Nitric Oxide Regulates Renal Hemodynamics and Urinary Sodium Excretion in Dogs

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Abstract The goal of this study was to determine whether nitric oxide has a long-term role in the control of renal hemodynamics and the relation between arterial pressure and urinary sodium excretion. Studies were conducted over a 25-day period in seven conscious dogs equipped with indwelling vascular catheters and an electromagnetic flow probe on the iliac artery. Nitric oxide synthesis was inhibited by continuous intravenous infusion of Nω-nitro-L-arginine methyl ester at 37.1 nmol/kg per minute, and the effects of low, normal, and high sodium intakes were determined. Significant nitric oxide synthesis inhibition was evidenced by a decrease in the depressor and flow responses to systemic acetylcholine administration. During the normal sodium intake plus nitro-arginine period, arterial pressure increased to hypertensive levels, averaging 120±4% of control; renal vascular resistance increased to an average of 134±8% of control; glomerular filtration rate and renal plasma flow decreased to 83±3% and 81±3% of control, respectively; and no changes occurred in filtration fraction, plasma renin activity, plasma concentrations of aldosterone and cortisol, urinary sodium excretion, sodium balance, fractional excretion of sodium, urine volume, and volume balance. Arterial pressure increased further to 130±3% of control during high salt intake, and sodium balance was achieved at each sodium intake despite the increase in arterial pressure because of a hypertensive shift in the relation between urinary sodium excretion and arterial pressure. In conclusion, the data suggest that nitric oxide has a long-term role in the regulation of arterial pressure, urinary sodium excretion, and renal vascular resistance during normal, low, and high sodium intakes. (Hypertension. 1994;23:619-625.)

Key Words • endothelium • vasodilation • hypertension, renovascular • nitric oxide • glomerular filtration rate

Several recent studies have shown that short-term administration of nitric oxide (NO) synthesis inhibitors causes increased arterial pressure in rats, rabbits, and guinea pigs.1-4 In addition, studies in our laboratory have shown that continuous intravenous infusion of the NO synthesis inhibitor Nω-nitro-L-arginine methyl ester (L-NAME) for 8 to 9 days caused sustained hypertension in both dogs and rats.5,6 fed a normal sodium diet. However, the long-term renal hemodynamic and excretory changes associated with this L-NAME-induced hypertension have not been clarified in dogs.

Previous experiments have shown that long-term changes in arterial pressure are due to changes in either sodium or water intake or the ability of the kidney to excrete sodium, which is usually depicted graphically by the relation between arterial pressure and urinary sodium excretion.7-13 Thus, when arterial pressure increases and the arterial pressure–urinary sodium excretion relation is unchanged, urinary sodium excretion will increase. During hypertension, the pressure–urinary excretion relation shifts to the right along the arterial pressure axis, which is referred to as a "hypertensive" shift. Because overall sodium and water intakes were unchanged and arterial pressure was increased during L-NAME administration in our experiment in dogs,7 the ability of the kidney to excrete sodium and water may have changed. In fact, urinary sodium excretion was normal after 1 day of L-NAME administration despite an increase in arterial pressure. This suggests that the long-term pressure-natriuresis relation may have shifted to the right along the arterial pressure axis.

Other investigators have shown that chronic L-NAME administration to rats causes renal vasconstriction, which could cause a hypertensive shift in the pressure-natriuresis relation. Oral L-NAME administration to rats for 9 hours14 or 2 to 8 weeks15-17 caused an increase in renal vascular resistance. Also, infusion of a very low dose of L-NAME into dogs for 3 days, which probably did not fully block NO synthesis, caused decreases in both glomerular filtration rate (GFR) and sodium excretion without a change in arterial pressure.18 In addition, the natriuretic effects of arterial pressure on urinary sodium excretion of anesthetized dogs have recently been shown to be significantly attenuated during L-NAME administration.19 Therefore, we studied changes in renal hemodynamics, arterial pressure, heart rate, the long-term pressure–sodium excretion relation, sodium and water balances, plasma renin activity, and plasma aldosterone and cortisol concentrations in seven conscious dogs during a 14-day period of NO synthesis inhibition with L-NAME in which sodium intake was varied from 5 to 330 mmol/d.

Methods

Animal Preparation and Experimental Protocol

Experiments were performed on seven conscious dogs with an average body weight of 25.0±1.3 kg. The project had approval from the local Institutional Animal Committee. Aseptic technique was used during all surgical procedures, and atropine sulfate (1 mL of 0.58 μg/mL IM, Elkins-Sinn) and acepromazine maleate (22.6 μg/mL IM, Tech America) were administered before surgery. Anesthesia was induced with pentothal sodium (Pentothal, 94.6 μg/kg IV, Abbott Laboratories) and thereafter maintained with a mixture of methoxyflurane (Penthrene, Abbott) and oxygen. Butorphanol

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backpack that held a Statham P23 AC or P23 ID transducer at a customize software enabled us to sample arterial pressure out the day, and arterial pressure and heart rate were determined over a 7-day control period and thereafter throughout the experiment. After the control period, an intravenous infusion of L-NAME (37.1 mmol/kg per minute [10 μg/kg per minute], Sigma Chemical Co) was begun to inhibit NO synthesis and continued for 14 days. This was immediately followed by a 5-day recovery period. Throughout the experiment, acetylcholine (1.38 μmol, Sigma), an NO agonist, was injected intravenously or intra-arterially in a bolus form to test NO synthesis inhibition. The intravenous acetylcholine was used to elicit a depressor response, whereas the intra-arterial acetylcholine went directly into the distal aorta and elicited a local increase in blood flow in the hind leg. On control day -3 and at the end of day 14, the last day of L-NAME infusion, L-arginine hydrochloride (1.42 mmol/kg IV, Sigma) was infused during a 30-minute period, and the resulting arterial pressure response was determined 15 minutes after the end of the infusion.

Water was available ad libitum throughout the experiment. Sodium intake was maintained at approximately 40 mmol/d during the control period, the first 6 days of the L-NAME infusion, and the recovery period by feeding the dogs 894 g/d of K-D Prescription Diet dog food (Hill’s Pet Products), which provided 30 mmol sodium and 26.8 mmol potassium. The sodium content from any injections was added to the dietary intake to determine the total sodium intake. Immediately after the normal sodium intake and L-NAME period, dietary sodium intake was decreased to approximately 5 mmol/d by feeding 894 g/d of H-D Prescription Diet dog food (Hill’s). Then for the next 6 days the L-NAME infusion continued, and daily sodium intake was increased to approximately 330 mmol/d by feeding the dogs 894 g/d of K-D dog food along with intravenous infusion of approximately 1.9 L/d isotonic saline. Volume balance was calculated by adding the water intake by drinking and the volume of solutions infused and subtracting urine volume. However, some water content in the food adds to the volume balance, and fecal and insensitive loss of water subtracts from the balance; the sum of these factors is equal to the volume balance correction. Volume balance correction was determined by taking the difference between total volume intake and excretion and averaging this over the 7-day control period. Then daily volume balances were adjusted by subtracting the volume balance correction, which gave a more accurate estimate of the true balance. Sodium balances were calculated in a similar way.

Experimental Methods and Instrumentation

Dogs were housed in metabolic cages and fitted with a backpack that held a Statham P23 AC or P23 ID transducer at heart level. The aortic catheter was connected to the pressure transducer, thus allowing continuous pressure recordings. The transducer wires were connected to a model 7D recorder (Grass Instrument Co) connected to a digital computer. Data were sampled at 200 Hz for 12 seconds every minute throughout the day, and arterial pressure and heart rate were determined every minute and stored on a computer disk. Also, customized software enabled us to sample arterial pressure and iliac flow rapidly during the intra-arterial infusion of acetylcholine. These data were analyzed, and the area under the iliac arterial flow-time curve above baseline after intra-arterial acetylcholine injection was determined. This provided the total volume of blood that flowed through the iliac artery due to the acetylcholine infusion.

GFR and renal plasma flow were estimated from the total clearance of $^{[125]}$Iothyamate (Glofil, Isotech Diagnostics) and $^{[131]}$Iodohippurate (Hippuran, ER Squibb & Sons) using the single-injection technique described by Hall et al.20 and assuming an extraction ratio of 1.0 for iodohippurate. The distribution volume of sodium iothalamate, an index of extracellular fluid volume, was determined using the technique of Sapirstein et al.21 Renal vascular resistance, filtration fraction, and fractional excretion of sodium were calculated using standard techniques. Plasma renin activity and plasma concentrations of aldosterone and cortisol were determined by radioimmunoassay. Plasma and urine concentrations of sodium and potassium were determined by flame photometry, and blood urea nitrogen and plasma creatinine concentrations were measured with an autoanalyzer.

The long-term relation between arterial pressure and urinary sodium excretion was determined by changing the level of sodium intake and measuring mean arterial pressure on the day when urinary sodium output equaled the intake. The relation between urinary sodium excretion and arterial pressure has been determined by a number of investigators in dogs,8,10-12 rats,9 and humans.13 In each of these studies, equilibrium between sodium intake and output was reached within 3 days of the change in sodium intake.

Because long-term L-NAME infusion tends to cause constipation in dogs,8 a small amount of poliyum hydrophilic muciloid (Metamucil, 2.5 g, Procter & Gamble) was added to the food twice a week throughout the experiment, preventing any constipation.

Statistical analysis was performed by first determining overall significance with ANOVA for repeated measures. Significance on individual experimental days was determined post hoc with Dunnett’s test for multiple comparisons with a control.22 All dogs served as their own controls, and experimental and recovery data were statistically compared with the average data from the entire control period, except the arterial pressure data in the pressure-natriuresis relation, which were compared to individual control days. Also, a paired t test was used to compare the acute effects of L-arginine on arterial pressure. Data were considered to be statistically different from control at a value of $P<0.05$ and are presented as mean±SEM.

Results

Changes in Mean Arterial Pressure and Heart Rate and the Arterial Pressure Responses to L-Arginine During L-NAME Infusion

Fig 1 shows that mean arterial pressure increased significantly during the periods of L-NAME infusion in combination with normal, low, or high sodium intake. Mean arterial pressure during the control period was 78±5 mm Hg, and arterial pressure increased significantly during the first 24 hours after the L-NAME infusion was initiated. After the L-NAME infusion was stopped at the beginning of day 15, arterial pressure remained significantly elevated for only 1 day.

Fig 1 also shows that heart rate was decreased significantly during the first 5 days of the L-NAME and normal sodium intake period; however, heart rate remained close to its control value throughout the low and high sodium intake periods. The control heart rate was 62±4 beats per minute.

The acute arterial pressure response to 1.42 mmol/kg IV L-arginine was tested on day -3 of the control period.
and at the end of day 14 just before the L-NAME infusion was stopped. L-Arginine was administered over 30 minutes, and on day -3 of the control period, arterial pressure increased 4.3±2.4 mm Hg (P=NS compared with the arterial pressure measured just before L-arginine was infused). On day 14, L-arginine administration resulted in a change in arterial pressure of -6.7±7.2 mm Hg (P=NS). Even though there was a greater tendency for arterial pressure to decrease in response to L-arginine during the L-NAME period, the resulting decrease in arterial pressure was not significantly different from the control period response.

Changes in GFR, Renal Plasma Flow, and Filtration Fraction During L-NAME Infusion

As seen in Fig 2, GFR averaged 62.7±5.9 mL/min on day -2 of control. During the normal sodium intake period, L-NAME caused GFR to decrease significantly on both days 2 and 4 of the L-NAME period, and the minimum value of 83.0±2.5% of control was reached on day 2 of L-NAME. After day 4, changes in GFR did not reach significance for the remainder of the L-NAME period.

Renal plasma flow, as shown in Fig 2, had a control value of 166.8±20.2 mL/min on day -2 of control. On day 2 of L-NAME, renal plasma flow significantly decreased to 80.7±29.9% of control, but no other significant changes occurred during the remainder of the L-NAME infusion period.

Filtration fraction, as seen in the bottom panel of Fig 2, changed very little from its average control value of 0.39±0.02 during the L-NAME period. The exception was that filtration fraction increased significantly during the high sodium and L-NAME period to 0.44±0.02.

Changes in Renal Vascular Resistance and Plasma Sodium and Potassium Concentrations During L-NAME Infusion

Renal vascular resistance, as seen in Fig 3, averaged 0.31±0.03 mm Hg/mL per minute on day -2 of control and was increased significantly when L-NAME infusion was combined with either normal, low, or high sodium intake. A maximum value of renal vascular resistance of 148.0±9.0% of control was reached during the high sodium plus L-NAME period.

Changes in MEAN ARTERIAL PRESSURE and HEART RATE during the study period are shown in Fig 1. Bar graphs show effects of changes in sodium intake and intravenous infusion of 37.1 nmol/kg per minute N^6-nitro-L-arginine methyl ester (L-NAME) on 24-hour average of mean arterial pressure and heart rate. On day -3 and at the end of day 14, 1.42 mmol/kg L-arginine hydrochloride was infused intravenously in 30 minutes, but no significant acute change in arterial pressure occurred. *P<.05 compared with average control (C) value.

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Plasma sodium and potassium concentrations changed very little from their control values during L-NAME. The exception was that plasma sodium concentration increased slightly from an average control value of 140.8±0.7 to 144.7±0.7 mmol/L on day 2 of L-NAME.

Changes in the Long-term Relation Between Urinary Sodium Excretion and Mean Arterial Pressure During L-NAME Infusion

Fig 4 shows that L-NAME caused a marked hypertensive shift in the relation between arterial pressure and sodium excretion. The slope of the arterial pressure–urinary sodium excretion relation during the control period, as indicated by the dotted line, was assumed to be the same as that previously determined in this department8,10 and is shown for ease of comparison with the L-NAME response. During the low sodium intake period, L-NAME infusion caused mean arterial pressure to increase to 116±6% of control (P<.05 compared with the control arterial pressure); during normal sodium intake plus L-NAME, arterial pressure was 127±6% of control (P<.05). When sodium intake was increased to approximately 330 mmol/d during L-NAME administration, mean arterial pressure increased to 130±3% of control (P<.05).

Changes in Plasma Renin Activity and the Plasma Concentrations of Aldosterone and Cortisol During L-NAME Infusion

As shown in Fig 5, plasma renin activity did not change significantly from its average control value of 0.5±0.05 ng angiotensin I/mL per hour during the L-NAME period. Plasma aldosterone concentration increased from its average control value of 5.6±1.4 ng/dL to a maximum value of 16.0±3.7 ng/dL (P<.05) during the low sodium intake period. Plasma cortisol concentration did not change significantly from its average control value of 1.1±0.2 μg/dL during the experiment, indicating that the dogs were not unduly stressed by the experimental procedures.

Changes in Sodium Intake, Urinary Sodium Output, and Sodium Balance During L-NAME Infusion

As shown in Fig 6, neither urinary sodium output nor sodium balance was significantly changed during the period of normal sodium intake plus L-NAME administration. In addition, there were no significant changes in
Changes in Volume Intake, Urinary Volume Output, and Volume Balance During L-NAME Infusion

As seen in Fig 7, urine volume and volume balance responded similarly to sodium output and balance. There were no significant changes in either urine volume or volume balance during the normal sodium and low sodium intake periods during L-NAME administration. However, urine volume increased significantly during the high sodium plus L-NAME period, and volume balance was positive on day 10. In addition, on the first day of recovery, day 15, volume balance was negative.

Changes in Fractional Excretion of Sodium and Iothalamate Space During L-NAME Infusion

As shown in Fig 8, fractional excretion of sodium had an average control value of 0.29±0.03%. During L-NAME administration, fractional excretion of sodium increased slightly during the low sodium period and markedly during the high sodium period. Iothalamate space, an index of extracellular fluid volume, had a control value of 270±13 mL/kg. Iothalamate space remained close to its control value throughout the experiment, except for a slight decrease to 236±12 mL/kg on day 6.

Changes in the Pressure and Flow Responses to Acetylcholine During L-NAME Infusion

Fig 9 shows that the arterial pressure responses to acetylcholine decreased significantly during L-NAME administration. The average control value of the depressor response to acetylcholine was -42±5%. In addition, as shown in Fig 9, the flow responses to acetylcholine, as indicated by the area under the iliac flow-time curve, were markedly decreased throughout the entire L-NAME period. These data suggest that NO synthesis was significantly inhibited during L-NAME administration.

Changes in Blood Urea Nitrogen and Plasma Creatinine Concentration During L-NAME Infusion

Blood urea nitrogen and plasma creatinine concentration were measured in three dogs during the control period and on day 6 of L-NAME administration. Blood urea nitrogen was 0.74±0.02 mmol/dL during the control period and 1.02±0.16 mmol/dL on day 6 of L-NAME administration.
L-NAME (P=NS). Plasma creatinine concentration was 10.8±0.8 mmol/dL during the control period and 12.1±0.3 mmol/dL (P=NS) on day 6 of L-NAME. These small changes in urea and creatinine could have been caused by the slight decrease in GFR that occurred on day 6 of L-NAME and were very similar to values of urea nitrogen and plasma creatinine determined in a previous study in our laboratory in which L-NAME was administered to dogs for 11 days. These data suggest that L-NAME caused little or no renal damage.

Discussion
Role of Nitric Oxide in the Regulation of Urinary Sodium Excretion and Arterial Pressure

The relation between arterial pressure and urinary sodium excretion has been shown to play a pivotal role in the long-term control of arterial pressure, and this relation can be influenced by a number of hemodynamic and humoral factors. A humoral factor that may affect renal sodium excretion is NO, and the role of NO in the regulation of urinary sodium excretion has been primarily studied with the use of NO synthesis inhibitors.

Although some investigators have found that urinary sodium excretion increases after either a 3723 or 29724 μmol/kg IV bolus of L-NAME into rats, other investigators have found that the direct effect of NO synthesis inhibition on the kidney was sodium retention. Lahera et al25 administered L-NAME into anesthetized rats at doses ranging from 0.37 to 185 nmol/kg per minute. The lower doses of L-NAME resulted in a decrease in urinary sodium excretion, and the higher doses caused increases in arterial pressure that overcame the tendency for renal sodium retention, which confirms the findings of Johnson and Freeman.24 In anesthetized dogs Salom et al19 found that the increases in sodium excretion and urine volume that normally occurred during increases in renal perfusion pressure were attenuated during L-NAME administration. The data of Salom et al suggest that the pressure-natriuresis relation experienced an acute hypertensive shift in these dogs during L-NAME infusion. However, whether the relation between arterial pressure and urinary sodium excretion is altered during long-term NO synthesis inhibition has not been previously studied in dogs.

In the present study, urinary sodium excretion, sodium balance, and fractional excretion of sodium were unchanged during the L-NAME plus normal sodium intake period despite a significant increase in arterial pressure. The reason sodium excretion was unchanged could have been due to the rightward shift along the arterial pressure axis that occurred in the relation between urinary sodium excretion and arterial pressure. Thus, a shift in this pressure-sodium excretion relation could be responsible for the long-term increase in arterial pressure that occurs during NO synthesis inhibition in dogs. The exact intrarenal mechanism responsible for this change in sodium excretory ability cannot be discerned from our data, but other researchers have shown that NO causes a decrease in sodium reabsorption in several nephron segments, including the cortical collecting duct.26

One of the factors that has been shown to change the slope of the long-term relation between arterial pressure and urinary sodium excretion is plasma angiotensin II concentration.19 In the present study, plasma renin activity did not increase significantly during normal sodium intake plus L-NAME even though other researchers have found that renin activity increases mildly18 or moderately17 or decreases slightly.27 However, no renal damage occurred in this experiment, as indicated by the lack of change in blood urea nitrogen and plasma creatinine concentration, and renal damage did occur in one study in which plasma renin activity was elevated.17 Also, during the combination of low sodium intake and L-NAME in our study, plasma renin activity did not increase as in normal dogs.10

Another factor that could have changed the relation between arterial pressure and urinary sodium excretion is aldosterone. However, plasma aldosterone concentration did not change significantly during the period of normal sodium intake plus L-NAME. Yet plasma aldosterone increased during L-NAME as expected during low sodium intake and tended to decrease during high sodium intake. Therefore, changes in aldosterone concentration behaved similarly to dogs without L-NAME infusion and thus probably had little influence on the changes in renal sodium handling during L-NAME administration.

Renal Hemodynamic Changes During NO Synthesis Inhibition

During the normal sodium intake period, long-term NO synthesis inhibition with L-NAME in conscious dogs in the present study resulted in an initial decrease of 17% and 19% in GFR and renal plasma flow, respectively. During this period, arterial pressure increased to hypertensive levels and renal vascular resistance markedly increased. By day 6 of normal sodium intake plus L-NAME infusion, arterial pressure remained elevated, but the decreases in GFR and renal plasma flow were no longer significant. During the periods of low and high sodium intakes plus L-NAME infusion, GFR and renal plasma flow were not significantly different from control, but renal vascular resistance remained elevated. To our knowledge, this is the first study demonstrating the long-term renal hemodynamic consequences of whole-body NO synthesis inhibition in dogs.

Other investigators, in studies primarily in the rat, have also shown that NO synthesis inhibition results in both short- and long-term renal vasoconstriction. The first studies on the renal hemodynamic effects of NO synthesis inhibition were performed on a short-term basis. Gardiner et al28-29 found that an intravenous bolus of the NO inhibitors Nω-monomethyl L-arginine or L-NAME produced renal vasoconstriction in conscious Long-Evans rats in experiments lasting between 5 and 60 minutes. In short-term experiments on conscious rats, intravenous bolus administration of NO synthesis inhibitors led to hypertension and decreases in both renal plasma flow and GFR.

The first long-term studies on the renal hemodynamic effects of NO synthesis inhibition showed that the arterial pressure of Brattleboro rats drinking L-NAME for 9 hours increased and renal blood flow decreased.14 Also, rats that drank L-NAME for 2 weeks to 2 months experienced large decreases in GFR and renal blood flow.15-17 In addition, Salazar et al18 found that intravenous infusion of a very low dose of L-NAME of 0.185 nmol/kg per minute for 3 days into dogs caused no
change in arterial pressure but a decrease in GFR; this dose of L-NAME probably did not fully block the systemic production of NO.

The increase in mean arterial pressure, and thus renal perfusion pressure, helped to overcome the tendency for renal plasma flow and GFR to decrease on or after day 6 of L-NAME administration in the present study, but renal vascular resistance remained elevated significantly throughout the periods of L-NAME infusion. Therefore, L-NAME caused persistent increases in arterial pressure and renal vascular resistance during either low, normal, or high sodium intakes, and GFR and renal plasma flow were decreased during the initial 4 days of L-NAME administration.

In summary, long-term inhibition of NO synthesis in dogs by continuous intravenous infusion of L-NAME for 14 days resulted in a sustained increase in arterial pressure during normal, low, or high sodium intake. Decreases in the acetylcholine depressor and flow responses indicate that NO synthesis was significantly inhibited. During the period of normal sodium intake plus L-NAME administration, both GFR and renal plasma flow decreased but without a change in filtration fraction, and renal vascular resistance increased markedly. Also, during this time no significant changes occurred in plasma renin activity, plasma aldosterone concentration, plasma cortisol concentration, urinary sodium excretion, sodium balance, fractional excretion of sodium, urine volume, and volume balance. Urinary sodium excretion was unchanged during increases in arterial pressure because of a hypertensive shift in the long-term relation between arterial pressure and urinary sodium excretion. In conclusion, the data suggest that NO is important in the long-term regulation of arterial pressure, urinary sodium excretion, and renal vascular resistance during normal or altered sodium intake.

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