Chronic effects of a physiological dose of ANP on arterial pressure and renin release

SALAH D. KIVLIGHN, THOMAS E. LOHMEIER, HUN M. YANG, AND YOJI SHIN
Department of Physiology and Biophysics, University of Mississippi Medical Center, Jackson, Mississippi 39216-4505

KIVLIGHN, SALAH D., THOMAS E. LOHMEIER, HUN M. YANG, AND YOJI SHIN. *Chronic effects of a physiological dose of ANP on arterial pressure and renin release.* Am. J. Physiol. 258 (Heart Circ. Physiol. 27): H1491–H1497, 1990.—To determine the long-term effects of a physiological dose of atrial natriuretic peptide (ANP) on renin release, the renin response to reductions in renal arterial pressure (RAP) was studied during *1*) control conditions and *2*) acute and *3*) chronic (5 days) intravenous infusion (5 ng·kg^{-1}·min^{-1}) of α-human ANP in conscious dogs maintained on a normal sodium intake. Renal perfusion pressure was servo controlled at reduced levels with an inflatable occluder placed around the abdominal aorta just above the renal arteries. Under control conditions, reducing RAP by 30 and 40 mmHg increased plasma renin activity (PRA) 4- to 5- and 9- to 10-fold, respectively. Acute ANP infusion had no significant effect on either basal levels of PRA or the PRA response to reduced RAP. During chronic ANP infusion there was a two- to threefold increment in plasma ANP concentration and approximately a twofold increase in urinary sodium excretion on *day 1*; however, there were no significant long-term changes in mean arterial pressure, basal PRA, or the levels of PRA achieved during reductions in RAP. These findings indicate that the changes in plasma ANP concentration that occur under normal physiological conditions do not appreciably alter either basal PRA or renin release in response to renal hypotension in conscious sodium-replete dogs studied under resting conditions.

plasma renin activity; renal perfusion pressure; conscious dogs

PHARMACOLOGICAL DOSES of atrial natriuretic peptide (ANP) produce pronounced natriuresis and, in many instances, suppression of renin release despite hypotension (3, 17, 19, 25, 28). Although increased delivery of sodium chloride to the macula densa during ANP infusion would be expected to inhibit renin release, there is some controversy as to the importance of this mechanism in mediating the renin suppressing effect of ANP (19, 28). Furthermore, while some in vitro studies indicate that ANP may have a direct inhibitory effect on juxtaglomerular cells (15, 18), others are inconsistent with such a mechanism of action (13, 21). Therefore, it is not clear how pharmacological doses of ANP inhibit renin secretion when, in fact, such an effect occurs.

From these studies where pharmacological doses of ANP have been administered, the notion has evolved that ANP may be an important controller of body fluid volume and arterial pressure as a result of both its direct natriuretic effects and its indirect effects on sodium excretion that are mediated via inhibition of renin secretion. However, recent studies employing physiological infusion rates of ANP have challenged this hypothesis. Most importantly, acute infusions of ANP that increase plasma ANP concentration to levels within the physiological or pathophysiological range indicate that ANP is not a potent natriuretic agent and does not suppress renin secretion when the renin-angiotensin system is not activated (1, 6).

Because of the importance of the renin-angiotensin system in the long-term control of arterial pressure (10) and because the natriuretic effects of ANP may be mediated, at least in part, by suppressing renin release, the primary objective of this study was to determine whether a chronic increase in plasma ANP concentration within the physiological range is capable of impairing renin release in normal dogs. Recently, a study in conscious dogs demonstrated that acute infusion of ANP at a rate (5 ng·kg^{-1}·min^{-1}) that increased plasma ANP concentration to only two to three times control levels markedly inhibited the renin response to a 30% reduction in renal perfusion pressure (23); therefore, we repeated this protocol and, in addition, extended the ANP infusion to 5 days to ascertain the long-term effects of ANP on renin release. It was of special interest to determine whether ANP inhibits renin secretion chronically; that is, beyond the acute period when the natriuresis induced by ANP would be expected to be most prominent.

METHODS

Five male dogs weighing 24.5 ± 1.0 kg were anesthetized with pentobarbital sodium (30 mg/kg iv) and chronic indwelling Tygon catheters (0.05 in. ID, 0.09 in. OD, Norton Plastics, Akron, OH) were placed in the femoral arteries and veins. The femoral arterial catheters were advanced into the aorta so that the tip of one catheter was positioned distal to and the tip of the other catheter proximal to the origin of the renal arteries. The ends of the femoral vein catheters were placed in the lower inferior vena cava. A Silastic elbow prevented kinking of the catheters in the femoral area. Additionally, an externally inflatable Silastic occluder was placed around the abdominal aorta immediately cephalad to the renal arteries and between the tips of the arterial catheters. The catheters and the occluder were tunneled subcutaneously and exteriorized between the scapulas. Patency of the catheters was maintained by flushing two to

three times weekly with sterile isotonic saline and then by filling the catheters with heparin (1,000 U/ml).

One week after surgery the dogs were placed in metabolic pens in a room maintained at 22 ± 2°C with a 12:12-h light-dark cycle. They were fitted with an aluminum and canvas backpack housing two blood pressure transducers (model P23 ID, Statham Laboratories, Hato Rey, PR) at heart level. Restraining lines from the sides of the pen were connected to the four corners of the backpack; this permitted the dogs to move freely in the cage but not to turn completely around. The electrical connections to the blood pressure transducers and the infusion lines were brought to the top of the cage through a flexible tube attached to the top of the backpack. Sterile isotonic saline (260 ± 5 ml/day) was infused continuously into one of the femoral vein catheters by means of a Sage tubing pump (model 375A). A disposable Millipore filter (Cathivex) was connected in series to prevent passage of bacteria and other contaminants.

The dogs were allowed free access to water and maintained on a fixed diet of two 15.5 oz cans of prescription heart diet (H/D; Hills pet products, Topeka, KS) per day. Two cans of H/D provide <5 meq sodium and ~55–60-meq potassium. Therefore, with the saline infusion, sodium intake was ~40 meq/day. Daily water consumption was monitored, and 24-h urine samples were collected at 1315 h, 15 min after feeding. During the 15-min period after feeding, several of the dogs would routinely void. Body temperature was measured daily and amoxicillin (250 mg, 2 times/day; Warner-Lambert) and dicloxacillin (250 mg, 2 times/day; Bristol Laboratories) were given prophylactically.

Before the control period, the dogs were trained to lie quietly in their cages from 0830 to 1230 h and were conditioned to handling. Experiments were begun only after adequate training and only after sodium, potassium, and water balance was achieved. This training and equilibration period usually lasted ~10 days. Throughout the entire training, control, and subsequent experimental periods, mean arterial pressure (MAP) was measured continuously (24 h/day) on a Grass polygraph (model 7D, Grass Instruments, Quincy, MA) from the arterial catheter below the renal arteries. Additionally, values for MAP were recorded simultaneously on an AT&T model 6300 personal computer using an analog-to-digital converter (DASH-16/16F, MetraByte, Taunton, MA) and software designed in our department. The analog signal from the Grass polygraph was sampled every 60 s and digitized to provide 60 sample points per hour. The daily values presented for MAP were calculated from the 720 data points generated during the 12-h period from 1800 to 0600 h. During this time, entrance into the animal room was not permitted.

Before each experiment, both blood pressure transducers were calibrated with a mercury manometer. Then one transducer was reconnected to the arterial catheter below the occluder for measurement of mean renal arterial pressure. Mean systemic arterial pressure was measured from the arterial catheter cephalad to the occluder, and heart rate was monitored. Additionally, the externally adjustable occluder was connected via an extension line to a servo-controlled syringe pump that, in turn, was connected to a proportional servo-control unit as previously described (12). The servo-control unit was driven by the output of the driver amplifier of the Grass polygraph, which continuously monitored renal arterial pressure. Thus, by continuously controlling the inflation of the occluder, renal perfusion pressure could be maintained very precisely at desired levels below control without disturbing the dogs. Typical polygraph recordings during servo control of renal arterial pressure can be seen in a recent study from our laboratory (32).

Experimental protocol. After the dogs had been in a recumbent position for 30–40 min and MAP and heart rate were stable, two blood samples (1–1.5 ml) were taken 5 min apart for measurement of plasma renin activity (PRA). During the latter sample an additional 4–5 ml of blood were taken for measurement of hematocrit, plasma sodium and potassium concentration, plasma protein concentration, and plasma ANP concentration. Then the servo-control unit was activated to reduce renal arterial pressure ~30 mmHg below control. Renal arterial pressure was maintained at this level for 45 min during which time blood samples for PRA were taken after 30 and 45 min of occlusion; during the latter sample, an extra 4–5 ml of blood were taken for determination of hematocrit and plasma protein, sodium, potassium, and ANP concentrations. Subsequently, renal arterial pressure was reduced an additional 10 mmHg for 45 min. Again, blood was sampled after 30 and 45 min (75 and 90 min total occlusion time, respectively) as described above. Finally, the servo-control unit was disconnected and the occluder was deflated. The dogs were observed for an additional 30 min but no blood samples were taken. This same control experiment was repeated 2–3 days later.

Two to 3 days after the control experiments described above, the same protocol was repeated during acute intravenous infusion of α-human ANP (Peninsula Labs, Belmont, CA) at 5 $ng \cdot kg^{-1} \cdot min^{-1}$. After a control blood sample, ANP was infused in isotonic saline at 0.2 ml/min via the femoral vein catheter not used for continuous saline administration. Thirty minutes later, additional blood samples were taken 5 min apart as described above for the control experiments. Then, while the ANP infusion was maintained, renal arterial pressure was reduced to the exact same levels achieved during the control experiments, and blood was sampled accordingly.

After the acute experiment, ANP was added to the saline that was continuously infused into one of the femoral vein catheters. The ANP infusion was maintained for 5 days during which time the above protocol was repeated on *days 1, 3,* and *5* of chronic ANP infusion. The ANP infusate was made fresh daily. Finally, the above protocol was repeated on recovery *days 1* and *5* following cessation of the ANP infusion.

Analytical methods. Plasma ANP concentration (27) and PRA (11) were measured by radioimmunoassay as previously described. PRA is expressed as nanograms of angiotensin I (ANG I) generated per milliliter of plasma per hour of incubation. All plasma samples from each dog were run in a single assay whenever possible. Plasma and urine concentrations of sodium and potassium were

determined by flame photometry (IL 943, Instrumentation Laboratories, Lexington, MA), plasma protein concentration by refractometry (American Optical, Buffalo, NY), and hematocrit by a micromethod (Autocrit II, Clay Adams, Franklin, NJ).

Statistics. Comparisons between control and ANP infusion were made by analysis of variance for repeated measures followed, when appropriate, by Duncan's multiple range test (31). Differences were considered significant when $P < 0.05$. Values stated in the text and elsewhere are means ± SE.

RESULTS

Figure 1 illustrates the relationship between PRA and renal arterial pressure before and after suprarenal aortic occlusion in two separate control experiments performed 2–3 days apart. As renal arterial pressure was reduced from control levels of 100 ± 2 to 71 ± 2 and 61 ± 2 mmHg, PRA increased significantly 4- to 5- and 9- to 10-fold, respectively. As expected, PRA achieved steady-state values within 30 min of each reduction in renal perfusion pressure. In addition, systemic arterial pressure increased significantly during aortic occlusion and in parallel with the increments in PRA. It is important to emphasize that the above responses to aortic occlusion in the two experiments performed 2–3 days apart were very reproducible quantitatively and were not significantly different from one another. Finally, control values for heart rate, hematocrit, and the plasma concentrations of sodium, potassium, and protein were 70 ± 4 beats/min, 36 ± 1%, 144 ± 1 meq/l, 4.0 ± 0.1 meq/l, and 6.6 ± 0.2 g/dl, respectively; there were no significant changes in any of these variables during aortic occlusion.

During acute infusion of ANP, there were no significant changes in any measured variable prior to aortic occlusion. Values for PRA before and 30–40 min after ANP infusion were 1.01 ± 0.19 and 0.89 ± 0.10 ng ANG $I \cdot ml^{-1} \cdot h^{-1}$. Moreover, ANP did not significantly affect the magnitude of the PRA response to 30 and 40% reductions in RAP (Fig. 2). In addition, after aortic occlusion, there were no significant differences in any other variables during control conditions and acute ANP infusion.

As illustrated in Fig. 3, during chronic infusion of ANP at 5 $ng \cdot kg^{-1} \cdot min^{-1}$, there was a sustained two- to threefold increase in plasma ANP concentration (control = 35 ± 8 pg/ml). Although ANP produced a modest and transient increase in urinary sodium excretion on *day 1* (from 35 ± 1 to 64 ± 5 meq/day), by *day 2* daily sodium balance was achieved and there were no measurable changes in MAP; conversely, there was significant retention of sodium during the 24-h period following cessation of ANP infusion. Chronic ANP infusion had no significant long-term effect on urinary potassium excretion, heart rate, hematocrit, or the plasma concentrations of sodium, potassium, or protein.

Most importantly, chronic infusion of ANP, like acute ANP infusion, had no significant effect on either basal levels of PRA or the levels of PRA achieved during reductions in renal arterial pressure (Fig. 4). If anything, the PRA responses to aortic occlusion tended to be higher during ANP infusion than during control conditions; however, these differences did not achieve statistical significance.

DISCUSSION

The present study indicates that the changes in plasma ANP concentration that occur under physiological con-

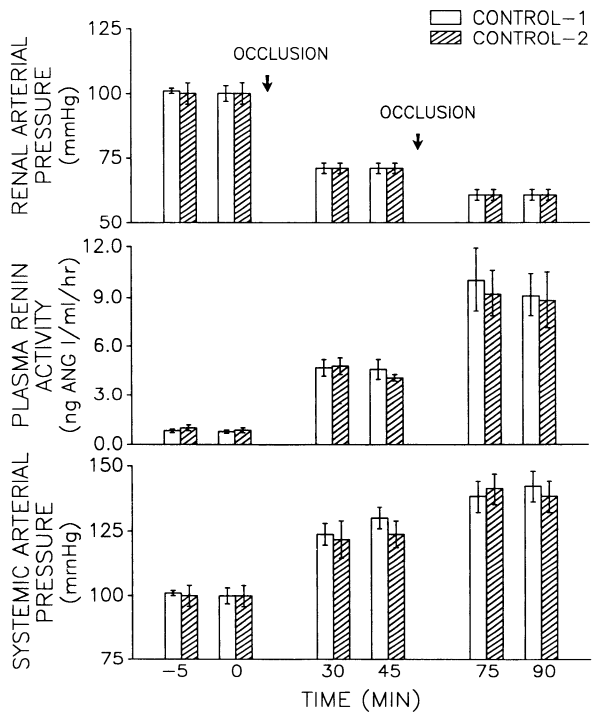

FIG. 1. Effects of reductions in renal arterial pressure on plasma renin activity and systemic arterial pressure in 2 separate control experiments performed 2–3 days apart. Values are means ± SE, $n = 5$.

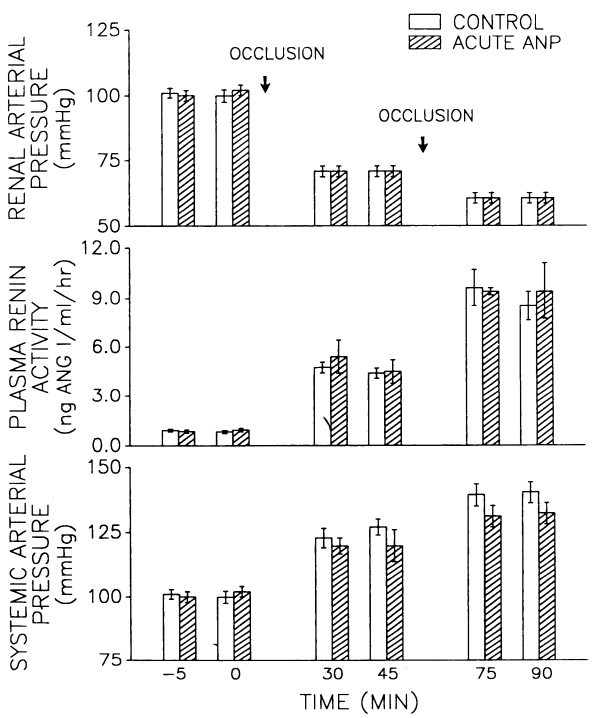

FIG. 2. Plasma renin activity and systemic arterial pressure in response to reductions in renal arterial pressure before and during acute infusion of ANP. Values are means ± SE, $n = 5$.

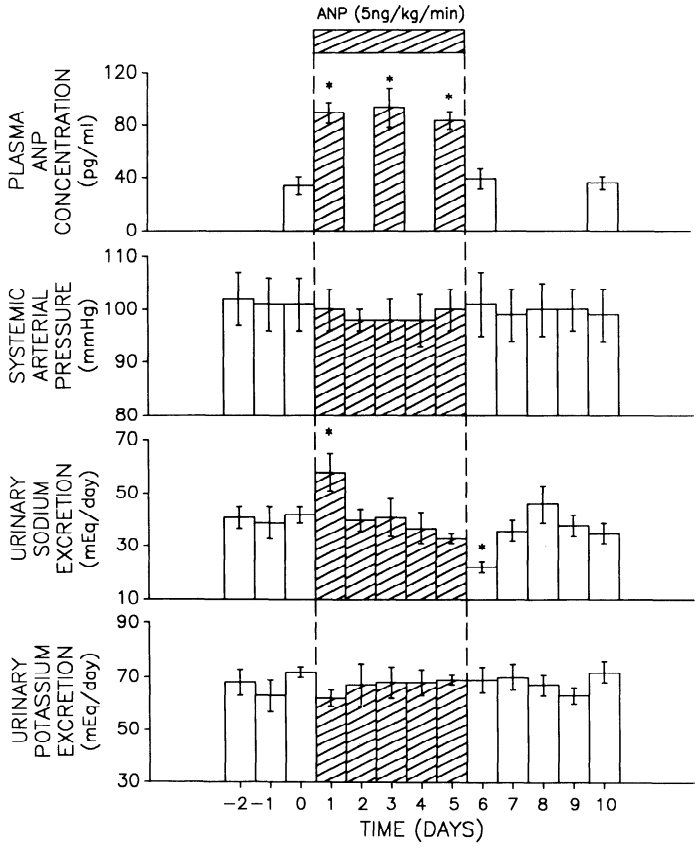

FIG. 3. Effects of chronic infusion of ANP on plasma ANP concentration, systemic arterial pressure, urinary sodium excretion, and urinary potassium excretion. Values are means ± SE, $n = 5$. * $P < 0.05$ vs. control.

ditions have relatively weak long-term effects on sodium excretion, renin secretion, and arterial pressure. If ANP had effected the ability of the kidneys to excrete salt and water to any appreciable degree, either directly or indirectly by suppressing renin release, then sodium and water balance would have been achieved at a reduced renal perfusion pressure (10). Clearly, this was not the case. Daily sodium balance was achieved by *day 2* of ANP infusion without attendant changes in MAP. Additionally, since ANP did not affect either basal or stimulated levels of PRA, these data fail to support the contention that physiological levels of ANP have an important inhibitory effect on renin secretion.

In contrast to earlier studies in which pharmacological doses of ANP produced pronounced natriuresis, recent findings indicate that ANP is not a potent natriuretic agent when present in physiological concentrations (1, 6). For example, Bie et al. (1) reported that a 60-min infusion of ANP at 12 $ng \cdot kg^{-1} \cdot min^{-1}$ in conscious dogs produced a threefold increase in plasma ANP concentration but less than a twofold increase in urinary sodium excretion. Similarly, our findings during chronic ANP infusion demonstrate that a two- to threefold increase in plasma ANP concentration induced an approximately twofold increase in urinary sodium excretion during the first 24 h of ANP infusion before daily sodium balance was achieved; furthermore, on the day following cessation of ANP infusion, there was modest sodium retention. Therefore, although ANP produced a moderate degree of sodium depletion, the current results indicate that the renal effects of this plasma level of ANP were insufficiently potent to produce a measurable fall in MAP in dogs chronically maintained on a normal sodium intake. It should be noted that the two- to threefold increment in plasma ANP concentration achieved in the present study is as high as that which occurs during acute and chronic saline loading (22), chronic aldosterone administration (8), and postprandial ingestion of a high-sodium meal (27).

In one of the few studies in which ANP has been infused chronically, Granger et al. (9) found that a high rate of ANP infusion (50 $ng \cdot kg^{-1} \cdot min^{-1}$) for 5 days, in dogs maintained on a normal sodium intake, produced approximately a 10-fold increase in plasma ANP concentration and a sustained fall in MAP of 15 mmHg; there were no significant changes in PRA throughout the 5-day ANP infusion period. Because PRA remained at control levels throughout this study and did not increase as arterial pressure fell, this observation suggests that ANP chronically inhibited renin release. Although this study indicates that ANP can increase renal excretory function and allow salt and water balance to be achieved at a reduced level of arterial pressure, it must be appreciated that a 10-fold increment in plasma ANP concentration is probably beyond the range encountered even in pathophysiological states such as heart failure (29).

In contrast to the study of Granger et al. (9), we found that increments in plasma ANP concentration within physiological levels, when sustained chronically, had insignificant effects on both renin secretion and MAP in dogs chronically maintained on a normal sodium intake. ANP failed to suppress renin secretion not only under basal conditions but also under conditions of renin stimulation by reduced renal perfusion pressure. In fact, although not statistically significant, when renin secretion was stimulated by reducing renal perfusion pressure PRA was higher during chronic ANP infusion than during the control and recovery periods. This exaggerated renin response to reduced renal perfusion pressure may reflect compensatory activation of renin secretion due to the modest sodium depletion induced by chronic ANP infusion. Regardless, under the conditions of the present study, the current findings provide no support for the hypothesis that physiological levels of ANP have important long-term effects on arterial pressure by effecting changes in sodium excretion either directly or indirectly by suppressing renin release.

Although the results obtained from acute studies have been somewhat inconsistent, supraphysiological doses of ANP have usually inhibited renin secretion (3, 17, 19, 25, 28). It has been suggested that this is the result of either increased sodium chloride load to the macula densa or a direct inhibitory effect of ANP on the juxtaglomerular cells. However, there are both studies that support and studies that refute these mechanisms whereby ANP might inhibit renin secretion (13, 15, 18, 19, 21, 28). In instances where high ANP doses have failed to inhibit renin release, ANP-induced hypotension and reflex activation of the sympathetic nervous system probably stimulated renin release sufficiently to over-

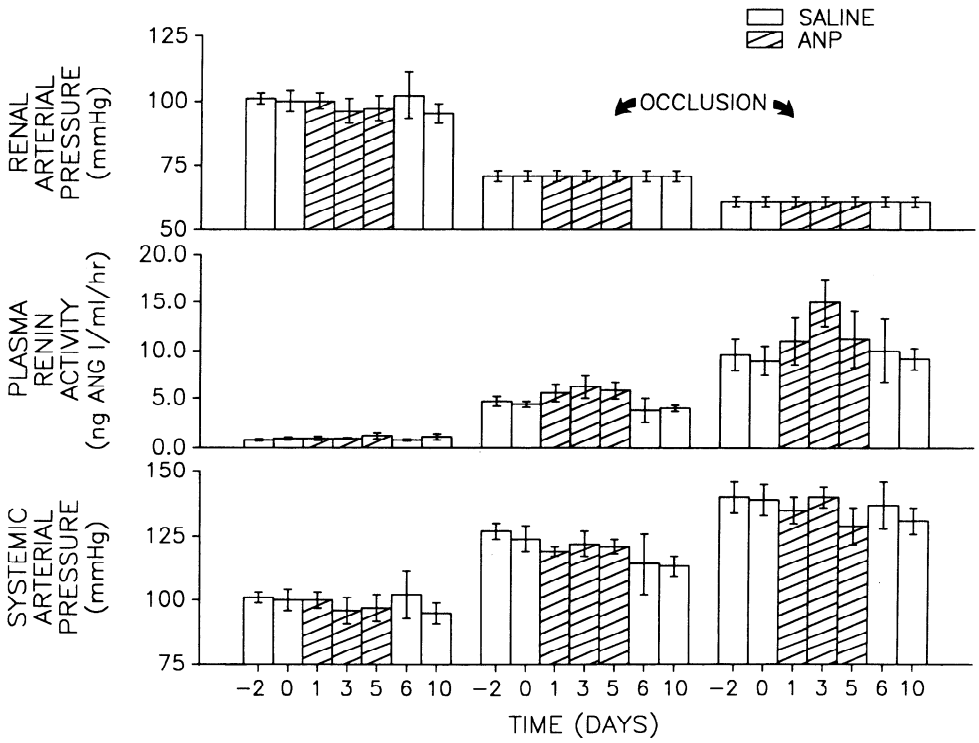

FIG. 4. Plasma renin activity and systemic arterial pressure in response to reductions in renal arterial pressure before, during, and after chronic infusion of ANP. Values are means ± SE, $n = 5$.

come the renin-inhibitory effect of ANP (2, 16). Because of these findings with pharmacological doses of ANP, the concept has developed that ANP may be an important regulator of renin secretion. However, it has not been established that ANP inhibits renin secretion at physiological concentrations. In fact, few studies have addressed this issue.

In the present study, acute infusion of ANP, like chronic ANP infusion, failed to inhibit either basal or stimulated levels of PRA. Similarly, others have reported that acute increments in plasma ANP concentration within the physiological range have no effect on PRA if basal levels are normal or low (1, 23). However, one may argue that when the renin-angiotensin system is not activated, inhibitory effects of ANP on renin release may not be manifested because reductions in PRA would not be detectable. Therefore, we also evaluated the effects of ANP on the renin response to reduced renal perfusion pressure. However, in this setting also, ANP did not exert a measurable inhibitory effect on renin secretion. This result differs from the findings of Scheuer et al. (23). These investigators infused ANP acutely, at the same rate we employed ($5\ ng \cdot kg^{-1} \cdot min^{-1}$), into conscious dogs studied in a sling, and found that the resultant two- to threefold increase in plasma ANP concentration eliminated the two- to threefold increment in PRA to a 10% reduction in renal perfusion pressure and markedly inhibited the sixfold increment in PRA to a 30% pressure reduction. In contrast, in our experiments ANP did not significantly affect the renin response to either 30% (4- to 5-fold increase in PRA) or 40% (9- to 10-fold increase in PRA) reductions in renal perfusion pressure. Because the natriuresis produced by ANP is attenuated as renal perfusion pressure decreases (20, 24, 26), one possibility that may account for the divergent renin responses to acute ANP infusion during 10 and 40% reductions in renal perfusion pressure is that the presence of ANP may have little effect on the delivery of sodium chloride to the macula densa when renal perfusion pressure is low. Consequently, if the inhibitory effects of ANP on renin release are mediated via the macula densa mechanism, one would expect ANP to have little effect on renin secretion when renal perfusion pressure is reduced as much as 40%. However, it is not clear why dissimilar renin responses to acute ANP infusion ($5\ ng \cdot kg^{-1} \cdot min^{-1}$) were observed in our experiments and those of Scheuer et al. when comparable reductions in renal perfusion pressure (30%) were achieved. One important consideration may be differences in renal neural tone between dogs supported in a sling and dogs lying quietly in a recumbent position (4, 7).

It is unlikely that failure to measure a physiologically significant attenuation of the renin response to reduced renal perfusion pressure was a result of the methodology employed. In a recent study, we constructed renin stimulus-response curves relating PRA to renal perfusion pressure in conscious dogs and found these curves to be, as have others (14, 32), very stable over periods of weeks. Moreover, in the present study, PRA responses to reduced renal perfusion pressure were very similar quantitatively during the two control experiments and during the control and recovery experiments. Thus it is unlikely that time-dependent changes in the relationship between PRA and renal perfusion pressure obscured any inhibitory effect of ANP on renin secretion. In addition, because PRA is very sensitive to even small changes in arterial pressure at the reduced levels of renal perfusion pressure studied, we used a servo-control unit to maintain renal perfusion pressure very precisely at the same reduced values in all experiments in each dog. Finally,

because variations in sodium intake affect the relationship between PRA and renal perfusion pressure (5), the dogs were fed a sodium-deficient diet, and all sodium was provided by a continuous intravenous infusion of isotonic saline. This ensured that sodium intake was constant throughout the study.

In summary, chronic intravenous infusion of a physiological dose of ANP in dogs maintained on a normal sodium intake produced a two- to threefold increment in plasma ANP concentration but only modest sodium depletion and no acute or chronic changes in either PRA or MAP. Additionally, ANP failed to inhibit the renin response to stimulation by reduced renal perfusion pressure. These findings indicate that physiological plasma levels of ANP have little effect on the ability of the kidneys to chronically regulate salt and water excretion and arterial pressure in normal dogs maintained on a normal sodium intake. Furthermore, these results fail to support the hypothesis that renin suppression is an important mechanism whereby ANP reduces arterial pressure. However, since the renal response to ANP is markedly altered by base-line sodium and volume status (30), these findings do not exclude the possibility that similar changes in plasma ANP concentration may exert more potent long-term effects on urinary sodium excretion, renin release, and arterial pressure under conditions other than those found in the present study, such as sodium depletion or situations characterized by high renal sympathetic tone. It will be of special interest to determine interactions between ANP and renin release in pathophysiological states such as heart failure, where there is high sympathetic tone as well as reduced renal perfusion pressure.

The authors thank D. Land Renfroe for technical assistance. We also express our appreciation to Drs. Manis J. Smith, Jr. and to Ronald H. Freeman for performing the PRA and ANP assays, respectively.

This work was supported in part by National Heart, Lung, and Blood Institute Grant HL-11678.

Address for reprint requests: T. E. Lohmeier, Dept. of Physiology and Biophysics, Univ. of Mississippi Medical Center, 2500 N. State St., Jackson, MS 39216-4505.

Received 25 September 1989; accepted in final form 15 December 1989.

REFERENCES

1. Bie, P., B. C. Wang, R. J. Leadley, Jr., and K. L. Goetz. Hemodynamic and renal effects of low-dose infusions of atrial peptide in awake dogs. *Am. J. Physiol.* 254 (*Regulatory Integrative Comp. Physiol.* 23): R161–R169, 1988.
2. Breuhaus, B. A., H. H. Saneii, M. A. Brandt, and J. E. Chimoskey. Atriopeptin II lowers cardiac output in conscious sheep. *Am. J. Physiol.* 249 (*Regulatory Integrative Comp. Physiol.* 18): R776–R780, 1985.
3. Burnett, J. C., Jr., J. P. Granger, and T. J. Opgenorth. Effects of synthetic atrial natriuretic factor on renal function and renin release. *Am. J. Physiol.* 247 (*Renal Fluid Electrolyte Physiol.* 16): F863–F866, 1984.
4. Chen, Y.-H., H. Hisa, K. J. Radke, J. L. Izzo, Jr., C. D. Sladek, and M. L. Blair. Adrenergic control of renin in euhydrated and water-deprived conscious dogs. *Am. J. Physiol.* 255 (*Endocrinol. Metab.* 18): E793–E800, 1988.
5. Farhi, E. R., J. R. Cant, and A. C. Barger. Alteration of renal baroreceptor by salt intake in control of plasma renin activity in conscious dogs. *Am. J. Physiol.* 245 (*Renal Fluid Electrolyte Physiol.* 14): F119–F122, 1983.
6. Goetz, K. L. Physiology and pathophysiology of atrial peptides. *Am. J. Physiol.* 254 (*Endocrinol. Metab.* 17): E1–E15, 1988.
7. Grandjean, B., G. Annat., M. Vincent, and J. Sassard. Influence of renal nerves on renin secretion in the conscious dog. *Pfluegers Arch.* 373: 161–165, 1978.
8. Granger, J. P., J. C. Burnett, Jr., R. C. Romero, T. J. Opgenorth, J. Salazar, and M. Joyce. Elevated levels of atrial natriuretic peptide during aldosterone escape. *Am. J. Physiol.* 252 (*Regulatory Integrative Comp. Physiol.* 21): R878–R882, 1987.
9. Granger, J. P., T. J. Opgenorth, J. Salazar, J. C. Romero, and J. C. Burnett, Jr. Long-term hypotensive and renal effects of atrial natriuretic peptide. *Hypertension Dallas* 8, *Suppl.* II: II-112–II-116, 1986.
10. Guyton, A. C., J. E. Hall, T. E. Lohmeier, R. D. Manning, Jr., T. E. Jackson, P. R. Kastner, and Y.-J. Pan. Role of the kidney and volume control in the pathogenesis of hypertension. In: *Handbook of Hypertension. Clinical Aspects of Essential Hypertension*, edited by W. H. Birkenhager and J. L. Reid. New York: Elsevier, 1983, p. 216–238.
11. Haber, E. T., T. Koerner, L. B. Page, B. Kliman, and A. Purnode. Application of radioimmunoassay of angiotensin I to physiological measurements of plasma renin activity in normal human subjects. *J. Clin. Endocrinol.* 29: 1349–1355, 1969.
12. Hester, R. L., J. P. Granger, J. Williams, and J. E. Hall. Acute and chronic servo-control of renal perfusion pressure. *Am. J. Physiol.* 244 (*Renal Fluid Electrolyte Physiol.* 13): F455–F460, 1983.
13. Hiruma, M., F. Ikemoto, and K. Yamamoto. Rat atrial natriuretic factor stimulates renin release from renal cortical slices. *Eur. J. Pharmacol.* 125: 151–153, 1986.
14. Kirchheim, H., H. Ehmke, S. Fischer, W. Lowe, and P. Persson. Sympathetic modulation of the pressure-dependent renin release in conscious dogs. *Clin. Exp. Hypertens. Part A Theory Pract.* 9, *Suppl.* 1: 167–180, 1987.
15. Kurtz, A., R. D. Bruna, J. Pfeilschifter, R. Taugner, and C. Bauer. Atrial natriuretic peptide inhibits renin release from juxtaglomerular cells by a cGMP-mediated process. *Proc. Natl. Acad. Sci. USA* 83: 4769–4773, 1986.
16. Lappe, R. W., J. A. Todt, and R. L. Wendt. Mechanism of action of vasoconstrictor responses to atriopeptin II in conscious SHR. *Am. J. Physiol.* 249 (*Regulatory Integrative Comp. Physiol.* 18): R781–R786, 1985.
17. Maack, T., D. N. Marion, M. J. F. Camargo, H. D. Kleinert, J. H. Laragh, Jr., E. D. Vaughan, and S. A. Atlas. Effects of auriculin (atrial natriuretic factor) on blood pressure, renal function, and the renin-aldosterone system in dogs. *Am. J. Med.* 77: 1069–1075, 1984.
18. Obana, K., M. Naruse, K. Naruse, H. Sakurai, R. Demura, T. Inagami, and K. Shizume. Synthetic rat atrial natriuretic factor inhibits in vitro and in vivo renin secretion in rats. *Endocrinology* 117: 1282–1284, 1985.
19. Opgenorth, T. J., J. C. Burnett, Jr., J. P. Granger, and T. A. Scriven. Effects of atrial natriuretic peptide on renin secretion in nonfiltering kidney. *Am. J. Physiol.* 250 (*Renal Fluid Electrolyte Physiol.* 19): F798–F801, 1986.
20. Paul, R. V., K. A. Kirk, and L. G. Navar. Renal autoregulation and pressure natriuresis during ANF-induced diuresis. *Am. J. Physiol.* 253 (*Renal Fluid Electrolyte Physiol.* 22): F424–F431, 1987.
21. Rodriguez-Puyol, D., G. Arriba, A. Blanchart, J. C. Santos, C. Caramelo, A. Fernandez-Cruz, L. Hernando, and J. M. Lopez-Novoa. Lack of a direct regulatory effect of atrial natriuretic factor on prostaglandins and renin release by isolated rat glomeruli. *Biochem. Biophys. Res. Commun.* 138: 496–501, 1986.
22. Salazar, F. J., J. C. Romero, J. C. Burnett, Jr., S. Schryver, and J. P. Granger. Atrial natriuretic peptide levels during acute and chronic saline loading in conscious dogs. *Am. J. Physiol.* 251 (*Regulatory Integrative Comp. Physiol.* 20): R499–R503, 1986.
23. Scheuer, D. A., T. N. Thrasher, E. W. Quillen, Jr., C. H. Metzler, and D. J. Ramsay. Atrial natriuretic peptide blocks renin response to renal hypotension. *Am. J. Physiol.* 252 (*Regulatory Integrative Comp. Physiol.* 21): R423–R427, 1987.
24. Seymour, A. A., S. G. Smith, E. K. Mazack. Effects of renal perfusion pressure on the natriuresis induced by atrial natriuretic factor. *Am. J. Physiol.* 253 (*Renal Fluid Electrolyte Physiol.* 22): F234–F238, 1987.
25. Seymour, A. A., S. G. Smith, E. K. Mazack, and E. H. Blaine.

A comparison of synthetic rat and human atrial natriuretic factor in conscious dogs. *Hypertension Dallas* 8: 211–216, 1986.

26. SOSA, R. E., M. VOLPE, D. N. MARION, S. A. ATLAS, J. H. LARAGH, E. D. VAUGHAN, JR., AND T. MAACK. Relationship between renal hemodynamic and natriuretic effects of atrial natriuretic factor. *Am. J. Physiol.* 250 (*Renal Fluid Electrolyte Physiol.* 19): F520–F524, 1986.
27. VERBURG, K. M., R. H. FREEMAN, J. O. DAVIS, D. VILLARREAL, AND R. C. VARI. Control of atrial natriuretic factor release in conscious dogs. *Am. J. Physiol.* 251 (*Regulatory Integrative Comp. Physiol.* 20): R947–R956, 1986.
28. VILLARREAL, D., R. H. FREEMAN, J. O. DAVIS, K. M. VERBURG, AND R. C. VARI. Renal mechanisms for suppression of renin secretion by atrial natriuretic factor. *Hypertension Dallas* 8, *Suppl.* II: II-28–II-35, 1986.
29. VILLARREAL, D., R. H. FREEMAN, J. O. DAVIS, K. M. VERBURG, AND R. C. VARI. Atrial natriuretic factor secretion in dogs with experimental high-output heart failure. *Am. J. Physiol.* 252 (*Heart Circ. Physiol.* 21): H692–H696, 1987.
30. WEIDMANN, P., B. HELLMUELLER, D. E. UEHLINGER, R. E. LANG, M. P. GNADINGER, L. HASLER, S. SHAW, AND C. BACHMANN. Plasma levels and cardiovascular, endocrine and excretory effects of atrial natriuretic peptide during different sodium intakes in man. *J. Clin. Endocrinol. Metab.* 62: 1027–1034, 1986.
31. WINER, B. J. *Statistical Principles in Experimental Design.* New York: McGraw-Hill, 1971.
32. YANG, H. M., T. E. LOHMEIER, S. D. KIVLIGHN, R. G. CARROLL, AND M. J. SMITH, JR. Sustained increases in plasma epinephrine concentration do not modulate renin release. *Am. J. Physiol.* 257 (*Endocrinol. Metab.* 20): E57–E64, 1989.