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Effects of NKH477 on renal nerve stimulation-induced responses in anesthetized dogs

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Abstract

We evaluated the effects of an adenylate cyclase activator, *N,N*-dimetyl-β-alanine[3*R*-(3α,4αβ,5β,6β,6*a*α,10α,10*a*β,10*b*α)]-5(acetyloxy)-3-ethenyldodecahydro-10,10*b*-dihydroxy-3,4*a*,7,7,10*a*-pentamethyl-1-oxo-1*H*-naphtho[2,1-b]pyran-6-yl ester hydrochloride (NKH477), on neural control of renal functions in anesthetized dogs. Renal nerve stimulation (2 Hz) increased renal norepinephrine efflux and reduced renal blood flow, glomerular filtration rate, urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion. Intrarenal arterial infusion of NKH477 (300 ng/kg/min) suppressed the stimulation-induced reductions in renal blood flow and glomerular filtration rate and attenuated the reductions in urine flow rate and urinary Na^+ excretion but not the changes in renal norepinephrine efflux and fractional Na^+ excretion. Infusion of NKH477 did not affect the urinary responses induced by renal nerve stimulation at a lower frequency (0.5–1 Hz) which had little influence on renal blood flow and glomerular filtration rate. The present results demonstrate that NKH477 inhibits renal vasoconstriction and hypofiltration but not the enhanced tubular Na^+ reabsorption during activation of the renal sympathetic nervous system. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: NKH477; Renal nerve; Glomerular filtration; Urinary Na^+ excretion; (Dog)

1. Introduction

Many compounds that affect the production or degradation of cAMP have been developed for the purpose of clinical application. *N,N*-dimetyl-β-alanine[3*R*-(3α,4αβ,5β,6β,6*a*α,10α,10*a*β,10*b*α)]-5(acetyloxy)-3-ethenyldodecahydro-10,10*b*-dihydroxy-3,4*a*,7,7,10*a*-pentamethyl-1-oxo-1*H*-naphtho[2,1-*b*]pyran-6-yl ester hydrochloride (NKH477), a water-soluble derivative of an authentic adenylate cyclase activator, forskolin, activates adenylate cyclase to elevate cellular cAMP content more potently than does forskolin (Shafiq et al., 1992; Toya et al., 1998). Many studies have provided experimental evidence that NKH477 is effective and useful for the treatment of heart failure as a cardiotonic and vasodilator agent (Hosono et al., 1992; Hirasawa et al., 1993; Sanbe and Takeo, 1995).

In the pathophysiological condition of chronic heart failure, the sympathetic nervous system and the renin–angiotensin system (Parmley, 1989) are activated to maintain blood circulation, but their excessive activation causes Na^+ and water retention which leads to edema and congestion. Therefore drugs that have a natriuretic action, as well as a positive inotropic action, are considered to be beneficial to improve the condition of heart failure (Packer, 1989). We have recently found that intrarenal arterial infusion of NKH477 enhances cAMP production and induces vasodilation and natriuresis in the denervated kidney of anesthetized dogs (Tanahashi et al., 1999). This natriuretic action may contribute to the clinical efficacy of NKH477. However, it is unknown whether NKH477 affects the reduction in Na^+ and water excretion during sympathetic activation. Answering this question could provide more information on pharmacological aspects of NKH477 as a drug used for the treatment of heart failure. In this regard, the present study was undertaken to evaluate effects of NKH477 on the adrenergic control of renal functions. Changes in renal hemodynamics and urine formation induced by renal nerve stimulation were compared in the control and drug infusion periods in the dog kidney in vivo.

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2. Materials and methods

2.1. Animal preparation

All animal protocols were reviewed and approved by the Animal Subjects Committee of the Graduate School of Pharmaceutical Sciences, Tohoku University. Mongrel dogs of either sex weighing 8 to 18 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. Decamethonium bromide (0.25 mg/kg, i.v.) was given to prevent spontaneous active respiratory movement. Anesthesia was maintained by a continuous intravenous infusion of sodium pentobarbital at a rate of 6 mg/kg/h throughout the experiments. Inulin, dissolved in 0.45% NaCl and 2.5% dextrose, was given i.v. at a priming dose of 50 mg/kg and at a maintenance dose of 1 mg/kg/min (0.1 ml/kg/min). The right brachial artery was cannulated for collection of arterial blood samples and measurement of mean arterial pressure with a pressure transducer (MPU-0.5, Nihon Kohden, Tokyo, Japan). The right and left kidneys were exposed by retroperitoneal flank incisions. Catheters for urine collection were inserted into both the right and left ureters. All visible renal nerves were dissected away from the renal vessels and cut after ligation. Platinum electrodes were placed on the peripheral site of the nerve bundles of either right or left kidney. A curved 25-gauge needle connected to a polyethylene tube was inserted into the renal artery of the same kidney for drug infusion. A curved 18-gauge needle connected to silicone tubes was inserted into the renal vein to collect renal venous blood. Electromagnetic flow probes (2.5–3.5 mm in diameter, Nihon Kohden) were attached at the right and left renal arteries to measure renal blood flow with square-wave flowmeters (MF-27, Nihon Kohden). Arterial pressure and renal blood flow were recorded with a polygraph system (RM-6000, Nihon Kohden).

2.2. Experimental protocol

After completion of surgery, more than 90 min was allowed for stabilization. When renal blood flow and urine flow rate had 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 a 10-min period, and arterial and renal venous blood was withdrawn simultaneously at the midpoint of urine collection.

2.2.1. Groups 1 ($n = 7$) and 2 ($n = 8$)

After sampling to determine basal values, renal nerve stimulation at 2 Hz (1-ms duration, supramaximal voltage, 10–20 V) was applied for 15 min. Urine and blood samples were collected 5 min after the start of renal nerve stimulation. About 30 min was allowed for recovery from the nerve stimulation with monitoring of renal blood flow and urine flow rate. Then, intrarenal arterial infusion of 0.9% saline (group 1) or NKH477 (Nippon Kayaku, Tokyo, Japan; dissolved in 0.9% saline; 300 ng/kg/min, group 2) was started using a motor-driven syringe pump (model 11, Harvard Apparatus, South Natick, MA) at a rate of 0.1 ml/min. Beginning 10 min after the start of infusion, urine and blood sampling were again carried out, then a series of renal nerve stimulation and blood and urine sampling was performed.

2.2.2. Group 3 ($n = 7$)

Before the start of experiments, the frequency of nerve stimulation had been adjusted to between 0.5–1 Hz to reduce urine flow rate by about 30% with little change in renal blood flow. Other experimental procedures were the same as in group 2.

2.3. Measurements

Blood samples were transferred into chilled tubes containing diammonium EDTA (5–10 mg/ml blood) and then centrifuged to obtain plasma samples. Glomerular filtration rate was determined as inulin clearance. Inulin concentration in plasma and urine was measured by the anthrone method (Davidson and Sackner, 1963). Na^+ and K^+ were measured by flame photometry (775A, Hitachi). Catecholamines were extracted from renal venous plasma by the alumina adsorption method, and plasma norepinephrine concentration was determined by high-performance liquid chromatography with an amperometric detector (LC-4C, Bioanalytical Systems, West Lafayette, IN, USA), as described previously (Hayashi et al., 1987). The norepinephrine efflux was calculated by multiplying the renal venous plasma norepinephrine concentration by the renal plasma flow.

2.4. Data analysis

All values are expressed as means ± S.E. The kidneys were removed at the end of experiments and weighed after decapsulation. Renal blood flow and urine flow rate and parameters derived from them are expressed per kidney weight (g). Data for urine formation were transformed to logarithms before the application of statistical procedures. Student's paired *t*-test was applied to evaluate statistical differences between the values before vs. during renal nerve stimulation. The effects of NKH477 on the values before and during renal nerve stimulation were analyzed by analysis of variance for multifactor repeated measures. When analysis of variance showed a statistically significant difference, the values before and during drug infusion were compared by simple main effects (Winer, 1971). Differences at $P < 0.05$ were considered to be statistically significant.

3. Results

3.1. Groups 1 and 2

In the control period (before infusion of vehicle or NKH477), renal nerve stimulation at 2 Hz reduced renal blood flow and increased renal vascular resistance (Table 1). The nerve stimulation also reduced glomerular filtration rate, urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion (Table 1). After the nerve stimulation was stopped, the values returned to their pre-stimulation levels except renal blood flow and glomerular filtration rate (data not shown). Intrarenal arterial infusion of vehicle (0.9% saline, group 1) did not affect these values. As a result, the basal renal blood flow and glomerular filtration rate in the vehicle infusion period were lower than those in the control period (Table 1). Intrarenal arterial infusion of NKH477 (300 ng/kg/min, group 2) reduced systemic blood pressure and renal vascular resistance and increased renal blood flow, urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion (Table 1). NKH477 also increased glomerular filtration rate to the same level as in the control period (Table 1). In the NKH477 infusion period, renal nerve stimulation reduced urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion, but failed to affect renal blood flow, renal vascular resistance and glomerular filtration rate (group 2, Table 1). Fig. 1 shows the nerve stimulation-induced responses (except renal vascular resistance) as percentage changes from basal levels; the reductions in urine flow rate and urinary Na^+ excretion, but not the reduction in fractional Na^+ excretion in the NKH477 infusion period were smaller than those in the control period. The vehicle infusion did not affect the nerve stimulation-induced renal responses (group 1, Fig. 1).

Renal nerve stimulation increased the renal norepinephrine efflux (Table 1). The infusion of vehicle (group 1) did not affect the renal norepinephrine efflux either before or during renal nerve stimulation. The NKH477 infusion (group 2) slightly increased the renal norepinephrine efflux during nerve stimulation.

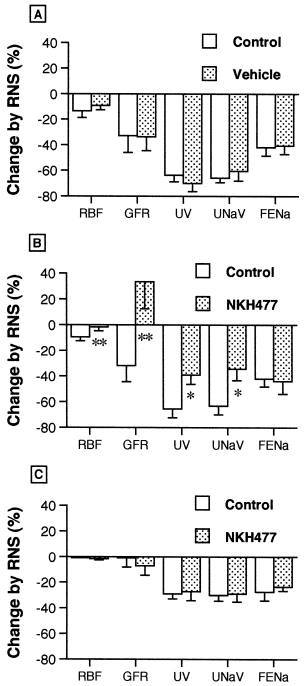

Fig. 1. Effects of vehicle (panel A: group 1, $n = 7$) and NKH477 (panel B: group 2, $n = 8$) on renal nerve stimulation (2 Hz)-induced changes in renal parameters and effects of NKH477 on renal nerve stimulation (0.5–1 Hz)-induced changes in renal parameters (panel C: group 3, $n = 7$). RNS, renal nerve stimulation; RBF, renal blood flow; GFR, glomerular filtration rate; UV, urine flow rate; UNaV, urinary Na^+ excretion; FENa, fractional Na^+ excretion. Values (means ± S.E.) are percentage changes from basal levels in response to renal nerve stimulation. Vehicle (0.9% saline, 0.1 ml/min) or NKH477 (300 ng/kg/min) was infused into the renal artery. $^*P < 0.05$, $^{**}P < 0.01$ compared with the corresponding control response.

Table 1
Effects of renal nerve stimulation (2 Hz) on renal functions in the control period and the vehicle or NKH477 infusion period
Values are means ± S.E. MAP, mean arterial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; RVR, renal vascular resistance; UV, urine flow rate; UNaV, urinary Na^+ excretion; FENa, fractional Na^+ excretion; NE eff, renal norepinephrine efflux. Vehicle (0.9% saline) or NKH477 (300 ng/kg/min) was infused into the renal artery.

Group 1 ($n = 7$)	Control		Vehicle	
	Basal	RNS	Basal	RNS
MAP (mm Hg)	116 ± 3	117 ± 3	114 ± 3[a]	113 ± 4[a]
RBF (ml/min/g)	3.8 ± 0.6	3.4 ± 0.7[b]	3.6 ± 0.7[c]	3.3 ± 0.7[b]
RVR (MAP/RBF)	33.2 ± 3.4	40.4 ± 5.9[b]	35.7 ± 4.1	39.8 ± 5.4[b]
GFR (ml/min/g)	0.63 ± 0.08	0.42 ± 0.10[b]	0.47 ± 0.05[c]	0.31 ± 0.08[b]
UV (μl/min/g)	7.1 ± 1.7	2.4 ± 0.6[d]	7.8 ± 1.6	2.0 ± 0.4[d]
UNaV (μEq/min/g)	1.6 ± 0.2	0.5 ± 0.0[d]	1.3 ± 0.3	0.4 ± 0.1[d]
FENa (%)	2.0 ± 0.3	1.2 ± 0.3[d]	2.1 ± 0.4	1.2 ± 0.2[d]
NE eff (ng/min/g)	0.6 ± 0.1	1.5 ± 0.2[d]	0.6 ± 0.1	1.4 ± 0.2[d]

Group 2 ($n = 8$)	Control		NKH477	
	Basal	RNS	Basal	RNS
MAP (mm Hg)	115 ± 2	115 ± 2	103 ± 3[a]	100 ± 4[a]
RBF (ml/min/g)	3.7 ± 0.6	3.4 ± 0.6[d]	4.7 ± 0.9[a]	4.7 ± 0.9[a]
RVR (MAP/RBF)	35.4 ± 4.1	39.8 ± 5.3[b]	25.6 ± 3.6[a]	25.6 ± 3.9[a]
GFR (ml/min/g)	0.51 ± 0.05	0.37 ± 0.10[b]	0.51 ± 0.10	0.60 ± 0.10[a]
UV (μl/min/g)	6.4 ± 1.5	1.7 ± 0.2[d]	18.9 ± 4.8[a]	11.8 ± 4.3[a,d]
UNaV (μEq/min/g)	1.1 ± 0.3	0.3 ± 0.0[d]	3.3 ± 0.8[a]	2.0 ± 0.5[a,b]
FENa (%)	1.7 ± 0.4	1.0 ± 0.3[d]	6.2 ± 1.9[a]	3.7 ± 1.7[a,d]
NE eff (ng/min/g)	0.6 ± 0.1	1.5 ± 0.2[b]	0.8 ± 0.1	2.1 ± 0.2[c,d]

[a] $P < 0.01$ compared with the corresponding value in the control period.
[b] $P < 0.05$ compared with the corresponding basal value.
[c] $P < 0.05$ compared with the corresponding value in the control period.
[d] $P < 0.01$ compared with the corresponding basal value.

Table 2
Effects of renal nerve stimulation (0.5–1 Hz) on renal functions in the control and NKH477 infusion periods
Values are means ± S.E. MAP, mean arterial pressure; RBF, renal blood flow; GFR, glomerular filtration rate; RVR, renal vascular resistance; UV, urine flow rate; UNaV, urinary Na^+ excretion; FENa, fractional Na^+ excretion; NE eff, renal norepinephrine efflux. NKH477 (300 ng/kg/min) was infused into the renal artery.

Group 3 ($n = 7$)	Control		NKH477	
	Basal	RNS	Basal	RNS
MAP (mm Hg)	108 ± 5	109 ± 5	95 ± 6[a]	91 ± 6[a]
RBF (ml/min/g)	3.6 ± 0.6	3.5 ± 0.6	4.8 ± 0.8[a]	4.7 ± 0.8[a]
RVR (MAP/RBF)	36.1 ± 5.9	36.4 ± 5.9	22.9 ± 3.4[a]	22.4 ± 3.2[a]
GFR (ml/min/g)	0.57 ± 0.06	0.55 ± 0.05	0.72 ± 0.10	0.68 ± 0.13
UV (μl/min/g)	7.3 ± 1.5	5.0 ± 0.8[b]	20.4 ± 6.0[a]	13.2 ± 3.3[a,c]
UNaV (μEq/min/g)	1.3 ± 0.4	0.9 ± 0.3[b]	3.7 ± 1.1[a]	2.6 ± 0.8[a,b]
FENa (%)	1.9 ± 0.6	1.2 ± 0.3[b]	3.8 ± 0.8[a]	2.8 ± 0.6[a,b]
NE eff (ng/min/g)	0.7 ± 0.1	1.1 ± 0.2[c]	0.9 ± 0.1	1.3 ± 0.3[c]

[a] $P < 0.01$ compared with the corresponding value in the control period.
[b] $P < 0.01$ compared with the corresponding basal value.
[c] $P < 0.05$ compared with the corresponding basal value.

3.2. Group 3

Renal nerve stimulation at 0.5–1 Hz reduced urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion without affecting renal blood flow, renal vascular resistance or glomerular filtration rate (Table 2). The values returned to their pre-stimulation levels after nerve stimulation was stopped (data not shown). The intrarenal arterial infusion of NKH477 (300 ng/kg/min) reduced mean arterial pressure and renal vascular resistance and increased renal blood flow, urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion (Table 2). The glomerular filtration rate also increased during NKH477 infusion although the change was not statistically significant (Table 2). Renal nerve stimulation reduced urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion in the NKH477 infusion period (Table 2), and their percentage changes were the same as those obtained in the control period (Fig. 1). Renal nerve stimulation increased the renal norepinephrine efflux, which was unaffected during NKH477 infusion (Table 2).

4. Discussion

We have recently shown that intrarenal arterial infusion of the novel adenylate cyclase activator, NKH477 (30–300 ng/kg/min), caused dose-dependent increases in renal blood flow, glomerular filtration rate, urinary Na^+ excretion and fractional Na^+ excretion with elevating renal cAMP release in anesthetized dogs (Tanahashi et al., 1999). The present study further evaluated pharmacological properties of NKH477 in relation to its influence on adrenergic control of renal functions in vivo. Renal hemodynamic and urinary responses induced by electrical renal nerve stimulation were compared before and during intrarenal arterial infusion of NKH477 (300 ng/kg/min) in anesthetized dogs.

Renal nerve stimulation at 2 Hz reduced renal blood flow and glomerular filtration rate while it increased renal norepinephrine efflux, which was used as an index for sympathetic neurotransmitter release (groups 1 and 2). The reduction in glomerular filtration rate (about 30%) was larger than the reduction in renal blood flow (about 10%), indicating that nerve stimulation affected the balance of the pre- and post-glomerular vascular resistance or the filtration coefficient. Renal nerve stimulation also reduced urine flow rate and urinary Na^+ excretion. Since a reduction in fractional Na^+ excretion was also observed, nerve stimulation may enhance tubular Na^+ reabsorption. The antinatriuretic response may thus result from the reduced glomerular filtration and the enhanced tubular reabsorption, as had been previously reported (DiBona and Kopp, 1997).

The infusion of NKH477 increased basal renal blood flow, urine flow rate, urinary Na^+ excretion and fractional Na^+ excretion (group 2). These effects are consistent with results obtained in our previous study (Tanahashi et al., 1998). NKH477 also increased glomerular filtration rate, but its level was not different from that in the control period since glomerular filtration rate did not completely recover from the 2-Hz nerve stimulation-induced reduction. An incomplete recovery of glomerular filtration rate was also observed in the control period of group 1 experiments. We cannot explain why this occurred.

In the NKH477 infusion period, the 2-Hz nerve stimulation failed to reduce renal blood flow and glomerular filtration rate (group 2). NKH477 also attenuated the percentage changes in urine flow rate and urinary Na^+ excretion in response to nerve stimulation. NKH477 did not suppress the renal norepinephrine efflux during nerve stimulation, indicating that NKH477 interferes with the nerve stimulation-induced renal responses at postsynaptic sites of the renal sympathetic nervous system. The suppressed renal responses do not result from deterioration of postsynaptic mechanisms caused by consecutive application of nerve stimulation since the first and second nerve stimulations affected the renal responses to the same extent (although renal blood flow and glomerular filtration rate before the second nerve stimulation were lower than those before the first nerve stimulation) in the absence of NKH477 (vehicle experiments, group 1). These results demonstrate that NKH477 inhibits the hypofiltration and blunts the antinatriuresis induced by sympathetic activation in the dog kidney in vivo.

Adenylate cyclase activators have been reported to suppress adrenergically induced vasoconstriction. Forskolin attenuates the electrical stimulation-induced constriction of the isolated rat tail artery (Ouedraogo et al., 1994) and reduces perfusion pressure in the presence of the α_1-adren-

oceptor agonist, methoxamine, in the isolated pump-perfused rat kidney (Heuzé-Joubert et al., 1992). NKH477 dilates the isolated rabbit mesenteric artery pre-constricted with norepinephrine (Ito et al., 1993). Afferent arterioles and efferent arterioles are crucial vascular segments for the control of glomerular filtration rate (Ichikawa and Harris, 1991). It has been suggested that forskolin raises the cAMP level in isolated afferent arterioles of dogs (Tamaki et al., 1989) and preferentially dilates the afferent arterioles in vivo in anesthetized dogs (Tamaki et al., 1991). Although we cannot rule out the possibility that NKH477 affects the filtration coefficient, NKH477 may preferentially inhibit the constriction of the afferent arterioles evoked by sympathetic activation and thereby abolish the reduction in glomerular filtration rate.

Renal nerve stimulation-induced vasoconstriction in the dog kidney is mediated by α_1-adrenoceptors (Chiba et al., 1990). Stimulation of α_1-adrenoceptors induces the breakdown of phosphatidylinositol and thereby elevates intracellular free Ca^{2+} through altering several kinds of Ca^{2+} movement pathways. The elevation of intracellular free Ca^{2+} initiates vasoconstriction by activating myosin light chain kinase. cAMP is known to exert opposite actions on these steps in vascular tissue (Scheid et al., 1979; Meisheri and Van Breemen, 1982). NKH477 may be able to increase cAMP in the renal vasculature in vivo since, in our previous study, NKH477 increased renal blood flow and the renal venous cAMP concentration, the responses of which in anesthetized dogs were enhanced in the presence of a cAMP-specific phosphodiesterase inhibitor (Tanahashi et al., 1999). The inhibition by NKH477 of the adrenergically induced renal vasoconstriction could thus be related to an elevated cAMP content in the kidney.

NKH477 did not affect the 2-Hz nerve stimulation-induced change in fractional Na^+ excretion. It is therefore possible that NKH477 does not affect the adrenergically evoked tubular Na^+ reabsorption, and that the attenuated antinatriuretic response is due to inhibition of the hypofiltration response. To confirm this possibility, we also examined the effects of NKH477 on the renal responses induced by renal nerve stimulation at a low frequency (group 3). Renal nerve stimulation at 0.5–1 Hz reduced urine flow rate and urinary Na^+ excretion and fractional Na^+ excretion with little change in renal blood flow or glomerular filtration rate. The antinatriuretic response under these conditions results from the enhanced tubular reabsorption (DiBona and Kopp, 1997). NKH477 did not attenuate the urinary responses induced by the low frequency renal nerve stimulation, suggesting that NKH477 cannot interfere with the adrenergically evoked tubular Na^+ reabsorption.

The enhanced tubular reabsorption, as well as vasoconstriction, during activation of the renal sympathetic nervous system is mediated by α_1-adrenoceptors (DiBona and Kopp, 1997). In this study, however, NKH477 attenuated the nerve stimulation-induced vasoconstriction but not the facilitation of Na^+ reabsorption. Since NKH477 increased basal fractional Na^+ excretion, this drug may be able to act on the renal tubular site. cAMP may interfere with the contractile process by phosphorylation of myosin light chain kinase rather than by affecting α_1-adrenoceptor-mediated signal transduction. Otherwise, α_1-adrenoceptor-mediated signal transduction and subsequent ion movements in the renal tubular epithelial cells might differ from those in the renal vascular smooth muscle cells.

In summary, the present study demonstrated that in the dog kidney in vivo, the novel adenylate cyclase activator, NKH477, can inhibit the renal nerve stimulation-induced hypofiltration and thereby blunt antinatriuresis although the drug does not affect the nerve stimulation-evoked tubular Na^+ reabsorption. NKH477 may thus be able to improve renal function during activation of the renal sympathetic nervous system.

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