion selective electrode method with an automatic analyzer (Type 7250; Hitachi, Ltd.). Determination of plasma NE concentration was performed at SRL Co. (Tokyo) by high-performance liquid chromatography with the diphenyl ethylenediamine method. NE secretion rate (NESR) was calculated by multiplying the difference between the renal venous and arterial NE concentrations by the renal plasma flow, which was calculated from the hematocrit of the arterial blood and RBF.

Drugs

Cilnidipine was synthesized at Ajinomoto Co., Inc. (Tokyo). Cilnidipine was dissolved in 0.9% saline / polyethylene glycol 400 / ethanol (70 : 15 : 15, vol./vol.). (-)-(R)-norepinephrine hydrogen tartrate monohydrate (Wako Pure Chemical Industries Ltd., Osaka) and angiotensin II (Peptide Institute, Inc., Osaka) was dissolved in 0.9% saline.

Statistics

All values were expressed as means±S.E.M. Data for urine formation and NESR were transformed to logarithms before application of statistical procedures. Analysis of variance for repeated measures was employed for overall statistical analysis by using SuperANOVA.
(Abacus Concepts, Inc., Berkeley, CA, USA), followed by contrasts for statistical analysis between control values and others. Differences at a P value <0.05 considered to be statistically significant.

RESULTS

Effects of cilnidipine on high-frequency RNS-, NE- and ANG II-induced renal vasoconstriction

In the control period, RNS, NE (100 ng/kg, i.r.a.) and ANG II (5 ng/kg, i.r.a.) evoked changes in RBF by \(-55.3 \pm 1.8\%\), \(-55.5 \pm 2.2\%\) and \(-52.9 \pm 2.9\%\), respectively. An increase in RBF and a decrease in MAP were observed during intrarenal arterial infusion of cilnidipine (Table 1). Both the RNS-, NE- and ANG II-induced reductions of RBF were dose-dependently suppressed by intrarenal arterial infusion of cilnidipine at 0.1 and 0.3 \(\mu g/kg/min\) (Fig. 2). The suppressed RBF responses reversed 1 hr after the stopping of cilnidipine infusion (shown as Recovery in the Figs.).

Effects of cilnidipine on low-frequency RNS-induced antinatriuresis and NE release

RNS at the low-frequencies evoked changes in urinary flow rate (UV), urinary sodium excretion (UNaV) and fractional excretion of sodium (FE_{Na}) by \(-65.5 \pm 7.1\%\), \(-70.8 \pm 5.2\%\) and \(-53.1 \pm 6.4\%\), respectively, without changes in RBF (Fig. 3). Intrarenal infusion of cilnidipine at 0.3 \(\mu g/kg/min\) significantly increased UV, UNaV and FE_{Na} and decreased MAP (Table 2). The change in FE_{Na} was significantly inhibited by intrarenal arterial infusion.

Table 1. Effects of intrarenal arterial infusion of cilnidipine on renal and systemic hemodynamics in dogs

| Cilnidipine (\(\mu g/kg/min\)) | Control | 0.1 | 0.3 | Recovery |
|--------------------------------|---------|-----|-----|---------|
| RBF (ml/min)                  | 83±8    | 91±10 | 97±13** | 87±10   |
| MAP (mmHg)                    | 120±1   | 114±3* | 106±13** | 108±3** |
| HR (beats/min)                | 128±13  | 126±12 | 129±12 | 121±12 |

Data were obtained at 10 min after the start of cilnidipine infusion. Values are means ± S.E.M. (n=6). *P<0.05, **P<0.01, compared with values in the control period. RBF, renal blood flow; MAP, mean arterial pressure; HR, heart rate.

Fig. 2. Effects of intrarenal arterial infusion of cilnidipine (n=6) on renal nerve stimulation (RNS)-, norepinephrine (NE)- and angiotensin II (ANG II)-induced renal vasoconstriction in anesthetized dogs. Values are expressed as means ± S.E.M. *P<0.05, **P<0.01, compared with the corresponding control values. RBF, renal blood flow.

Fig. 3. Effects of intrarenal arterial infusion of cilnidipine at 0.3 \(\mu g/kg/min\) on renal nerve stimulation (RNS)-induced decrease in urinary flow rate (UV), urinary sodium excretion (UNaV) and fractional excretion of sodium (FE_{Na}) in anesthetized dogs (n=5). Values are expressed as means ± S.E.M. *P<0.05, compared with the corresponding control values.
Table 2. Effects of intrarenal arterial infusion of cilnidipine on urinary parameters, renal and systemic hemodynamics in dogs

|                | Control       | Cilnidipine  | Recovery      |
|----------------|---------------|--------------|---------------|
| UV (ml/min)    | 0.30±0.08     | 1.68±0.58**  | 0.42±0.16     |
| UNaV (mEq/min) | 58.2±22.7     | 224.3±76.4** | 77.4±34.6     |
| FENa (%)       | 1.8±0.6       | 7.1±1.7**    | 2.6±1.0       |
| RBF (ml/min)   | 86±10         | 98±19        | 82±12         |
| Ccr (ml/min)   | 21.5±2.0      | 20.5±3.2     | 20.7±1.6      |
| MAP (mmHg)     | 147±8         | 132±7**      | 130±9**       |
| HR (beats/min) | 119±11        | 126±9        | 119±11        |

Values are means±S.E.M. (n=5). Cilnidipine was infused into the renal artery at a dose of 0.3 µg/kg/min. *P<0.05, **P<0.01, compared with values in the control period. UV, urinary volume; UNaV, urinary sodium excretion; FENa, fractional excretion of sodium; RBF, renal blood flow; Ccr, creatinine clearance; MAP, mean arterial pressure; HR, heart rate.

DISCUSSION

In the present study, we examined whether the L- and N-type Ca2+ channel blocker cilnidipine interferes with adrenergic control of renal functions in anesthetized dogs. Changes in RBF induced by high-frequency RNS and in urinary parameters induced by low-frequency RNS were compared before and during intrarenal arterial infusion of cilnidipine.

The RNS-induced renal vasoconstriction, which is mediated by α1-adrenoceptors located on the renal vasculatures (16), is shown to be resistant to L-type Ca2+ channel blockers, verapamil (6) and nifedipine (8), in the dog kidney. The α1-adrenoceptor-mediated renal vasoconstriction induced by RNS does not seem to depend on influx of extracellular Ca2+ through L-type Ca2+ channels. We also confirmed that nifedipine at 0.1–0.3 µg/kg/min failed to inhibit the RNS-induced RBF response (data not shown). On the other hand, cilnidipine at 0.1–0.3 µg/kg/min suppressed the decrease in RBF induced by RNS, demonstrating that cilnidipine can interfere with the neurally regulated renal vasoconstriction in the dog kidney.

Low-frequency RNS is known to enhance the renal tubular sodium reabsorption, which is also mediated by α1-adrenoceptors (17, 18), and thereby induce antinatriuresis with little change in renal hemodynamics. In the present study, % changes in urinary parameters by the low-frequency RNS were attenuated by cilnidipine, although basal urinary parameters were increased by cilnidipine. Other Ca2+ channel blockers, nifedipine (7), diltiazem and nicardipine (9), have been reported not to affect RNS-induced % change in the urinary parameter at natriuretic doses, suggesting that the α1-adrenoceptor-mediated antinatriuretic response does not depend on influx of extracellular Ca2+ through L-type Ca2+ channels. The present result may demonstrate that cilnidipine is different from other Ca2+ channel blockers in the aspect of interference with the neurally enhanced tubular sodium reabsorption in the dog kidney.

Recently, cilnidipine has been suggested to attenuate the pressor response induced by electrical stimulation of the spinal cord but not the response induced by intravenous injection of NE in the pithed rats (19). In the perfused mesenteric vasculatures of spontaneously hypertensive rats, cilnidipine at 0.1 µM, but not nicardipine at 1 µM, reduces [3H]-NE overflow evoked by periarterial nerve stimulation (19). In the present study, we also examined whether cilnidipine affects the neural NE release in the kidney. An increase in renal NESR by the low-frequency RNS was attenuated by cilnidipine infusion. This result suggests that cilnidipine may act on the presynaptic site and thereby modulates the postsynaptic responses in

Graph: Fig. 4. Effects of intrarenal arterial infusion of cilnidipine at 0.3 µg/kg/min on renal nerve stimulation (RNS)-induced increase in norepinephrine secretion rate (NESR) in anesthetized dogs (n=5). Values are expressed as means±S.E.M. *P<0.05, compared with the corresponding control values.

of cilnidipine. The changes in UV and UNaV were also attenuated, although the effects were not statistically significant (Fig. 3). RNS at the low-frequencies increased NESR. This response was significantly inhibited by intrarenal arterial infusion of cilnidipine (Fig. 4). The suppressed renal responses recovered 1 hr after the stopping of cilnidipine infusion (shown as Recovery in the Figs.).
vivo. The inhibitory effect of cilnidipine on the low-frequency RNS-induced antinatriuresis may be due to the reduced NE release from the renal nerve endings. The inhibitory effect of cilnidipine on the high-frequency RNS-induced RBF response could also be related to the presynaptic action of cilnidipine, although we did not determine the changes in NE release in this experimental group.

It is well-established that the influx of extracellular Ca$^{2+}$ at nerve endings plays an essential role in the neurotransmitter release. Some studies demonstrated that L-type Ca$^{2+}$ channel blockers suppressed the electrical nerve stimulation-induced NE release in the isolated rabbit heart (20) and dog saphenous veins (21). However, high concentrations (more than 10 μM) of Ca$^{2+}$ channel blockers were required to induce the presynaptic inhibition in these studies. N-type Ca$^{2+}$ channels have been considered to regulate the release of neurotransmitters from the sympathetic nerve endings (10). The renal sympathetic nervous system is also shown to be modulated by N-type Ca$^{2+}$ channels, since the N-type Ca$^{2+}$ channel blocker ω-conotoxin suppresses NE release and vasoconstriction induced by periarterial nerve stimulation in perfused rat kidney (11). Cilnidipine can inhibit N-type Ca$^{2+}$ currents in acutely dissociated sympathetic neurons of the rat (15). We could therefore postulate that cilnidipine blocks the presynaptic N-type Ca$^{2+}$ channels to reduce the neurotransmitter release and thereby attenuates the RNS-induced vasoconstriction and antinatriuresis, although we have no direct evidence that N-type Ca$^{2+}$ channels are presynaptically present in the dog kidney.

Endogenous NE produced by RNS stimulates α$_1$-adrenoceptors on the renal vasculatures and tubules. Cilnidipine is confirmed not to replace $[^{3}H]$-prazosin binding in the rat brain membrane (19). TMB-8, a putative inhibitor of intracellular Ca$^{2+}$ release, is reported to inhibit RNS-induced antinatriuresis in dogs (7). It is not known whether cilnidipine affects intracellular signal transduction, but it has no effect on the pressor response to intravenous injection of NE in pithed rats (19). Thus, cilnidipine may not affect intracellular signal transduction.

Exogenous NE- and ANG II-induced renal vasoconstriction has been reported to be inhibited by L-type Ca$^{2+}$ channel blockers, such as diltiazem, verapamil, nifedipine and CD-349 (6, 8, 22, 23). Cilnidipine also suppressed NE- and ANG II-induced renal vasoconstriction in the present study. The renal vasoconstrictor response to exogenously administered NE and ANG II seems to be mediated by Ca$^{2+}$ through L-type Ca$^{2+}$ channels. In the dog kidney, the α$_1$-adrenoceptor predominates, but α$_2$-adrenoceptor agonists can also cause renal vasoconstriction (24). Renal vasoconstriction induced by α$_2$-adrenoceptor agonists but not that by α$_1$-adrenoceptor agonists was suppressed by the L-type Ca$^{2+}$ channel blocker verapamil in dogs (25). NE administered exogenously to the renal artery may in part affect α$_2$-adrenoceptors. Cilnidipine shows almost equipotent inhibitions of both L- and N-type Ca$^{2+}$ currents in rat dorsal root ganglion neurons (14). Cilnidipine probably affects renal function by both direct inhibition of L-type Ca$^{2+}$ channels in the kidney and the inhibition of N-type Ca$^{2+}$ channels in the renal sympathetic nerves.

In conclusion, the present study shows that cilnidipine attenuates the RNS-induced renal vasoconstriction and antinatriuresis in anesthetized dogs in vivo. Cilnidipine also attenuated the RNS-induced NE release, which may contribute to the inhibitory effects of cilnidipine on the RNS-induced renal vascular and tubular responses.

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REFERENCES
1 Bell A and Lindner A: Effects of verapamil and nifedipine on renal function and hemodynamics in the dogs. Renal Physiol 7, 329–343 (1984)
2 Roy M, Guthrie GJ, Holladay F and Kotchen T: Effects of verapamil and nifedipine on renin and aldosterone in the dog and rat. Am J Physiol 245, E410–E416 (1983)
3 Abe Y, Komori T, Miura K, Takeda T, Imanishi M, Okahara T and Yamamoto K: Effects of the calcium antagonist nicardipine on renal function and renin release in dogs. J Cardiovasc Pharmacol 5, 254–259 (1983)
4 DiBona GF and Sawin LL: Renal tubular site of action of felodipine. J Pharmacol Exp Ther 228, 420–424 (1984)
5 Imagawa J, Kurosawa H and Satoh S: Effects of nifedipine on renin release and renal function in anesthetized dogs. J Cardiovasc Pharmacol 8, 636–640 (1986)
6 Ogawa N, Kushida H and Satoh S: Effect of verapamil on renal vasoconstriction induced by angiotensin II, norepinephrine or renal nerve stimulation in anesthetized dogs. Arch Int Pharmacodyn Ther 268, 113–121 (1984)
7 Ogasawara A, Hisa H and Satoh S: An intracellular calcium release inhibitor TMB-8 suppresses renal nerve stimulation-induced antinatriuresis in dogs. J Pharmacol Exp Ther 264, 117–121 (1993)
8 Imagawa J, Kusaba-Suzuki M and Satoh S: Preferential inhibitory effect of nifedipine on angiotensin II-induced renal vasoconstriction. Hypertension 8, 897–903 (1986)
9 Johns E and Manitius J: A study in the rat of renal actions of nitrendipine and diltiazem on the adrenergic regulation of calcium and sodium reabsorption. Br J Pharmacol 89, 99–107 (1986)
10 Hirning L, Fox A, McCleskey E, Olivera B, Thayer S, Miller R and Tsen R: Dominant role of N-type Ca$^{2+}$ channels in evoked release of norepinephrine from sympathetic neurons. Science 239, 57–61 (1988)
11 Mohy El-Din M and Malik K: Differential effect of ω-conotoxin on release of the adrenergic transmitter and the vasoconstrictor
response to noradrenaline in the rat isolated kidney. Br J Pharmacol 94, 355–362 (1988)
12 Yoshimoto R, Hashiguchi Y, Dohmoto H, Hosono M, Iida H, Fujiyoshi T, Ikeda K and Hayashi Y: Effects of a new dihydro-.pyridine derivative, FRC-8653, on blood pressure in conscious spontaneously hypertensive rats. J Pharmacobiodyn 15, 25–32 (1992)
13 Hosono M, Hiruma T, Watanabe K, Hayashi Y, Ohnishi H, Takata Y and Kato H: Inhibitory effect of cilnidipine on pressor response to acute cold stress in spontaneously hypertensive rats. Jpn J Pharmacol 69, 119–125 (1995)
14 Fujii S, Kameyama K, Hosono M, Hayashi Y and Kitamura K: Effects of cilnidipine, a novel dihydropyridine Ca$^{2+}$-channel antagonist, on N-type Ca$^{2+}$ channel in rat dorsal root ganglion neurons. J Pharmacol Exp Ther 280, 1184–1191 (1997)
15 Uneyama H, Takahara A, Dohmoto H, Yoshimoto R, Inoue K and Akaike N: Blockade of N-type Ca$^{2+}$ current by cilnidipine (FRC-8653) in acutely dissociated rat sympathetic neurones. Br J Pharmacol (in press)
16 Chiba K, Hayashi Y, Hisa H, Kusaba-Suzuki M and Satoh S: Effects of a novel $\alpha_2$-adrenoceptor antagonist, SGB-1534, on adrenergically induced renal vasoconstriction in dogs. Eur J Pharmacol 176, 263–269 (1990)
17 Hesse I and Johns E: The subtype of $\alpha$-adrenoceptor involved in the neural control of renal tubular sodium reabsorption in rabbit. J Physiol (Lond) 352, 527–538 (1984)
18 Osborn J, Holdaas H, Thames M and DiBona G: Renal adrenoceptor mediation of antinatriuretic and renin secretion responses to low frequency renal nerve stimulation in the dog. Circ Res 53, 298–305 (1983)
19 Hosono M, Fuji S, Hiruma T, Watanabe K, Hayashi Y, Ohnishi H, Takata Y and Kato H: Inhibitory effect of cilnidipine on vascular sympathetic neurotransmission and subsequent vasoconstriction in spontaneously hypertensive rats. Jpn J Pharmacol 69, 127–134 (1995)
20 Göthert M, Nawroth P and Neumeyer H: Inhibitory effects of verapamil, prenylamine and D600 on Ca$^{2+}$-dependent noradrenaline release from the sympathetic nerves of isolated rabbit hearts. Naunyn Schmiedebergs Arch Pharmacol 310, 11–19 (1979)
21 Takata Y and Kato H: Effects of Ca antagonists on the nor.epinephrine release and contractile responses of isolated canine saphenous veins to transmural nerve stimulation. Jpn J Pharmacol 34, 397–409 (1984)
22 Takahara A, Kusaba-Suzuki M, Hisa H and Satoh S: Effects of a novel Ca$^{2+}$ entry blocker, CD-349, and TMB-8 on renal vasoconstriction induced by angiotensin II and vasopressin in dogs. J Cardiovasc Pharmacol 16, 966–970 (1990)
23 Yamaguchi I, Ikezawa K, Takada T and Kiyomoto A: Studies on a new 1,5-benzothiazepine derivative (CRD-401) VI. Effects on renal blood flow and renal function. Jpn J Pharmacol 24, 511–522 (1974)
24 DiBona GF and Kopp UC: Neural control of renal function. Physiol Rev 77, 75–197 (1997)
25 Wolff DW, Buckalew VM Jr and Strandhoy JW: Renal $\alpha_1$- and $\alpha_2$-adrenoceptor mediated vasoconstriction in dogs: Comparison of phenylephrine, clonidine, and guanabenz. J Cardiovasc Pharmacol 6, S793–S798 (1984)