Comparative Vascular Pharmacology of the Atriopeptins

Korekiyo Wakitani, Takeshi Oshima, Arthur D. Loewy, Sandra W. Holmberg, Barbara R. Cole, Steven P. Adams, Kam F. Fok, Mark G. Currie, and Philip Needleman

From the Washington University School of Medicine, Departments of Pharmacology, Anatomy, and Neurobiology and Pediatrics, St. Louis, Missouri, and Monsanto Research Laboratories, St. Louis, Missouri

SUMMARY. The atriopeptins are potent relaxants of norepinephrine-constricted aortic strips or are dilators of renal blood vessels in isolated perfused rat kidneys that are constricted by norepinephrine. This vasorelaxant property of the atriopeptins requires the presence of phenylalanine arginine (i.e., atriopeptin II, III, or ser-leu-arg-arg atriopeptin III) residues in the carboxy terminus which are considerably more effective than atriopeptin I (the 21 amino acid peptide which lacks the phe-arg C-terminus) or the core peptide (residues 3-19). However, these artificially in vitro precontracted preparations do not accurately predict the vascular effectiveness of the atriopeptins in intact rats. Intravenous administration of the atriopeptins (including atriopeptin I) to anesthetized rats produces concentration-dependent hypotension, a selective decrease in renal resistance in low doses (determined with microspheres), and pronounced diuresis. At higher doses, atriopeptins increase blood flow in other vascular beds. On the other hand, in the anesthetized dog, injection (intraarterially) of the phe-arg-containing peptides produces a concentration-dependent increase in both renal blood flow and sodium excretion, whereas atriopeptin I is inactive. Although there is a species difference in responsiveness to atriopeptin I, these data demonstrate a direct correlation between the renal vasodilation and diuresis produced by this novel family of atrial peptides. (Circ Res 56: 621–627, 1985)

The pioneering observation of deBold and his colleagues (1981) that intravenous administration of atrial extracts in rats resulted in pronounced natriuresis-diuresis elicited extensive interest in the isolation and characterization of the intrinsic substance causing the response. Within the course of several months, a number of laboratories reported the purification and amino acid sequence of a family of small peptides ranging in size from 19-33 amino acids which were derived from atrial extracts and which possessed biological activity (Flynn et al., 1983; Currie et al., 1984a; Kangawa and Matsuo, 1984; Geller et al., 1984; Napier et al., 1984; Misono et al., 1984; Seidah et al., 1984). All these peptides exhibited the same core sequence of 17 amino acids within a cystine disulfide bridge, but differed in their N- and C-termini. The high molecular weight peptide fraction was demonstrated to be the precursor of the more active low molecular peptides (Currie et al., 1984b, and Trippodo et al., 1984), and purification and sequence analysis indicated that the biologically active fragment was at the C-terminus (Geller et al., 1984; Thibault et al., 1984; Kangawa et al., 1984; Lazure et al., 1984). Oligonucleotide probes were prepared from the sequenced peptide and were utilized to clone the appropriate cDNA (Yamanaka et al., 1984; Maki et al., 1984; Oikawa et al., 1984; Seidman et al., 1984).

The natriuretic and diuretic effectiveness of these peptides has been extensively described. Another prominent biological effect of the atrial peptides is their ability to act as vasorelaxants when tested on isolated blood vessel segments (Currie et al., 1983; Geller et al., 1984; Currie et al., 1984a). Furthermore, the atrial peptides reduce renal resistance in blood autoperfused rat kidneys (Oshima et al., 1984) and in vivo in conscious trained unanesthetized dogs (Hintze et al., 1984).

Knowledge of the structure of the atrial peptides allowed the production of synthetic peptides for more extensive biological testing. The demonstration of reduced content of biologically active peptide in the atria of spontaneous hypertensive rats (Sonnenberg et al., 1983) or in syrian hamsters with cardiomyopathy (Chimoskey et al., 1984) implies that a deficiency of circulating atrial peptide may be related to the disease process and suggests the possibility for replacement therapy. In the present study, several of the naturally occurring peptides were subjected to structure-activity and dose-response analyses in a variety of in vitro and in vivo preparations. The selection of peptides for our study was based on our initial finding that there were two groups of substances that we had sequenced which had minor differences in length and which elicited different biological effects (Currie et al., 1984a; Geller et al., 1984). We termed the low molecular weight substances "atriopeptins" (AP) (Currie et al., 1984a). Atriopeptin I contains 21 amino acid residues possessing a core 17 amino acid ring enclosed
within a cystine disulfide ring with an N-terminal ser-ser extension and a C-terminal asn-ser terminal. Atriopeptin I (API) relaxes intestinal smooth muscle strips, but is impotent on blood vessel segments (Currie et al., 1984a). In this study, we evaluated one N-terminal- and two C-terminal-extended atrial peptides that were isolated from rat atria. Atriopeptin II and III (APII and APIII) are vasodilators which contain 23 and 24 amino acid residues with a phe-arg or a phe-arg-tyr C-terminal extension of API, respectively. We also studied the N-terminal-extended peptide originally characterized by Flynn et al. (1983) which we term ser-leu-arg-arg-APIII (SLRR-APIII). From such quantitative and qualitative studies, the utility of exogenously administered atrial peptides for therapeutic advantage can be evaluated.

Methods

Materials

The atrial peptides studied were prepared by solid-phase peptide synthesis (Merrifield et al., 1963), and their structures were confirmed by amino acid analysis and verified by gas-phase sequence analysis.

Procedures

Smooth Muscle Preparations

Strips obtained from the thoracic aorta of anesthetized (pentobarbital) rabbits were continuously bathed by superfusion with Krebs-Henseleit media (10 ml/min). The strips were contracted with norepinephrine, and application of atriopeptins caused a concentration-dependent relaxation, as originally described (Currie et al., 1983, 1984).

Isolated Perfused Rat Kidney Preparation

Sprague-Dawley rats (300–500 g) were anesthetized with pentobarbital sodium (30 mg/kg, ip) and heparinized (1000 U/kg, iv). The renal artery was cannulated with PE 50 tubing (I.D., 0.59 mm), and the kidney was removed from the animal and attached to a non-recirculating perfusion system of oxygenated (O2/CO2-95%/5%) Krebs-Henseleit medium at 37°C flowing at 8 ml/min at a basal perfusion pressure of 60–80 mm Hg. With a constant flow of perfusion media, measurement of renal pressure provides an indication of renal resistance changes. Renal pressure was elevated to 140 mm Hg by the continuous infusion of 10 ng/ml of norepinephrine.

Rat Blood Pressure Experiments

Female Sprague-Dawley rats (200 g) were anesthetized with pentobarbital sodium (30 mg/kg, ip). The blood pressure was recorded with a Statham blood pressure transducer and a Beckman R511 recorded via a femoral artery cannula (PE50). The animals were maintained on a saline:5% dextrose mixture via a jugular vein cannula (pentobarbital) rabbits were continuously bathed by superfusion with 0.3 μm in diameter and labeled with 52Cr or 57Co, were suspended in an 84% dextrose solution containing several drops of 0.05% Tween 80, dispersed by ultrasonication, and mixed on a vortex shaker for 3 minutes before infusion. A 0.1 ml suspension of the 51Cr microspheres was transferred to a 70-cm length of coiled PE-50 tubing, and the number of microspheres was determined by gamma counting (Tracor 1191 gamma counter). A coincidence loss of 11.5% was calculated for counts exceeding 100,000 counts/min, and the necessary corrections were made to compensate for this error. The microsphere coil was connected to the left ventricular cannula and flushed with 0.5 ml heparinized-saline for 60 seconds with a Gilford infusion pump. A reference sample of blood (1 ml) was withdrawn at 1 ml/min beginning 10 seconds before microsphere injection was begun. Simultaneously, 0.5 ml of heparinized rat blood was infused intravenously to compensate for the blood loss. To minimize geometric counting error, the reference blood sample was mixed with 1.0 ml of a 20% hot gelatin solution and its radioactivity was determined. Then the atrial peptide was infused intravenously for 5 minutes, at which time the 57Co microspheres were administered. At the end of the experiment, the rat was killed with an overdose of pentobarbital sodium, and the organs were excised, blotted on gauze, and placed into weighed plastic tubes for counting of radioactivity. The blood samples were used as reference flows in the calculation of cardiac outputs and organ flow, as previously described (Stanek et al., 1983, 1984). A computer (VAX 11/780) was used to correct the counts for interaction between the two isotopes, as well as to calculate tissue flow (ml/min per g) and regional vascular resistance. Paired Student’s t-test was used to determine the level of statistical significance, comparing the pretreatment data with the treatment data (at 5 minutes of atriopeptin infusion) for each rat. Thus, each value served as its own control, and P values were determined for five animals in each group.

Rat Diuresis Studies

Anesthetized (pentobarbital sodium, 30 mg/kg, ip) female rats (200 ± 20 g) were infused with 0.15 ml/min of a saline:5% dextrose mixture via a jugular vein cannula. After the animals were permitted 1 hour of equilibration time to recover from the catheter insertion and to allow volume expansion, urine was collected via a urethral catheter at 10-minute intervals. The peptides were administered intravenously as a bolus injection. The peak response to the administered peptide was exhibited in the first 10 minutes, and recovery was complete by the 30-minute collection. The diuretic response to the peptides was reported as the total volume collected in 30 minutes.
Mongrel dogs (8–16 kg) were anesthetized with pentobarbital sodium (30 mg/kg, iv), and the trachea was intubated with a cuffed endotracheal tube connected to a Harvard respirator. Blood pressure (femoral artery cannulation) and heart rate were recorded on a Beckman recorder. A continuous infusion (1.2 ml/min) of saline was delivered into the cannulated brachial vein. The renal artery was exposed via a retroperitoneal incision, and renal blood flow was measured with a 2.5-mm (i.d.) electromagnetic flow probe (Carolina Instrument Flowmeter). A 22-gauge needle attached to PE-50 tubing was introduced into the right renal artery distal to the flow probe for infusions of peptide. The ureter was catheterized with PE-160 tubing (1.14 mm, i.d.) for urine collection at 5-minute intervals in a fraction collector. Urinary electrolytes were measured by flame photometry.

Results

Spasmyolytic Properties of The Atrial Peptides

The relative potency of the atrial peptides as blood vessel relaxants is shown in Figure 1. The presence of the phe-arg C-terminus appears to be a critical determinant of vasorelaxant activity. Thus APII, APIII, and SLRR-APIII are extremely potent compounds. C-terminus truncation of either the arg (des arg-APII) or the phe-arg (API) decreases vascular potency, compared to APIII, by 10- and 100-fold, respectively. The N- and C-terminal truncated core peptide (residues 3–19) is essentially inactive as a vascular relaxant, and it does not exhibit inhibitory activity against the active atriopeptins. SLRR-APIII (i.e., the N-terminal extension of APIII) facilitated the vascular spasmyolytic activity.

Isolated Krebs-Perfused Rat Kidney

The isolated perfused rat kidney was employed for the quantitative and qualitative evaluation of the naturally occurring atrial peptides on renal vasculature, independent of any non-renal or plasma hydrolysis of the atriopeptins or neuronal or extra-renal hormonal influences. The advantage of using the perfused kidney over the isolated aorta strip is that changes in pressure in the intact organ directly reflect alterations in resistance vessels, and, furthermore, the kidney is a likely target organ for the atrial peptides. Consistent with the data obtained on the isolated rabbit aorta strips, the phe-arg-containing atrial peptides (APII, III, and SLRR-APIII) were potent renal vasodilator substances (Fig. 2). Loss of the C-terminal phe-arg residues (i.e., API and the 3–19 core peptide) caused a 90% reduction in potency.

![Figure 1. The blood vessel relaxant potency of the atrial peptides. Rabbit thoracic aorta strips were precontracted with norepinephrine (2 × 10^{-6} m) and calibrated by performing a glyceryl trinitrate (GTN) dose-response curve. The atriopeptin responses were compared to the 30-ng GTN response (ED_{50}) which corrected for the differences in sensitivity between different aorta strips. The values are the mean ± SEM (n = 5). The following abbreviations were employed: GTN-glyceryl trinitrate (nitroglycerin); API (1-21)-atriopeptin I, the 21 amino acid peptide which serves as the basis for a comparative numbering and nomenclature system; APII and APIII are extensions of API containing phe-arg or phe-arg-tyr, respectively, added to the C-terminus of API. SLRR-APIII indicates atriopeptin III with tetrapeptide N-terminal extension of ser-leu-arg-arg; 3–19 indicates the 17 amino acid core peptide contained within the cystine disulfide ring thus lacking the ser-ser from the N-terminal and the asn-ser from the C-terminal of API; and des arg-APII (1-22), which lacks the arg C-terminal of APII.

![Figure 2. Comparative vasodilator potency of the naturally occurring, low molecular weight atriopeptins in the isolated perfused rat kidney. The values represent the mean ± SEM (n = 5). For comparison, a 10-µg dose of glyceryl trinitrate (GTN) caused a 24 ± 7 mm Hg (n = 5) fall in renal perfusion pressure.](http://circres.ahajournals.org/)

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The Comparative Vasodepressor Potency and Duration of Action of Atrial Peptides* in Pentobarbital-Anesthetized Rats

<table>
<thead>
<tr>
<th>Peptide</th>
<th>n</th>
<th>Fall in blood pressure (mm Hg)</th>
<th>Duration of action (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLRR-APIII</td>
<td>4</td>
<td>36 ± 9</td>
<td>68 ± 6</td>
</tr>
<tr>
<td>APIII</td>
<td>4</td>
<td>29 ± 7</td>
<td>77 ± 11</td>
</tr>
<tr>
<td>APII</td>
<td>5</td>
<td>40 ± 6</td>
<td>64 ± 13</td>
</tr>
<tr>
<td>API</td>
<td>4</td>
<td>30 ± 10</td>
<td>34 ± 9</td>
</tr>
<tr>
<td>3-19</td>
<td>4</td>
<td>31 ± 4</td>
<td>16 ± 2</td>
</tr>
</tbody>
</table>

* 50 µg/kg bolus iv injection. The duration of action represents the time required for the blood pressure to return to pretreatment control levels following the 50 µg/kg (iv) injection. The abbreviations are listed in the legend for Figure 1, and the values are the mean ± SEM.

Changes in Regional Blood Flow

We selected API, APIII, and SLRR-APIII, because of their varying N- and C-terminal extensions, for more extensive study of regional vascular changes as measured by microsphere studies in anesthetized rats. Use of anesthetized animals permits comparison to the blood pressure studies and reduces variability. We observed a blood flow for the whole organs of 0.5–1.5 ml/min for brain, stomach, spleen, skin (flow/10 g), skeletal muscle (flow/10 g), large intestine, and cecum; 4–5 ml/min for liver and heart (7% of cardiac output); 7 ml/min for each kidney (i.e., approximately 10% of the cardiac output to each kidney); and 9.5 ml/min for the small intestine. In these experiments, the first injection of 51Cr microspheres was given before drug treatment, thereby permitting the animal to serve as its own control. Then the test compound was infused for 5 minutes, which permitted the development of a stable hemodynamic response, and during the peptide infusion, the 57Co microspheres were injected. Table 2 presents the detailed analysis of the effect of a 5 µg/kg per min infusion of APIII on regional vascular blood flow per gram of tissue. This dose of peptide produced a 15 mm Hg fall in blood pressure, with little effect on cardiac output. The stomach and intestine exhibited a significant reduction in blood flow, but when the fall of blood pressure was taken into account, only slight changes in vascular resistance were noted, and the kidney was the only vascular bed which showed a significant reduction in resistance (Table 2). Infusion of a higher concentration of APIII (i.e., 30 µg/kg per min for 5 minutes) resulted in a greater fall in blood pressure, an enhanced renal blood flow, and a marked reduction in renal resistance (Table 3), as well as a significant decrease in brain, heart, and skin resistance (data not shown). In the anesthetized rat, API produced a selective renal vasodilation analogous to that achieved with APIII. SLRR-APIII at 1 µg/kg per min caused only renal vasodilation; however, at 5 µg/kg per min, a

kg.(iv) to elicit a 10–18 mm Hg fall in blood pressure, and a maximum hypotensive effect was achieved with 300–500 µg/kg of the various atrial peptides. There was no significant quantitative difference in the potency of the initial hypotensive response to bolus injections of the atriopeptins (Table 1). However, structural features of the peptides clearly influenced the duration of the hypotensive response. SLRR-APIII, APIII, and API (i.e., the phe-arg-containing peptides) were extremely long lasting, compared to nitroglycerin, and required more than an hour to recover to control (preinjection) blood pressure levels following a 50 µg/kg injection (iv) of the peptide (Table 1). On the other hand, the truncated peptides (lacking the phe-arg C-terminus) API and the 3–19 core peptide were more transient hypotensives, requiring 35 and 15 minutes, respectively to recover to control values (Table 1).
pronounced blood pressure reduction was elicited that blunted the increase in renal blood flow, although there also was a significant decrease in vascular resistance in the kidney (Table 3), as well as in skeletal muscle, brain, and skin (data not shown). Nitroglycerin (GTN) infusion was employed for comparison purposes, and a 5 /ig/kg per min infusion significantly decreased vascular resistance nonselectively in the kidney (Table 3), and in brain, intestines, skeletal muscle, and skin (not shown).

Atriopeptin Diuresis in Rats

We previously demonstrated that API and APII, obtained by purification of rat atrial extracts, were natriuretic and diuretic in anesthetized rats (Currie et al., 1984), but only small amounts of material were available; thus, careful quantitative comparison was not practical. In view of the ability of API to produce a hypotensive response and renal vasodilation in anesthetized rats (comparable to the pherarg-containing peptides), we performed a quantitative comparison with pure synthetic API and APIII. These experiments were facilitated by establishing volume expansion conditions which markedly reduced the variability between animals. We found that API produced a concentration-dependent diuresis following bolus intravenous injections of the peptide (Fig. 4). No response was produced by 0.1 Hg API, and no tachyphylaxis was produced by the 3.3-fig dose, since it could be repeated at 40-minute intervals and elicited the same volume excretion as the previous dose. APIII produced a parallel but

## Table 2

The Regional Blood Flow and Vascular Resistance of Pentobarbital-Anesthetized Rats after an Intravenous Infusion of APIII

<table>
<thead>
<tr>
<th>Regions</th>
<th>Tissue flow (ml/min per g)</th>
<th>Vascular resistance (mm Hg/min per g per ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-APIII</td>
<td>+APIII</td>
</tr>
<tr>
<td>Brain</td>
<td>0.74 ± 0.13</td>
<td>0.78 ± 0.16</td>
</tr>
<tr>
<td>Heart</td>
<td>3.37 ± 0.43</td>
<td>3.19 ± 0.31</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.40 ± 0.06</td>
<td>0.32 ± 0.05*</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1.88 ± 0.21</td>
<td>1.60 ± 0.15*</td>
</tr>
<tr>
<td>Large intestine</td>
<td>0.64 ± 0.09</td>
<td>0.59 ± 0.08</td>
</tr>
<tr>
<td>Cecum</td>
<td>1.67 ± 0.33</td>
<td>1.59 ± 0.24</td>
</tr>
<tr>
<td>Kidney</td>
<td>4.41 ± 0.46</td>
<td>4.96 ± 0.41†</td>
</tr>
<tr>
<td>Spleen</td>
<td>1.73 ± 0.49</td>
<td>1.03 ± 0.29</td>
</tr>
<tr>
<td>Liver</td>
<td>0.38 ± 0.04</td>
<td>0.37 ± 0.04</td>
</tr>
<tr>
<td>Skeletal M</td>
<td>0.052 ± 0.01</td>
<td>0.05 ± 0.04</td>
</tr>
<tr>
<td>Skin</td>
<td>0.057 ± 0.014</td>
<td>0.06 ± 0.01</td>
</tr>
</tbody>
</table>

The values obtained from the microsphere experiments are the means ± SEM for five animals (419 ± 9 g). Each animal served as its own control. The blood pressure was 127 ± 8 and 112 ± 7* mm Hg before and during the 5-minute infusion of APIII at 5 Mg/kg per min. Neither the heart rate (392 beats/min control vs. 387 beats/min with APIII) nor the cardiac output (83 ± 12 ml/min control vs. 76 ± 10 ml/min with APIII) changed significantly during the infusion of the peptide.

* P < 0.05.
† P < 0.01 (paired t-test).

## Table 3

Comparative Effectiveness of Atrial Peptides as Renal Vasodilators in Pentobarbital-Anesthetized Rats

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Dose (µg/kg per min)</th>
<th>Blood pressure (mm Hg)</th>
<th>Renal blood flow (ml/min per g)</th>
<th>Vascular resistance (mm Hg/min per g per ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Treated</td>
<td>Control</td>
</tr>
<tr>
<td>APIIII</td>
<td>5</td>
<td>127 ± 8</td>
<td>112 ± 7*</td>
<td>4.41 ± 0.48</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>137 ± 8</td>
<td>105 ± 8*</td>
<td>3.98 ± 0.34</td>
</tr>
<tr>
<td>API</td>
<td>5</td>
<td>130 ± 5</td>
<td>113 ± 7*</td>
<td>3.91 ± 0.54</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>136 ± 6</td>
<td>104 ± 6*</td>
<td>3.94 ± 0.51</td>
</tr>
<tr>
<td>SLRR-API III</td>
<td>1</td>
<td>132 ± 6</td>
<td>123 ± 6*</td>
<td>4.27 ± 0.36</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>132 ± 10</td>
<td>74 ± 6*</td>
<td>3.40 ± 0.40</td>
</tr>
<tr>
<td>GTN</td>
<td>5</td>
<td>137 ± 5</td>
<td>113 ± 7*</td>
<td>4.68 ± 0.49</td>
</tr>
</tbody>
</table>

Determined by microsphere technique. The values reported indicate the mean ± SEM from control (n = 5) after a 5-minute (iv) infusion.

* P < 0.05.
The peptides were administered as bolus intravenous injections into 200 ± 20 g female rats. There was no cross-tolerance between peptides; thus, injection of two consecutive doses of 3.3 ng of API, followed by a 3.3-ng APH dose, produced 6.17, 6.21, and 6.73 ml urine/30 min, respectively, when injected into a pentobarbital-anesthetized rat. The values are the means ± SEM (n = 4).

slightly less potent concentration-dependent diuretic response (Fig. 4).

Renal Vascular and Natriuretic Response to Atrial Peptides in the Intact Dog

In the above microsphere experiments, the atrial peptides had to be administered intravenously to the anesthetized rats, and efforts to deliver the compounds directly into renal arteries would compromise measurement of renal resistance. We therefore performed structure-activity and dose-response curve analysis of the renal vasodilator and sodium excretory effect of atrial peptides in intact anesthetized dogs. When atrial peptides are administered directly into the renal artery of pentobarbital-anesthetized dogs, the phe-arg-containing atriopeptins are potent renal vasodilator (flowmeter measurements) and natriuretic (U_{Na}V) substances (Table 4). On the other hand, API was two to three orders of magnitude less potent than the other atrial peptides. A bolus injection of 100 nmol of API (the largest dose tested) caused a 13 ± 4 ml/min increase in renal blood flow and a 45 ± 20% increase in U_{Na}V. The N-terminal-extended peptide (SLRR-APIII) was about eight times as effective as APIII and APIII (which were equipotent) in the canine kidney.

**Discussion**

A primary finding in this paper is the renal selectivity of atriopeptins in anesthetized rats. Under our experimental conditions, we could not detect significant reductions in the vascular resistance of other organs, except at high concentrations of infused atriopeptins. Utilizing the microsphere technique in anesthetized rats, others have demonstrated that partially purified rat atrial (but not ventricular) extract increases renal blood flow and causes a shift of blood flow from outer to inner cortex (Borenstein et al., 1983). However, such an extract would include a number of the low molecular weight peptides, and these experiments did not describe the blood flow distribution changes of the other vascular beds. Injection of the atrial peptides into tissues with high vascular tone, such as the isolated perfused kidney or aorta strips (Figs. 1 and 2) or the autoperfused rat kidney (Oshima et al., 1984), appears to result in a renal vasodilation with phe-arg-containing atriopeptins, but not with API. On the other hand, intravenous injection of the atrial peptide in anesthetized rats (with or without phe-arg in the C-terminus) causes a fall in blood pressure (Fig. 3), an increase in renal blood flow (Table 3), and diuresis (Fig. 4). The hypotensive effect of these agents was not abolished in nephrectomized rats (data not shown), suggesting that vascular beds (for example the venous bed) other than those analyzed are relaxed by the atriopeptins. We previously observed that both API and APIII were effective in producing natriuresis and diuresis in anesthetized rats (Currie et al., 1984). The mechanisms underlying this paradox are unclear. Interestingly, in a preliminary report, administration of a rat atrial extract caused a fall in blood pressure in unanesthetized spontaneously hypertensive rats, but produced no effect in the normotensive Wistar-Kyoto control rats (Pegram et al., 1984). Others have found that the spontaneously hypertensive rat (but not the Wistar-Kyoto control) exhibited diminished atrial levels of stored natriuretic factor (Sonnenberg et al., 1983). Perhaps a reflex mechanism which blunts the hypotensive effects of the atrial peptides is abolished by anesthesia, and is suppressed in the spontaneous hypertensive rat.

Since it was impractical to study sodium excretion following intrarenal arterial injections in anesthetized rats, we studied some of the naturally occurring...
Atriopeptins: A family of potent biologically active peptides

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Dr. Oshima's current address is: Sankyo Biological Research Laboratories, Tokyo, Japan.

Dr. Wakatani's current address is: Ono Research Institute, Osaka, Japan.

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