Inhibitory Effects of Nisoldipine and Saralasin on Angiotensin II-Induced Antidiuresis in Anesthetized Dogs

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Accepted October 12, 1989

Abstract—Inhibitory effects of the calcium channel blocker nisoldipine on angiotensin II-induced antidiuresis were investigated in anesthetized dogs, and the findings were compared with those of saralasin. Intrarenal arterial infusion of 10 ng/kg/min angiotensin II resulted in marked decreases in renal blood flow (RBF) and urine formation, with a relatively moderate decrease in glomerular filtration rate. There were marked reductions in the fractional excretion of lithium, which is used as an index of the fractional proximal excretion of sodium, and the fractional distal excretion of sodium. Nisoldipine (50 ng/kg/min) administered intrarenally produced a partial inhibition on the decreased response of RBF to angiotensin II. The peptide-induced decreases in urine flow, urinary excretion of electrolytes and fractional excretion of electrolytes were abolished by nisoldipine. In contrast, when saralasin was administered intrarenally at 10 ng/kg/min, a dose which could partially inhibit the angiotensin II-induced decrease in RBF to the same extent as seen with nisoldipine, the antagonist attenuated, but did not abolish, the antidiuretic action of angiotensin II. Significant decreases in urine formation by angiotensin II were observed, even in the presence of saralasin. These results suggest that nisoldipine, unlike saralasin, preferentially interferes with the stimulatory effect of angiotensin II, as related to the renal tubular reabsorption of sodium and water.

Nisoldipine (NIS) is a dihydropyridine-type calcium channel blocker that exerts a potent vasodilation by inhibiting calcium influx into vascular smooth muscle cells. Only limited information has been obtained about the effects of NIS on renal function, including urine formation. Intravenous administration of NIS was reported to produce a diuretic action in anesthetized rats (1, 2). In anesthetized dogs, we found that NIS administered intrarenerally produced a diuresis and natriuresis, in a dose-related manner and without affecting renal hemodynamics (3). The results of micropuncture studies indicated that NIS inhibits the tubular reabsorption of sodium and water (1, 2).

The inhibitory effect of calcium channel blockers on renal vasoconstriction induced by angiotensin II (ANG II) has been studied. Ichikawa et al. (4) found that verapamil markedly inhibits the ANG II-induced decreases in glomerular plasma flow and filtration coefficient. Nifedipine was reported to suppress the decreasing action of ANG II on renal blood flow (RBF) (5, 6). Similar results were observed with other calcium channel blockers, such as diltiazem (7) and nitrendipine (8). In these studies, the inhibitory effects of calcium channel blockers on renal hemodynamic actions of ANG II were given attention. Little is known about the influence of these agents on ANG II-induced antidiuresis, an important renal action of this peptide. We found that NIS effectively inhibited ANG II-induced renal vasoconstriction and antidiuresis, in contrast to findings in the case of norepinephrine (3).

The present study was designed to investigate the effects of NIS on ANG II-induced renal vasoconstriction and antidiuresis in
anesthetized dogs. First, the effects of ANG II on renal hemodynamics and function were examined in the absence or presence of NIS. The tubular site of action of ANG II, with or without NIS treatment, was assessed using the lithium clearance technique. Secondly, the effects of NIS on ANG II-induced renal actions were compared with those of saralasin (SAR), an ANG II receptor antagonist.

Materials and Methods

General procedure

Adult mongrel dogs with an average body weight of 14 kg were used. For at least 1 week before the study, all the dogs were maintained on standard laboratory chow and provided tap water ad libitum. About 12 hr before the experiment, each dog was orally given 300 mg of lithium carbonate. At the time of the experiment, the animals were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and supplemental doses were administered, as needed, to maintain an appropriate level of anesthesia. After tracheotomy, the animals were artificially ventilated with room air using a Harvard respirator. The right and left brachial arteries were catheterized for blood sampling and to measure mean arterial pressure (MAP). The right and left brachial veins were catheterized for infusion of inulin solution and drugs. Renal arterial pressure (RAP) was measured via a catheter inserted into the right femoral artery and advanced into the aorta just below the origin of the left renal artery. The left kidney was exposed through a retroperitoneal flank incision, and the renal artery was dissected free from the surrounding tissue. To eliminate neuronal influence, the renal artery was denervated by stripping of all visible nerve fibers, followed by application of 5% phenol in 70% ethanol. An electromagnetic flow probe (2.5–3.5 mm in diameter, Nihon Kohden Kogyo Co., Tokyo, Japan) was attached at the renal artery, to measure RBF and to maintain RAP at the preinfusion level during ANG II infusion, was placed around the aorta just above the origin of the left renal artery. After the completion of surgery, a priming dose of inulin (20 mg/kg) was given, followed by a sustaining infusion of 0.9% saline containing 0.5% inulin at a rate of 2.0 ml/min. MAP, RAP and RBF were continuously recorded on a polygraph (RM 6000, Nihon Kohden Kogyo Co., Tokyo, Japan) throughout the experiments. Glomerular filtration rate (GFR) was estimated from the inulin clearance. A 60- to 90-min equilibration period of MAP, RBF and urine flow (UF) was allowed before measurements for the controls.

Protocol

Experiment A. Effects of NIS on renal actions induced by ANG II: The experiments were performed on 7 dogs. After an equilibration period, urine samples were collected during two 10-min control periods. Following the control periods, ANG II was infused into the renal artery at a rate of 10 ng/kg/min for 30 min. Ten minutes after starting the ANG II infusion, urine was collected during two consecutive 10-min periods. ANG II infusion was terminated; and after an equilibration period of at least 1 hr, NIS infusion into the renal artery (50 ng/kg/min) was started. Ten minutes after starting the NIS infusion, two 10-min urine samples were collected; and then ANG II infusion for 30 min and two 10-min urine collections were repeated in the same manner as described above. In some experiments, we verified the reproducibility of ANG II-induced renal actions in the absence of NIS. Arterial blood samples were obtained at the midpoint of each 10-min clearance period.

Experiment B. Comparison between effects of NIS and SAR on ANG II-induced renal actions: The experiments were performed on 8 dogs. After an equilibration period, NIS was infused into the renal artery, at a rate of 50 ng/kg/min. Ten minutes after starting the NIS infusion, urine samples were collected during two 10-min control periods, and then ANG II infusion for 30 min and two 10-min urine collections were repeated in the same manner as described above. In some experiments, we verified the reproducibility of ANG II-induced renal actions in the absence of NIS. Arterial blood samples were obtained at the midpoint of each 10-min clearance period.
termination of ANG II and NIS infusion, SAR was intrarenally infused at a rate of 10 ng/kg/min. The dose of SAR was chosen to inhibit the ANG II-induced decrease in RBF to the same extent as seen with NIS. Ten minutes after starting the SAR infusion, two 10-min urine samples were collected, and then ANG II infusion for 30 min and two 10-min urine collections were repeated in the same manner as described above. Blood samples were obtained at the midpoint of each 10-min clearance period. The order of infusion of NIS and SAR was reversed in some dogs. In some experiments, we confirmed the effectiveness of ANG II at 2 hr after termination of NIS or SAR infusion.

In both experiments, RAP was maintained at a preinfusion level during ANG II infusion, to eliminate the possible modification of urine formation by the increase in RAP. In addition, the angiotensin converting enzyme inhibitor captopril was used to minimize the influence of endogenous ANG II on renal function. After the completion of surgery, captopril was infused into the left brachial vein at a rate of 14 μg/kg/min throughout the experiments. We verified that administration of the drug at this dose produced a 80-90% inhibition of the pressor response to intravenous injection of angiotensin I. It has been also demonstrated that captopril given in this dose effectively blocks the pressor and renal hemodynamic responses to intravenous injection of angiotensin I in anesthetized dogs (9).

**Analytical procedures**

Plasma and urinary inulin concentrations were measured by spectrofluorometry (650-60, Hitachi, Tokyo, Japan), according to Vurek and Pegram (10). Plasma and urinary sodium and potassium were determined by a flame photometer (205D, Hitachi, Tokyo, Japan); lithium, by an atomic absorption spectrophotometer (AA-670, Shimadzu, Kyoto, Japan); and chloride, by a chloride meter (Buchler, Fort Lee, VA, U.S.A.).

Fractional proximal sodium excretion (FE_{Na proximal}) was estimated as:

\[ FE_{Na proximal} (%) = \frac{FELT} {100} \times \frac{CLi}{GFR} \]

where FELT is the fractional excretion of lithium, and CLi is the lithium clearance. Fractional distal sodium excretion (FE_{Na distal}), which reflects sodium and water reabsorption at all the portions of tubules beyond the proximal tubules, was estimated as:

\[ FE_{Na distal} (%) = 100 \times \frac{C_{Na}}{CLi} \]

where C_{Na} is sodium clearance.

Throughout the experiment, plasma lithium concentration was kept at a constant low level (about 0.2 mEq/1).

**Drugs**

NIS was a kind gift from Bayer AG, Wuppertal, FRG. Captopril was a generous gift from Sankyo Co., Ltd. (Tokyo, Japan). ANG II and SAR were obtained from Peptide Institute, Inc. (Osaka, Japan). Other chemicals were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan).

**Statistical analysis**

In each dog, all parameters were represented as the mean value of the data of two clearance periods in the preinfused and ANG II-infused periods, respectively. In the text and the figures, “g” expresses grams of kidney weight. The data were analyzed statistically for significant differences between preinfused and ANG II-infused periods by Student’s paired t-test. The difference was considered to be significant at P<0.05.

**Results**

**Experiment A. Effects of NIS on ANG II-induced renal actions:** Table 1 shows the change in renal hemodynamics and function observed during ANG II infusion, with or without NIS treatment. MAP increased by 8 mmHg during the administration of ANG II without NIS treatment. RBF decreased to about 55% of the control value. There was a relatively moderate decrease in GFR (28%) and an increase in filtration fraction (FF). During ANG II infusion, there was a marked reduction in urine formation. UF, urinary excretion of sodium (U_{Na}V), urinary excretion of potassium (U_{K}V) and urinary excretion of chloride (U_{Cl}V) decreased by 72%, 72%, 47% and 88%, compared with the respective control value. Fractional excretion of sodium (FE_{Na}) and fractional excretion of
### Table 1. Effects of intrarenal arterial infusion of 10 ng/kg/min angiotensin II on renal hemodynamics and function with or without nisoldipine treatment

|                  | MAP (mmHg) | RBF (ml/g·min) | GFR (ml/g·min) | FF (%) | UF (μl/g·min) | U_NaV (μEq/g·min) | U_KV (μEq/g·min) | U_CaV (μEq/g·min) | F_ENa (%) | F_EK (%) | F_ECl (%) |
|------------------|------------|----------------|----------------|--------|--------------|-------------------|------------------|------------------|------------|----------|-----------|
| **without nisoldipine treatment** |            |                |                |        |              |                   |                  |                  |            |          |           |
| Control          | 106±2      | 5.5±0.5        | 0.96±0.09      | 33±4   | 12.3±1.7     | 4.15±0.72         | 0.85±0.15        | 1.93±0.37        | 3.3±0.7    | 25.3±5.7   | 2.1±0.6    |
| Angiotensin II   | 114±3**    | 3.0±0.3**      | 0.69±0.05*     | 44±3*  | 2.8±0.5**    | 0.75±0.16**       | 0.45±0.07*       | 0.24±0.04*       | 0.8±0.2*   | 16.0±2.0   | 0.3±0.1*   |
|                  |            |                |                |        |              |                   |                  |                  |            |          |           |
| **with nisoldipine treatment (50 ng/kg/min, i.r.a.)** |            |                |                |        |              |                   |                  |                  |            |          |           |
| Control          | 101±2      | 4.9±0.3        | 0.88±0.05      | 34±3   | 21.6±8.3     | 4.64±1.22         | 0.93±0.16        | 2.85±1.33        | 3.7±1.0    | 27.9±4.1   | 3.2±1.5    |
| Angiotensin II   | 110±2**    | 3.6±0.3**      | 0.73±0.07*     | 38±4   | 21.2±7.1     | 4.25±1.20         | 0.89±0.18        | 2.91±1.33        | 4.4±1.8    | 37.4±11.3  | 4.3±2.0    |

Each value represents the mean±S.E. of 7 dogs. *P<0.05, **P<0.01, compared with the values observed before the administration of angiotensin II.

### Table 2. Effects of intrarenal arterial infusion of 10 ng/kg/min angiotensin II on renal hemodynamics and function with nisoldipine or saralasin treatment

|                  | MAP (mmHg) | RBF (ml/g·min) | GFR (ml/g·min) | FF (%) | UF (μl/g·min) | U_NaV (μEq/g·min) | U_KV (μEq/g·min) | U_CaV (μEq/g·min) | F_ENa (%) | F_EK (%) | F_ECl (%) |
|------------------|------------|----------------|----------------|--------|--------------|-------------------|------------------|------------------|------------|----------|-----------|
| **with nisoldipine treatment (50 ng/kg/min, i.r.a.)** |            |                |                |        |              |                   |                  |                  |            |          |           |
| Control          | 109±9      | 5.8±0.6        | 0.90±0.09      | 27±3   | 17.1±3.5     | 6.39±1.60         | 1.18±0.17        | 2.82±0.82        | 3.9±0.8    | 28.1±3.4   | 2.4±0.7    |
| Angiotensin II   | 116±9**    | 3.5±0.2**      | 0.77±0.07*     | 32±3   | 19.2±4.1     | 5.95±1.70         | 1.08±0.16        | 2.40±0.80        | 4.3±1.2    | 29.9±3.5   | 2.4±0.8    |
|                  |            |                |                |        |              |                   |                  |                  |            |          |           |
| **with saralasin treatment (10 ng/kg/min, i.r.a.)** |            |                |                |        |              |                   |                  |                  |            |          |           |
| Control          | 113±10     | 4.6±0.2        | 0.83±0.08      | 28±2   | 8.4±1.8      | 2.09±0.39         | 0.63±0.03        | 0.80±0.26        | 1.6±0.2    | 19.0±1.9   | 1.0±0.2    |
| Angiotensin II   | 122±9**    | 3.2±0.2**      | 0.73±0.07      | 33±4*  | 5.0±0.9*     | 1.07±0.30*        | 0.54±0.03*       | 0.33±0.11*       | 0.9±0.2*   | 18.4±3.2   | 0.3±0.1*   |

Each value represents the mean±S.E. of 8 dogs. *P<0.05, **P<0.01, compared with the values observed before the administration of angiotensin II.
chloride (FE_{Cl}) were also decreased to 24% and 14% of the respective control value by the peptide. There was a non-significant decrease in fractional excretion of potassium (FE_{K}).

During NIS infusion at 50 ng/kg/min, a slight renal vasodilation (20–30% increase in RBF) and a significant diuretic effect (2–3-fold increase in UF) were observed, but these increasing effects were stable throughout the NIS infusion period in each dog. When ANG II was infused with NIS treatment, MAP increased by 9 mmHg, a level similar to the increase in MAP observed during the ANG II infusion, without NIS treatment. The peptide significantly decreased RBF by 27% even in the presence of NIS. A slight decrease in GFR and an increase in FF were observed. UF, urinary excretions of electrolyte (UEE) and fractional excretions of electrolyte (FEE) were not affected by the peptide in the presence of NIS, in contrast to findings in the absence of NIS.

Since ANG II produced a marked decreasing effect on FE_{Na}, which was completely abolished by NIS, the tubular site of action of NIS was assessed using the lithium clearance technique. Figure 1 shows the effects of ANG II in the absence or presence of NIS on RBF, FE_{Na}, FE_{Li} and FE_{Na distal}.

Fig. 1. Effects of 10 ng/kg/min angiotensin II on RBF, FE_{Na}, FE_{Li} and FE_{Na distal} with or without nisoldipine treatment. Each value represents the mean±S.E. of 7 dogs. *P<0.05, **P<0.01, compared with the values observed before angiotensin II administration.
During ANG II infusion without NIS treatment, there were marked decreases in RBF and \( \text{FE}_{\text{Na}} \), as described above. Simultaneously, statistically significant decrease in \( \text{FE}_{\text{Li}} \) and \( \text{FE}_{\text{Na distal}} \) were observed. In the presence of NIS, ANG II did not influence \( \text{FE}_{\text{Na}}, \text{FE}_{\text{Li}} \) and \( \text{FE}_{\text{Na distal}} \), although the peptide did produce a significant reduction in RBF.

**Experiment B. Comparison between the effects of NIS and SAR on ANG II-induced renal actions:** To further investigate the inhibitory effect of NIS on ANG II-induced renal actions, the effects of NIS were compared with those of the ANG II receptor antagonist SAR. As shown in Table 2, results obtained during ANG II infusion with NIS treatment were qualitatively similar to those in experiment A. When ANG II was infused with SAR treatment, the hemodynamic changes were comparable to those seen in the NIS treatment group, i.e., MAP increased slightly and RBF decreased more markedly (about 30%) than did GFR, the result being a slight increase in FF. On the other hand, there was some difference between the effects of NIS and SAR on the ANG II-induced antidiuresis. The infusion of ANG II with NIS treatment produced no change in UF, \( U_{\text{NaV}}, U_{\text{KV}} \) and \( U_{\text{ClV}} \). There

![Fig. 2. Effects of 10 ng/kg/min angiotensin II on RBF, \( \text{FE}_{\text{Na}}, \text{FE}_{\text{Li}} \) and \( \text{FE}_{\text{Na distal}} \) with nisoldipine or saralasin treatment. Each value represents the mean±S.E. of 8 dogs. \(*P<0.05, **P<0.01\), compared with the values observed before angiotensin II administration.](image-url)
were no significant alterations in FE_{Na}, FE_{K}, and FE_{Cl}. In contrast, during the infusion of ANG II with SAR treatment, UF, U_{Na}V, U_{K}V and U_{Cl}V decreased significantly, being about 60%, 50%, 85% and 40% of the respective control value. FE_{Na} and FE_{Cl} were also decreased by about 44% and 70%, respectively.

A comparison between effects of NIS and SAR on ANG II-induced decreases in RBF, FE_{Na}, FE_{K}, and FE_{Na, distal} is illustrated in Fig. 2. In contrast to results in the NIS treatment group, ANG II with SAR treatment led to a significant decrease in FE_{Na} and FE_{Na, distal}, but there was no significant change in FE_{K}.

SAR by itself at 10 ng/kg/min had no significant effect on renal hemodynamics and urine formation.

Discussion

When we administered NIS intrarenally at 50 ng/kg/min, there was a partial inhibition of the ANG II-induced decrease in RBF and GFR. In contrast, the same dose of NIS abolished the peptide-induced decreases in UF, U_{EE} and FE_{E}, thereby indicating that NIS preferentially inhibits the antidiuresis induced by ANG II, compared with renal vasoconstriction by the peptide. One possible explanation for this phenomenon is that a slight inhibitory action of NIS on the decreased response of GFR to ANG II may contribute to abolishment of the peptide-induced antidiuresis. However, the finding that ANG II produced a significant antidiuresis in the presence of the ANG II receptor antagonist SAR, a drug which exerted an inhibitory effect on ANG II-induced decrease in GFR, does not support the above possibility. Rather, the action of NIS on ANG II-induced antidiuresis may result from the inhibitory effect of NIS on the enhanced renal tubular reabsorption of sodium and water by ANG II. As deduced from findings that the ANG II-induced marked decrease in FE_{Na} was abolished by NIS.

ANG II seems to exert stimulatory effects on renal tubular reabsorption of electrolytes and water via two mechanisms: 1) a direct action on the tubules, independently of changes in intrarenal hemodynamics and 2) changes in intrarenal hemodynamics, which may alter peritubular capillary physical forces. (11). In the present study, NIS abolished the decreasing action of ANG II on UF, U_{EE} and FE_{E}, although the inhibitory effect of the compound on the RBF response to the peptide was only partial. Thus, NIS may inhibit direct stimulatory actions of ANG II on the renal tubular reabsorption of sodium and water. It would be necessary to consider the possibility that partial inhibition of the ANG II-induced renal vasoconstriction by NIS may lead to the abolishment of antidiuresis induced by the peptide. We compared the inhibitory effects of NIS on ANG II-induced renal actions with those of SAR. If abolishment of the ANG II-induced antidiuresis by NIS is due to a partial inhibition of renal vasoconstriction, SAR should also abolish the antidiuretic action of the peptide when the agent is given in a dose producing the same effect on the renal hemodynamic response to the peptide as seen with NIS. The results clearly showed that SAR, unlike NTS, did not abolish the antidiuretic action induced by ANG II. Therefore, the possibility that the partial inhibition of ANG II-induced renal vasoconstriction by NIS is responsible for abolishment of antidiuretic action of the peptide can be ruled out.

There are data indicating that lithium ions are reabsorbed by the renal proximal tubules, in the same proportion as sodium and water, but reabsorption by the more distal portion of tubules is minor (12). Therefore, lithium clearance reflects the extrusion of sodium and water from the proximal tubules to the more distal portion of tubules and can be used as an index of renal proximal tubular reabsorption of sodium and water. The lithium clearance technique has been used to determine the tubular site of action of various drugs such as ANG II (13), atrial natriuretic peptide (14), furosemide (15) and amlodipine (16). Thus, in our study, the tubular sites of action of NIS and SAR were assessed using the lithium clearance technique.

It has been reported that ANG II stimulates tubular reabsorption of sodium and water at the proximal tubules (17). In addition, Ploth and Navar (18) suggested that the peptide stimulates sodium and water transport at distal portions of tubules, beyond the proximal tubules. We also noted the markedly de-
creased responses of $\text{FE}_{\text{Li}}$ and $\text{FE}_{\text{Na distal}}$ to ANG II, thereby indicating that ANG II exerts a stimulatory action on renal tubular sodium and water reabsorption at the proximal tubules and at the more distal portion of the tubules. On the other hand, when NIS was administered intrarenally, ANG II did not affect $\text{FE}_{\text{Li}}$ and $\text{FE}_{\text{Na distal}}$. These results suggest that abolishment of the ANG II-induced antidiuresis by NIS is due to inhibition of the effects of the peptide on the proximal and more distal portion of the tubules. In contrast, ANG II with SAR treatment significantly reduced $\text{FE}_{\text{Na distal}}$ as well as $\text{FE}_{\text{Na}}$. Thus, NIS appears to preferentially inhibit the direct stimulatory action of ANG II on renal tubular reabsorption of sodium and water. It is unclear why SAR antagonized the effect of ANG II on the proximal tubules. For clarification, micropuncture and microperfusion techniques are required.

In anesthetized dogs, the angiotensin converting enzyme inhibitor captopril was reported to cause an additional renal vasodilation during a continuous verapamil infusion, whereas ANG II was found to reverse the above renal vasodilation (18). In addition, it has been indicated that nitrendipine produces an only partial inhibition of ANG II-induced renal vasoconstriction in the isolated perfused rat kidney (8). These results suggest that part of the ANG II-induced renal vasoconstriction may be resistant to calcium channel blockers. On the other hand, a recent study (20) on isolated toad skin, a tissue which has structural and functional properties similar to those of the mammalian nephron (21), demonstrated that ANG II elicited increases in potential differences and short-circuit currents, and these were completely blocked by calcium channel blockers. If indeed there are differences in postreceptor mechanisms for the actions of ANG II, between the renal vasculature and the tubules, such a difference may explain our results that ANG II-induced antidiuresis was inhibited preferentially by NIS.

In conclusion, we found that NIS preferentially inhibited ANG II-induced antidiuresis, compared with the renal vasoconstriction by the peptide. In contrast, SAR inhibited equally both the antidiuresis and renal vasoconstriction. It is likely that abolishment of the ANG II-induced antidiuresis by NIS may be due to inhibition of the stimulatory effect of the peptide on renal tubular sodium and water reabsorption, probably at the proximal and more distal portions of the tubules.

Acknowledgment: We thank M. Ohara for critical comments.

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