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Effects of Calcitonin Gene-Related Peptide on Renal Blood Flow in the Rat (42740)

DANIEL VILLARREAL, RONALD H. FREEMAN, KENNETH M. VERBURG, AND MICHAEL W. BRANDS

Departments of Physiology and Medicine, University of Missouri School of Medicine and Harry S. Truman Veterans Administration Medical Center, Columbia, Missouri 65212

Abstract. The effects of α-rat calcitonin gene-related peptide (α-rCGRP) on systemic and renal hemodynamics and on renal electrolyte excretion were examined in normal anesthetized rats. In one group of rats (n = 7), infusions of α-rCGRP at doses of 10, 50, 100, and 500 ng/kg/min for 15 min each produced dose-related and significant decreases in mean arterial pressure from a control of 130 ± 3 mm Hg to a maximal depressor response of 91 ± 2 mm Hg. During the first three doses of α-rCGRP, renal blood flow progressively and significantly increased from a control of 5.0 ± 0.3 ml/min to a peak level of 6.3 ± 0.3 ml/min achieved during the 100 ng/kg/min infusion. With the highest infusion rate of 500 ng/kg/min, renal blood flow fell below the control level to 4.5 ± 0.2 ml/min ($P < 0.05$). The responses in renal blood flow and mean arterial pressure were associated with reductions in renal vascular resistance. After cessation of α-rCGRP infusions, arterial pressure, renal blood flow, and renal vascular resistance gradually returned toward the baseline values. In another group of rats (n = 9), infusion of α-rCGRP for 30 min at 100 ng/kg/min produced a significant reduction in urinary sodium excretion from 0.28 ± 0.06 to 0.14 ± 0.5 μEq/min ($P < 0.05$). Urine flow and urinary potassium excretion also appeared to decrease, but the changes were not significantly different ($P > 0.05$) from their respective baselines. These results demonstrate that α-rCGRP is a potent and reversible hypotensive and renal vasodilatory agent in the anesthetized rat. The data also suggest that α-rCGRP may have significant effects on the excretory function of the kidney.

Calcitonin gene-related peptide (CGRP) is encoded in the calcitonin gene. This novel peptide is predicted to occur as a consequence of alternative, tissue-specific processing of the primary RNA transcript to produce messenger RNA specific for the synthesis of CGRP (1, 2). Both rat and human sequences of an α and a β form of CGRP have been described. Each of the four peptides consists of 37 amino acids and there is a highly conserved structure among them. Human α- and β-CGRP differ in 3 of the 37 amino acids contained in the primary structure, while rat α and β forms differ only in one amino acid (3, 4).

CGRP has been localized in the nervous, vascular, and endocrine systems of rats and humans (5–7). Based on its extensive distribution in the central and peripheral nervous system, it has been suggested that CGRP may function as a neurotransmitter or neuromodulator (8–11). Immunohistochemical studies have shown that a high density of CGRP-containing fibers are present in the peripheral vasculature as well as in the myocardium (6). Recent evidence obtained in the rat suggests that the perivascular nerves may be a major source of circulating CGRP (12, 13). Numerous studies also indicate that synthetic CGRP has potent vasorelaxant actions *in vitro* (14–18) and *in vivo* (14, 19–23). These observations support the concept that CGRP may modulate vascular tone and blood flow under some conditions.

Intravenous administration of synthetic CGRP in rats (8, 21) and humans (20, 23) produces a reduction in arterial blood pressure, presumably due to systemic vasorelaxation. Regional vasodilation induced by synthetic CGRP has been demonstrated in rabbit and human skin (14), isolated rat and rabbit mesenteric vasculature (18), and rat and rabbit coronary vessels (17). More recently, a study in normal conscious rats (24) reported that intravenous administration of CGRP selectively increased blood flow to the heart, stomach, liver, and skin while blood flow to the kidneys, brain, and spleen was decreased. In this rat study (24), however, the changes in regional organ blood flow were

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determined only during two iv bolus infusions of CGRP. Since the kidney normally receives 20 to 25% of the cardiac output and since this organ is involved in the regulation of blood volume and pressure, the importance of delineating the effects of CGRP on the renal vasculature is readily apparent. Thus, the present study in normal anesthetized rats was designed primarily to examine the systemic and renal hemodynamic effects of sustained, graded infusions of α-rCGRP. In addition, the actions of a sustained infusion of α-rCGRP on renal fluid and electrolyte excretion were evaluated in a separate group of anesthetized rats. Administration of α-rCGRP was selected since it has been suggested that this peptide has potent coronary vasodilating effects in the rat (17).

Methods. *General procedures.* Sprague-Dawley male rats with body weights between 250 and 350 g were used. The animals were fed a commercial chow diet containing 0.11 and 0.23 mEq of sodium and potassium per gram, respectively. Rat chow and tap water were available *ad libitum.* For the acute experiments the rats were anesthetized with 5-*sec*-butyl-5-ethyl-2-thiobarbituric acid (Inactin, 100 mg/kg, ip) and placed on a surgical tray over a heating pad to maintain body temperature between 37 and 39°C. A tracheostomy was performed to facilitate spontaneous respiration. Indwelling heparinized polyethylene catheters (PE 50) were positioned in the left jugular vein (Series I) or in the left femoral vein (Series II) for infusion of solutions and in the right femoral artery for blood sampling and measurement of mean arterial pressure (MAP) and heart rate (HR) via a Statham P23Db pressure transducer and a Hewlett-Packard 7702 B recorder.

Series I. Effects of graded doses of synthetic α-rCGRP infusions on systemic and renal hemodynamics in anesthetized rats. Following placement of the catheters, a ventral midline incision was made and the left renal artery was fitted with a precalibrated, squarewave electromagnetic flow probe (1.5-mm circumference, Carolina Medical Electronics, Inc.) connected to an electromagnetic flow meter (Model 501, Carolina Medical Electronics, Inc.) for continuous measurement of renal blood flow (RBF). After completion of surgery, a maintenance infusion of isotonic sodium chloride at a rate of 50 μl/min via a syringe pump (Sage Instruments, Model 355) was begun and continued throughout the experiment. Thirty minutes was allowed for recovery from the preparatory procedures. Mean arterial pressure, heart rate, and renal blood flow were continuously monitored and recorded at the end of each period of the experimental protocol. Following 30 min of equilibration after surgery, control measurements were obtained. Immediately after these baseline observations, synthetic α-rCGRP (Peninsula Lab, Belmont, CA) was infused intravenously in successive doses of 10, 50, 100, and 500 ng/kg/min for 15 min each (Group 1, $n = 7$). This was followed by two 15-min recovery periods with infusion of the isotonic saline vehicle. Hematocrit was obtained at the end of the control, the last experimental period, and the second recovery period. Control animals (Group 2, $n = 7$) were infused with the saline vehicle alone.

Series II. Effects of synthetic α-rCGRP infusion on renal fluid and electrolyte excretion in anesthetized rats. The evening before the experiments, the rats were deprived of food but not from drinking water. On the day of the acute experiment the animals were prepared as outlined under *General procedures.* In addition, through a suprapubic incision a catheter (PE 90) was inserted into the dome of the bladder for the collection of urine. After completion of the surgical procedures, the rats were given an intravenous injection of 5 ml/kg of isotonic saline followed by a continuous infusion of the same solution at a rate of 50 μl/min throughout the experiment. Mean arterial pressure and heart rate were continuously monitored. After 30 min of equilibration, one 30-min control period was obtained. During the last 15 min of the period all urine was collected in a graduated cylinder for determination of urine flow ($\dot{U}V$) and urinary sodium ($U_{Na}\dot{V}$) and potassium ($U_K\dot{V}$) excretion rates. Immediately after the control observations, one 30-min experimental period was obtained either with a sustained intravenous infusion of synthetic α-rCGRP at a dose of 100 ng/kg/min (Group 3, $n = 9$) or with saline infusion alone (Group 4, $n = 9$). Urine collections were made during the last 15 min of the ex-

perimental periods for measurements of $U\dot{V}$, $U_{Na}\dot{V}$, and $U_K\dot{V}$.

Analytical methods. Urinary sodium and potassium concentrations were determined by flame photometry. Hematocrit was determined by the microcapillary tube method.

The results are presented as means ±SE. Analysis of variance with repeated measurements was performed on the hemodynamic data of Series I. Significance was determined with the least significance difference test (LSD) within and between appropriate group means. Student's paired and unpaired *t* tests were used on the hemodynamic and renal excretory data of Series II where appropriate. Differences at the 5% level were considered significant.

Results. *Series I. Effects of graded doses of synthetic α-rCGRP infusion on systemic and renal hemodynamics in anesthetized rats.* Body weights were not significantly different between groups, averaging 325 ± 6 g in Group 1 (α-rCGRP infusion; $n = 7$) and 327 ± 7 g in Group 2 (vehicle infusion; $n = 7$). The systemic and renal hemodynamic data are presented in Fig. 1. In Group 1, infusion of α-rCGRP at incremental doses of 10, 50, 100, and 500 ng/kg/min produced dose-related and significant reductions in MAP (Fig. 1, top panel) from a control (C) of 130 ± 3 mm Hg to a maximal depressor response of 91 ± 2 mm Hg during the administration of 500 ng/kg/min. After cessation of α-rCGRP infusion, MAP progressively returned toward baseline levels, averaging 124 ± 4 mm Hg at the end of the second recovery period. Heart rate (Fig. 1, bottom panel) exhibited an opposite directional response compared to MAP, with dose-related increases from a control of 403 ± 11 beats/min to a peak of 464 ± 16 beats/min during the infusion of 500 ng/kg/min. Heart rate gradually decreased after α-rCGRP was stopped, and at the end of the second recovery period it averaged 424 ± 15 beats/min. Renal blood flow (Fig. 1, top middle panel) increased from a control of 5.0 ± 0.3 ml/min to a peak response of 6.3 ± 0.3 ml/min ($P < 0.05$) during the infusion dose of 100 ng/kg/min of α-rCGRP, an increase of approximately 21%. In association with this increase in RBF, renal vascular resistance (RVR; Fig. 1, bottom middle panel) decreased significantly from a control of 27 ± 2 mm Hg/ml · min^{-1} to a peak response of 18 ± 2 mm Hg/ml · min^{-1} during the α-rCGRP infusion dose of 100 ng/kg/min. With the α-rCGRP infusion dose of 500 ng/kg/min, in the presence of a large reduction in MAP, renal blood flow decreased below control to a value of 4.5 ± 0.2 ml/min ($P < 0.05$ from C). At this time, RVR remained significantly reduced from control, suggesting a persistent renal vasodilation in spite of the marked fall in MAP. During the recovery periods both RBF and RVR returned toward their preinfusion baseline levels. Hematocrit did not change during α-rCGRP infusion, from a control of 45 ± 1% to a level of 44 ± 1% during the 500 ng/kg/mm infusion dose. During the second recovery period, however,

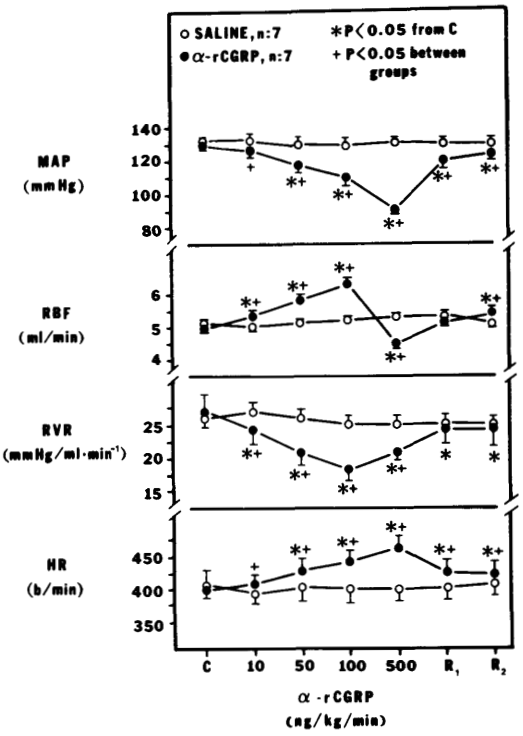

FIG. 1. Effects of synthetic α-rat calcitonin gene-related peptide (α-rCGRP) infusions (closed circles) or isotonic saline vehicle infusions (open circles) in anesthetized rats. C, Control period; R1–2, recovery periods; MAP, mean arterial pressure; RBF, renal blood flow; RVR, renal vascular resistance; HR, heart rate; *n*, number of rats in each group. $^*P < 0.05$ from C. $^+P < 0.05$ between groups.

hematocrit was significantly lower than control at a value of 42 ± 1%.

In the group of rats with saline vehicle infusion alone (Group 2) no significant changes ($P > 0.05$) in MAP, HR, RBF, and RVR were noted throughout the experimental protocol. Hematocrit (data not shown) also remained unchanged. Comparisons between the α-rCGRP and vehicle infusion groups (Fig. 1) showed no differences in control MAP, HR, RBF, and RVR. Significant differences ($P < 0.05$) between Groups 1 and 2 were observed for all of these hemodynamic functions during each of the four experimental periods. In the recovery periods slight but significant differences between groups were noted for MAP, HR, and RBF. No differences in hematocrit were observed between the two groups throughout the experimental protocol.

Series II. Effects of synthetic α-rCGRP infusion on renal fluid and electrolyte excretion in anesthetized rats. Body weights were not significantly different between groups, averaging 279 ± 6 g in Group 3 (α-rCGRP infusion; $n = 9$) and 287 ± 4 g in Group 4 (vehicle infusion; $n = 9$). The renal excretory and systemic arterial pressure data are presented in Fig. 2. In the two groups of rats of this series, the systemic hemodynamic functions remained stable during the control period, and no differences between groups were noted for MAP or HR. Similarly, no significant differences were observed between groups for baseline values of $U\dot{V}$, $U_{Na}\dot{V}$, or $U_K\dot{V}$. In Group 3, an α-rCGRP infusion dose of 100 ng/kg/min was selected because peak renal hemodynamic responses were obtained with this dose in Group 1 (Fig. 1). During the experimental period in Group 3, α-rCGRP administration produced a significant 50% reduction in $U_{Na}\dot{V}$ from a control of 0.28 ± 0.06 μEq/min to a level of 0.14 ± 0.05 μEq/min (Fig. 2, bottom middle panel). Urinary potassium excretion and urine flow also appeared to decrease from controls of 0.42 ± 0.08 μEq/min and 3.06 ± 0.36 μl/min, respectively, to values of 0.29 ± 0.10 μEq/min and 1.96 ± 0.40 μl/min during α-rCGRP infusion, but these changes were not statistically significant ($P > 0.05$). Associated with these renal excretory responses, MAP fell from 128 ± 2 to 107 ± 2 mm Hg (Fig. 2, top panel) and HR increased from a control of 436 ± 12 to 487 ± 17 beats/min ($P < 0.05$). In the vehicle-infused rats (Group 4) no changes in MAP (Fig. 2) and HR (data not shown) were observed throughout the control and experimental periods. Urinary potassium excretion and urine flow showed modest but significant increases from controls of 0.29 ± 0.06 μEq/min and 2.9 ± 0.19 μl/min, respectively, to levels of 0.63 ± 0.07 μEq/min and 5.0 ± 0.6 μl/min during the experimental interval ($P < 0.05$ for both values). Urinary sodium excretion also appeared to increase from a control value of 0.26 ± 0.05 μEq/min to a level of 0.41 ± 0.09 μEq/min during the experimental period, but this increment was not statis-

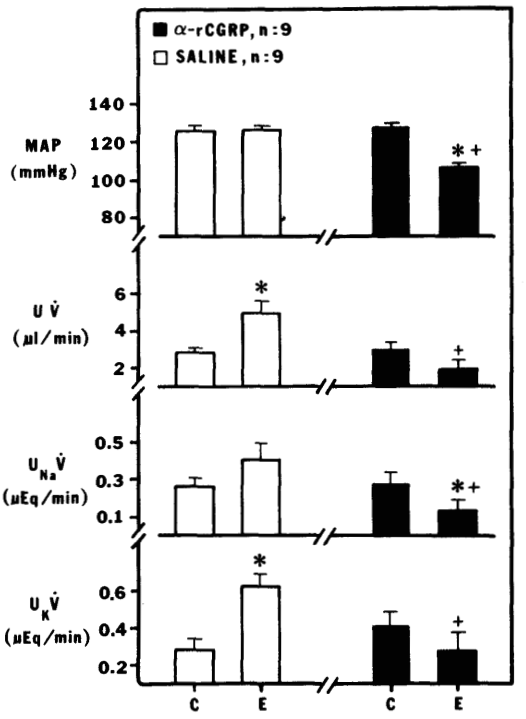

FIG. 2. Effects of synthetic α-rat calcitonin gene-related peptide (α-rCGRP) infusions (closed bars) or isotonic saline vehicle infusions (open bars) in anesthetized rats. C, Control period; E, experimental period with saline vehicle (open bars) or α-rCGRP (closed bars) at a dose of 100 ng/kg/min for 30 min. MAP, Mean arterial pressure, $U\dot{V}$, $U_{Na}\dot{V}$, and $U_K\dot{V}$, urinary fluid, sodium, and potassium excretions, respectively. *n*, Number of rats in each group. $^*P < 0.05$ from C. $^+P < 0.05$ between groups.

tically significant ($P > 0.05$). These modest increases in urinary fluid and electrolyte excretion may have been related to further hydration in the vehicle-infused rats. Although the animals treated with α-rCGRP received a similar degree of hydration, opposite directional changes in urinary sodium, potassium, and fluid excretion occurred in this group compared to the vehicle-infused rats during the experimental periods (Fig. 2). Comparison of these responses revealed significant differences ($P < 0.05$) between the two groups.

Discussion. This study in normal anesthetized rats demonstrates that synthetic α-rCGRP is a potent renal vasodilating agent, with a rapid onset of action and reversible effects. In addition, the present results suggest that α-rCGRP may produce a significant reduction in urinary sodium excretion. These data represent, to our knowledge, the first report on the biological effects of sustained infusions of CGRP on renal blood flow and electrolyte excretion in the rat.

The present experiments extend previous observations which have indicated that CGRP can induce vasodilation in a variety of vascular beds, including skin (14), mesenteric (18), and coronary vasculature (17). Indeed, graded doses of α-rCGRP starting as low as 10 ng/kg/min resulted in significant increases in RBF accompanied by significant reductions in RVR. Moreover, although the highest dose of 500 ng/kg/min produced a 39 mm Hg reduction in MAP, RBF fell only slightly below control and the calculated RVR remained significantly depressed from baseline by approximately 22%. This persistent reduction in RVR in the presence of a marked fall in MAP may represent a combined effect of the vasorelaxant action of α-rCGRP as well as autoregulatory adjustments in renal vascular resistance. Thus, these data suggest that under the present experimental conditions, the renal vasculature is very sensitive to the vasorelaxant effects of CGRP. This conclusion is in agreement with the findings of a recent study by Lappe *et al.* (25) in which iv bolus injections of CGRP significantly increased renal blood flow in the conscious spontaneously hypertensive rat. In contrast to the present results and those of Lappe *et al.* (25), in the study of DiPette *et al.* (24) renal blood flow failed to increase in the normal conscious rat following iv bolus injections of CGRP. The reasons for these discrepancies are unclear. However, since basal renal vascular resistance may be elevated in both the spontaneously hypertensive and anesthetized rats when compared to the normal conscious rat, it is possible that increases in renal vascular tone may render the renal vasculature sensitive to the vasodilatory actions of CGRP.

The mechanisms of CGRP-induced vasorelaxation have not been completely elucidated. CGRP does not appear to exert its vasorelaxant effect through adrenergic, histaminergic, or muscarinic cholinergic smooth muscle receptors (16, 22). In addition, prostaglandin synthetase inhibition with indomethacin does not appear to suppress intradermal CGRP-induced vasodilation in the rabbit (14), although indomethacin partially inhibited CGRP-induced relaxation of rat aortic rings in the same study (14). These findings suggest that prostaglandins may not be essential mediators for the vasorelaxant response to the peptide. On the other hand, CGRP-induced relaxation of isolated rat aorta reportedly required an intact endothelium, suggesting that the vasodilatory actions of the peptide may be dependent on the release of an endothelial factor (14). In addition, in rat aortic smooth muscle cells (26) and cat cerebral arteries (15) CGRP has been shown to stimulate the production of cyclic AMP which, in turn, may be related to the arterial relaxation. Regardless of the precise mechanism of CGRP-induced vasodilation, it is clear that networks of immunoreactive CGRP nerve fibers exist in numerous blood vessels, including the renal artery (6), and that CGRP circulates in plasma in significant concentrations (13, 27). Thus, it is reasonable to suggest that CGRP may be involved in the modulation of vascular tone and blood flow.

In a separate group of rats in the present study (Group 3), a significant reduction in urinary sodium excretion was observed during the infusion of α-rCGRP at a dose of 100 ng/kg/min. Urine flow and potassium excretion also appeared to decrease. The mechanism(s) for these renal excretory responses is unclear. During administration of the pep-

tide a fall in MAP of approximately 20 mm Hg occurred, and it is likely that this degree of reduction in renal perfusion pressure may have produced, at least in part, the observed decreases in urinary fluid and electrolyte excretion. Both glomerular filtration rate and sodium excretion may be sensitive to acute reductions in renal perfusion pressure of this magnitude. Additional potential mechanisms for the decrease in sodium excretion include direct and/or hypotension-induced activation of the renin–angiotensin–aldosterone system (28) and the renal sympathetic nerves (29) for the promotion of tubular sodium reabsorption. Also, a direct tubular action of CGRP to enhance sodium reabsorption cannot be excluded, although recent studies with membranes isolated from whole rat kidneys (30) or cultured porcine renal tubular ($LLC\text{-}PK_1$) cells (31) have revealed an absence of specific binding sites for CGRP. Additional investigations are needed to evaluate the mechanisms by which the peptide alters renal hemodynamic and excretory functions.

In the present experiments, the dose-related hypotensive effects of α-rCGRP were accompanied by simultaneous gradual increases in heart rate. It is possible that this tachycardic response represents a hypotension-induced reflex sympathetic activation. Also, it has been reported that CGRP may exert a direct positive chronotropic effect on the heart, perhaps via specific CGRP receptors (12, 22). Thus, a combination of these two mechanisms probably contributed to the tachycardia during α-rCGRP administration.

In summary, the present study demonstrates that in the rat, intravenous administration of synthetic α-rCGRP increases RBF and decreases RVR in a dose-related fashion. Synthetic α-rCGRP also appears to produce a significant reduction in urinary sodium excretion, but at present the mechanism(s) for this reponse is undefined.

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