Evidence That Atriopeptin Is Not a Physiological Regulator of Sodium Excretion

Kenneth L. Goetz

Although much experimental evidence is consistent with the concept that atrial natriuretic factor (atriopeptin) is an important physiological regulator of renal sodium excretion, this hypothesis remains unproven. Indeed, a rapidly expanding collection of experimental data appears to be more compatible with the opposite conclusion, namely that circulating atriopeptin exerts only a trivial effect on renal sodium excretion during normal day-to-day living conditions. In this review, the substantial evidence demonstrating that elevations of plasma atriopeptin from threefold to 13-fold produce only a slowly developing and relatively modest natriuresis is reassessed in light of recently published data indicating that the acute intake of food (the pathway by which essentially all sodium enters the body under normal living conditions) does not increase circulating atriopeptin. These considerations imply that atriopeptin does not contribute to the process that elicits a postprandial natriuresis, a process that presumably is of primary importance in the physiological regulation of sodium balance. In addition, consideration is given to a number of common physiological, experimental, and pathophysiological conditions in which circulating atriopeptin does not correlate with renal sodium excretion. This lack of correlation implies that atriopeptin is not an important regulator of sodium excretion in these situations. (Hypertension 1990;15:9-19)

The widespread belief that atrial natriuretic factor (atriopeptin) plays an important role in the homeostatic regulation of renal sodium excretion appears to have developed largely because of three factors. The factors, not necessarily in order of importance, are: 1) extensive use of the term atrial natriuretic factor, a designation that implies that this hormone plays a primary role in the regulation of sodium excretion; 2) evidence demonstrating that infusion of this peptide into experimental animals and human subjects elicits a natriuresis; and 3) evidence demonstrating that certain stimuli cause both an increase in circulating atrial peptide and an increase in renal sodium excretion.

The evidence mentioned above is well documented in scores of papers. Indeed, it is doubtful that anyone would attempt to refute the abundant data indicating that elevations of plasma atriopeptin of severalfold are capable of inducing a natriuresis. In addition, it is well established that certain natriuretic stimuli (e.g., volume expansion or left atrial distension) evoke an elevation in circulating atriopeptin that may correlate temporally with the evoked rise in sodium excretion.

Although these lines of evidence are consistent with the hypothesis that atriopeptin is an important physiological regulator of body fluid homeostasis, they fall short of proving it.

This brief review will consider evidence that supports the opposite point of view, namely that atriopeptin exerts at best only a trivial influence on the regulation of renal sodium excretion under normal day-to-day living conditions. The scope will be limited to a relatively small number of selected topics. Two related reviews may be consulted for additional relevant information.1,2

Redundant Control of Sodium Excretion and Extracellular Volume

The renal excretion of sodium is regulated by redundant control systems (see References 3 and 4). It is difficult, therefore, to identify the specific contribution that any postulated natriuretic agent may make to the overall process. Although there is no consensus concerning the factors that do participate in the physiological regulation of sodium excretion, a number of factors are mentioned frequently. These include the renin-angiotensin-aldosterone system, renal nerve activity, plasma and interstitial oncotic pressures, renal perfusion pressure, one or more natriuretic hormones (regardless of their structure or source), and the renal prostaglandins.4
Hypertension Vol 15, No 1, January 1990

Control Normal Dog LA Stretch Recovery

Cardiac Denervated Dog Control LA Stretch Recovery

**FIGURE 1.** Left panel: Graphs showing effect of left atrial distension on urine flow (UV), sodium excretion ($U_{NaV}$), potassium excretion ($U_{KV}$), and plasma atriopeptin (PANF) in five normal conscious dogs. Right panel: Graphs showing effect of left atrial distension on same variables in four cardiac-denervated conscious dogs. Reprinted with permission from the American Journal of Physiology (1986;250:R946-R950).

Because sodium balance is an important determinant of extracellular fluid volume and because alterations in extracellular fluid volume are known to affect renal sodium excretion, the factors that regulate sodium excretion often are studied under conditions in which extracellular fluid volume is increased, often massively, by the intravenous infusion of fluids. However, from a physiological point of view, alterations in volume that occur in response to changes in dietary sodium intake should be measured; unfortunately this is often considered impractical because the volume changes are small and not easily detected. Accordingly, some of the mechanisms activated by the intravenous infusion of fluids may not be normally activated or important in the daily excretion of dietary sodium. The data reviewed here indicate that atriopeptin is a factor that normally is not activated by daily sodium intake and therefore would not seem to be important as a physiological regulator of sodium excretion.

**Atrial Distension and Natriuresis**

The contribution of endogenously released atrial peptide to the natriuretic response elicited by atrial distension was evaluated by our group several years ago. In those experiments, the mitral valve was partially occluded to increase left atrial pressure by about 8 mm Hg in conscious dogs. As shown in Figure 1 (left), the elevation in left atrial pressure elicited an increase in urine flow and sodium excretion as had been observed earlier. Circulating atriopeptin measured by radioimmunoassay increased about fourfold during this period of atrial distension. Although these results were consistent with the possibility that the rise in plasma atriopeptin caused the renal response, an additional experiment cast doubt on this interpretation. In that experiment, atrial distension was produced in dogs with chronically denervated hearts. As shown in Figure 1 (right), neither urine flow nor sodium excretion increased during the period of left atrial distension in the cardiac-denervated dogs; nevertheless, plasma atriopeptin increased during atrial distension to levels comparable with those obtained in the intact dogs. We concluded that atriopeptin was not responsible for the diuresis and natriuresis elicited during left atrial distension in the conscious dog. Rather, the renal responses appeared to be mediated by cardiac reflexes because they were absent after the heart had been denervated.

**Low Dose Atriopeptin Infusion**

Animal Experiments

The results from the atrial distension experiments prompted Bie and his colleagues to study the effects of infusing relatively small amounts of human atriopeptin-(99–126) into normal conscious dogs; this peptide is identical to the endogenous peptide of the dog. Hemodynamic responses elicited by infusion of atriopeptin in these experiments are illustrated in Figure 2. Infusion of atriopeptin at 12.5, 25, and 50 ng/kg/min increased the plasma concentration of the peptide by approximately threefold, sevenfold, and 12-fold, respectively. The most consistent hemodynamic response detected was a decrease in both right and left atrial pressure that achieved statistical significance at all three infusion rates. Aortic pressure declined slowly and progressively during each infu-
sion, but significant decreases occurred only after infusion of the two highest doses had ended.

The renal responses elicited by atriopeptin in these dogs are summarized in Figure 3. Atriopeptin produced a small gradual increase in sodium excretion at each dose level. The response, however, was relatively modest. Even the highest infusion rate, which elevated plasma atriopeptin by 12-fold (a change greater than that expected to occur under physiological conditions), produced only a doubling of urinary sodium excretion. These data, which are quite representative of results obtained from other experiments on conscious animals, demonstrated that concentrations of atriopeptin within or slightly above the normal range do not cause potent or rapidly developing natriuretic responses in experimental animals.

Human Experiments

Anderson and his colleagues11 infused human atriopeptin-(99–126) for 3 hours at 1.2 pmol/kg/min into healthy human subjects. The infusion caused a 5.5-fold increase in circulating atriopeptin. Urinary sodium excretion was unchanged during the first hour of infusion, was increased by 60% at the end of the 3-hour infusion period, but was unchanged by infusion of placebo. Plasma renin activity decreased during the atriopeptin infusion; this change may have contributed to the modest natriuretic response. No changes in plasma renin activity occurred during the infusion of the placebo. Cottier and his colleagues12 investigated the renal response caused by a step-up infusion of human atriopeptin in healthy male subjects. Infusion of atriopeptin at 4, 8, and 16 ng/kg/min during successive 30-minute intervals produced a progressive rise in plasma atriopeptin that peaked at a concentration 12.9-fold above the control level. Sodium excretion increased gradually during the infusion and achieved a value 42% higher than the control value at the end of the 90-minute infusion period. Similar data were obtained recently by Freestone et al.13 These investigators infused atriopeptin into human volunteers at 7.5 pmol/kg/min and increased circulating atriopeptin by approximately 13-fold. The infusion elicited an approximate doubling of sodium excretion at the end of a 1-hour infusion.

The increases in circulating atriopeptin in these three studies ranged from about 5.5- to 13-fold above control values. These elevated levels increased urinary sodium excretion from 1.42-fold to twofold above control rates. If it is assumed that the renal response to atriopeptin is linearly related to plasma concentration over this range, a reasonable assumption for changes in concentration within about one order of magnitude, it can be estimated that a doubling of plasma atriopeptin in these subjects would have caused peak increases in renal sodium excretion in the range of 3.5–13% above control excretion values. From these data, it is difficult to escape the conclusion that atriopeptin, in concentrations within and slightly above physiological levels, is neither rapidly acting nor particularly potent as a natriuretic agent in normal human subjects.

Richards and his colleagues14 compared the effects of a 2-hour infusion of atriopeptin-(99–126) (2 pmol/kg/min) into human subjects with the renal response
elicited by an intravenous administration of isotonic saline (15 ml/kg/hr) given over a 2-hour period. The infusion of atrial peptide increased plasma atriopeptin eightfold and caused approximately a 60% increase in sodium excretion. With the assumption of a linear response between plasma atriopeptin and sodium excretion as described above, it can be estimated that a doubling of plasma atriopeptin would have caused about an 8.6% increase in sodium excretion in these subjects. In contrast, the infusion of saline did not quite double circulating atriopeptin, but it produced a greater increase in sodium excretion than did the eightfold elevation in plasma atriopeptin produced by infusion of the peptide.

Richards and his colleagues also performed another investigation in which an extremely low dose of atrial peptide (0.75 pmol/kg/min) was infused during a 3-hour period. This rate of administration caused approximately a twofold elevation of atriopeptin in arterial blood and a 50% increase in venous blood. During the initial two 30-minute urine collection periods when atriopeptin was being administered, sodium excretion increased slightly. However, it then declined progressively and by the end of the infusion period was below the control value. A placebo infusion was given to the same subjects on another day, and the rate of sodium excretion during the placebo infusion was lower than it was during administration of atriopeptin. The authors concluded that atriopeptin at this dose was natriuretic even though urinary sodium excretion declined in response to the atriopeptin infusion. This conclusion was based on the differences in the rate of sodium excretion between placebo and atriopeptin infusions. This interpretation may be valid, but it is unusual to argue that a decline in sodium excretion over the last 2 hours of an infusion period indicates that the infused substance is a natriuretic agent. Nevertheless, plasma renin activity and plasma aldosterone decreased significantly during infusion of the atrial peptide. Consequently, it is possible that atriopeptin may have influenced sodium excretion indirectly in this study via its effect on the renin-angiotensin-aldosterone system. No changes in plasma renin activity or plasma aldosterone occurred during the placebo infusion.

**Alterations in Dietary Sodium**

Because a twofold increase in circulating atriopeptin caused by infusion of the peptide into normal human subjects produces only a relatively trivial natriuresis, it might be anticipated that plasma atriopeptin would change substantially in response to alterations in dietary sodium intake if this peptide were to contribute appreciably to sodium homeostasis. Information pertinent to this point has been obtained from experiments that examined the effects of marked changes in dietary sodium intake over the course of several days and from experiments that evaluated the acute effects of food intake on plasma atriopeptin.

A number of investigators reported that plasma atriopeptin increased in subjects after they were changed from a low to a high sodium diet; plasma
Goetz: Function of Atriopeptin

8 Figure 4. Left panel: Line graph showing dietary sodium intake (horizontal lines) and urinary sodium excretion (filled circles) in six male subjects during dietary intakes of 172, 20, and 285 meq sodium/day. Right panel: Line graph showing plasma atrial peptide levels measured during these experiments. Values were calculated as ratios of experimental to control values on each subject, and moving average of 3 consecutive days (mean±SEM) is plotted. Reprinted with permission from Japanese Journal of Physiology (1988;38:677-687).

Atriopeptin during the high sodium diet was from 1.4- to 3.5-fold higher than during the low sodium diet. Others, however, detected no difference after marked changes in daily sodium intake. For example, Weidmann and his colleagues reported that a change of sodium consumption from 10 to 310 meq/day caused no detectable changes in plasma atriopeptin in normal human subjects even though urinary sodium excretion necessarily increased approximately 30-fold after the subjects switched to the high sodium diet. The dissociation between plasma atriopeptin and renal sodium excretion in this type of experiment is illustrated graphically in the report of Shirataka et al. Normal human subjects began the study on a diet containing approximately 172 meq/day (Figure 4, left). They then changed to an intake of 20 meq/day for 7 days and then to 285 meq/day for an additional 7 days. Urinary sodium excretion followed sodium intake quite closely (Figure 4, left), but there was a 1-2-day lag before the subjects came into balance after each dietary change. Although the maximal difference in plasma atriopeptin between high and low sodium intakes was less than 20% (Figure 4, right), this difference did achieve statistical significance. Accordingly, the authors suggested that atriopeptin may be an important component in the regulation of body fluid during ingestion of a high sodium diet. However, the importance of atriopeptin in this situation could be questioned because the difference in its mean plasma concentration between the low and high sodium diets was less than 5 pg/ml. The evidence reviewed earlier indicates that such a small change in circulating atriopeptin would cause essentially no alteration in sodium excretion. Accordingly, an alternate conclusion would be that the marked changes in renal sodium excretion that occur in response to modifications in dietary intake are mediated independently of atriopeptin.

Data obtained from experiments that use long-term alterations in sodium intake, however, are insufficient to establish that a peptide with a short half-life exerts little or no influence on the excretion of dietary sodium. The measurement of plasma atriopeptin only once each day would be unlikely to detect changes in this hormone that might occur transiently after sodium ingestion. Saville and his coworkers attempted to detect postprandial changes by measuring circulating atriopeptin before and after normal human subjects ate a high sodium breakfast containing 100 mmol sodium chloride. On a separate morning several weeks later, the subjects ate a low sodium breakfast that contained the same number of calories but only 4 mmol sodium chloride. Fluid intake with
each meal was identical. As illustrated in Figure 5, the high salt meal elicited an increase in sodium excretion and a decrease in urine flow, whereas the low salt meal elicited a diuresis but no increase in sodium excretion. Osmolar clearance increased after the high salt meal and decreased after the low salt meal. The key observation, however, was that plasma atriopeptin did not increase after either meal. Saville and his colleagues concluded that atriopeptin was not responsible for the natriuresis induced by the high salt meal or for the diuresis induced by the low salt meal.

Other evidence consistent with the above data has been published. Solomon and colleagues reported that circulating atrial peptide actually declined after a high protein meal and remained unchanged after a low protein meal although each produced a transient increase in sodium excretion. Consequently, the authors concluded that it was unlikely that atriopeptin was responsible for the natriuresis elicited by either high or low protein meals. On the other hand, Rodriguez-Iturbe et al. reported that plasma atriopeptin increased after a high protein meal, but not after a carbohydrate meal even though both meals contained the same amount of salt. These investigators did not believe, however, that atriopeptin played a major role in mediating the postprandial natriuresis. There is no apparent explanation for the differences between the results of Solomon et al and Rodriguez-Iturbe et al.

Most other evidence corroborates the data indicating that the intake of food does not affect circulating atriopeptin acutely. For example, in an investigation designed to detect diurnal variations of circulating atriopeptin in human subjects, Weil and his colleagues studied nine healthy volunteers throughout a 24-hour period. Meals were taken at 8:00 AM, 12:30 PM, and 7:30 PM, and the data presented provide no indication that circulating atriopeptin was influenced by the meals (see Figure 1 in Reference 24). Similarly, Richards et al studied normal volunteers who ate meals at 10:00 AM, 1:00 PM, and 7:00 PM. No effect of food intake on plasma atriopeptin was discernible (Figure 6). This study is also noteworthy because the pattern of sodium excretion throughout the day showed no correlation with plasma atriopeptin, but there was an obvious inverse relation between plasma renin activity and urine sodium (Figure 6). Circulating angiotensin II and aldosterone showed similar patterns. These data appear to implicate the renin-angiotensin-aldosterone system, not atriopeptin, in the daily regulation of sodium excretion.

At least two groups who investigated diurnal changes in humans took plasma samples at 4:00 AM and detected an increase in atriopeptin at this time. The increase reported by Winters et al was dramatic and occurred both in subjects who worked throughout the night and in others who slept from midnight to 8:00 AM. The peak in plasma atriopeptin that occurred at 4:00 AM presumably does not affect renal sodium excretion, because normal human subjects are in an antinatriuretic state at this time.28

**Correlations and Cause and Effect**

A considerable amount of evidence compatible with the notion that atrial peptides are important regulators of fluid balance has been derived from experiments in which changes in plasma atriopeptin were correlated with changes in sodium excretion. Such correlations are suggestive, but they do not establish a cause-and-effect relation between circulating atriopeptin and the attendant sodium excretion. On the other hand, when two variables do not correlate with each other, the absence of correlation

**Table 1. Examples of Physiological Conditions in Which Plasma Atriopeptin Does Not Correlate With Urinary Sodium Excretion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Correlation with Sodium Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postprandial natriuresis</td>
<td>No increase in plasma atriopeptin occurs postprandially in human subjects, but a natriuresis routinely occurs.</td>
</tr>
<tr>
<td>Diurnal rhythm</td>
<td>Plasma atriopeptin was highest at 4:00 AM in two studies that sampled blood from human subjects at this time. However, urine flow and sodium excretion are decreased during nighttime hours.</td>
</tr>
<tr>
<td>Intense exercise</td>
<td>Plasma atriopeptin levels increase during strenuous exercise, but sodium excretion decreases during such exercise.</td>
</tr>
<tr>
<td>Newborn infants</td>
<td>High levels of plasma atriopeptin in first few days of life do not correlate with sodium excretion.</td>
</tr>
</tbody>
</table>
The infusion of atriopeptin then was stopped, and we devised a method to lower the circulating plasma atriopeptin is necessary to cause the natriuretic response does not necessarily correlate with plasma atriopeptin levels.35,36

A substantial increase in circulating atriopeptin for several days produces no changes or trivial increases in urinary sodium excretion.33,38

Marked increase in sodium excretion after release of caval constriction correlates poorly with plasma atriopeptin.39

isotonic saline (24 ml/kg) was given intravenously over a 5-minute period. Plasma atriopeptin declined during the infusion, but a marked diuresis and natriuresis developed at this time (Figure 7, left panel). In other words, the natriuretic stimulus of the saline infusion greatly overshadowed any antinatriuretic effect of the concomitant decline in plasma atriopeptin. Results from the control experiment in which saline was not administered are shown in Figure 7 (right panel). This study and others that have demonstrated an absence of correlation between plasma atriopeptin and urinary sodium excretion are listed in Table 2.

The elevated level of plasma atriopeptin that is associated with sodium retention in congestive heart failure40-41 is well known. However, the inability of the kidneys to excrete appropriate amounts of fluid and electrolytes in congestive heart failure is not necessarily attributable to an abnormal response to atriopeptin by the kidneys.42 As pointed out above, a dissociation between plasma atriopeptin and renal sodium excretion occurs commonly. Several examples in which a dissociation between plasma atriopeptin

may be taken as evidence for the lack of a cause-and-effect relation in these situations.

Table 1 contains a number of examples in which plasma atriopeptin levels do not correlate with renal sodium excretion under normal physiological conditions. The lack of correlation between these two variables during postprandial natriuresis and during diurnal variations in sodium excretion has been discussed earlier. Intense exercise, another common physiological occurrence, is accompanied by an increase in circulating atriopeptin and a decrease in sodium excretion. The lack of correlation between plasma atriopeptin and renal sodium excretion during these common conditions of daily living provides compelling evidence that atriopeptin is not a physiological regulator of renal sodium excretion. Newborns also demonstrate a lack of correlation between plasma atriopeptin and sodium excretion (Table 1).

Many experimental maneuvers are capable of increasing both plasma atriopeptin and renal sodium excretion. For example, the intravenous infusion of saline is a highly effective natriuretic stimulus that usually is accompanied by an elevation of plasma atriopeptin. To test the hypothesis that the rise in plasma atriopeptin is necessary to cause the natriuresis, we devised a method to lower the circulating concentration of atriopeptin during the infusion of saline.35 This was achieved by infusion of atriopeptin-(99-126) into conscious dogs at 50 ng/kg/min during the control period before saline was administered. The infusion of atriopeptin then was stopped, and

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**FIGURE 7.** Line graphs showing effect of saline infusion (24 ml/kg) on renal function during period when concentration of atriopeptin was declining (left panel). Results from control experiment without saline infusion is illustrated in right panel. Black horizontal bar represents period of atriopeptin infusion. Short bar illustrates time of saline infusion. See text for details. Reprinted with permission from American Journal of Physiology (1988;255:R259–R267).

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**TABLE 1. Examples of Experimental Conditions in Which Plasma Atriopeptin Does Not Correlate With Urinary Sodium Excretion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect of Atriopeptin and Sodium Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute saline infusion</td>
<td>Natriuretic response does not necessarily correlate with plasma atriopeptin levels.35,36</td>
</tr>
<tr>
<td>Chronic atriopeptin infusion</td>
<td>A substantial increase in circulating atriopeptin for several days produces no changes or trivial increases in urinary sodium excretion.33,38</td>
</tr>
<tr>
<td>Thoracic inferior vena caval constriction</td>
<td>Marked increase in sodium excretion after release of caval constriction correlates poorly with plasma atriopeptin.39</td>
</tr>
</tbody>
</table>

**TABLE 2. Examples of Pathophysiological Conditions in Which Plasma Atriopeptin Does Not Correlate With Urinary Sodium Excretion**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Effect of Atriopeptin and Sodium Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>Plasma atriopeptin is elevated, yet sodium is retained in excess in patients with CHF.40,41</td>
</tr>
<tr>
<td>Paroxysmal tachycardia</td>
<td>A consistent increase in plasma atriopeptin occurs during an attack of paroxysmal tachycardia, but inconsistent increases in urinary sodium excretion have been reported.43,44</td>
</tr>
<tr>
<td>Acute mountain sickness</td>
<td>An increase in plasma atriopeptin and a concomitant decrease in sodium excretion have been reported in healthy male mountaineers in whom severe AMS developed after ascending from 550 m to 4,559 m over 2 days.45</td>
</tr>
<tr>
<td>Korean hemorrhagic fever</td>
<td>Acute disease is characterized by fever, hemorrhage of right atrium, increased plasma atriopeptin, and decreased urinary sodium excretion.46</td>
</tr>
</tbody>
</table>

CHF, coronary heart failure; AMS, acute mountain sickness.
### TABLE 4. Anatomic Locations Where Biological Responses or Binding Sites to Atriopeptin Have Been Detected

<table>
<thead>
<tr>
<th>Location</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal glands</td>
<td>47, 48</td>
</tr>
<tr>
<td>Zona glomerulosa</td>
<td>49, 50</td>
</tr>
<tr>
<td>Medulla</td>
<td>51, 52</td>
</tr>
<tr>
<td>Aorta</td>
<td>53</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>54, 55</td>
</tr>
<tr>
<td>Brain</td>
<td>56</td>
</tr>
<tr>
<td>Brown adipose tissue</td>
<td>57, 58</td>
</tr>
<tr>
<td>Circumventricular organs</td>
<td>59, 60</td>
</tr>
<tr>
<td>Eye</td>
<td>61, 62</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>63, 64</td>
</tr>
<tr>
<td>Ganglion cells</td>
<td>65, 66</td>
</tr>
<tr>
<td>Hypothalamus</td>
<td>67, 68</td>
</tr>
<tr>
<td>Juxtaglomerular cells</td>
<td>69</td>
</tr>
<tr>
<td>Kidneys</td>
<td>70</td>
</tr>
<tr>
<td>Mesangial cells</td>
<td>71, 72</td>
</tr>
<tr>
<td>Pancreas</td>
<td>73, 74</td>
</tr>
<tr>
<td>Platelets</td>
<td>75–77</td>
</tr>
<tr>
<td>Pulmonary vessels</td>
<td>78, 79</td>
</tr>
<tr>
<td>Spleen</td>
<td>80, 81</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>82, 83</td>
</tr>
<tr>
<td>Sympathetic system</td>
<td>84</td>
</tr>
<tr>
<td>Testes</td>
<td>85</td>
</tr>
<tr>
<td>Thymus</td>
<td>86, 87</td>
</tr>
</tbody>
</table>

This list is to be considered as representative, not exhaustive.

and renal sodium occurs during pathophysiological conditions are listed in Table 3.

### Multiple Effects of Atriopeptin

Although atriopeptin may not contribute appreciably to the regulation of renal sodium excretion, it should not necessarily be concluded that this peptide does not have important biological effects. Table 4 lists a number of sites where biological effects of the atrial peptides may occur. For example, atriopeptin is capable of affecting the cardiovascular system in several key areas. It causes aortic relaxation at low concentrations and might therefore influence aortic compliance under physiological conditions. In addition, changes in the precapillary-to-postcapillary resistance ratio elicited by atriopeptin appear to influence the distribution of fluid between the intravascular and extravascular sites. This probably is the mechanism by which an increase in circulating atriopeptin lowers cardiac filling pressure. We have speculated that atriopeptin released by atrial stretch may serve as part of a negative feedback system that enables the heart to influence its own filling pressure. Atriopeptin also appears to be an effective hypotensive agent, perhaps through its ability to antagonize effects of the renin-angiotensin-aldosterone system or perhaps via its actions on the central nervous system or on the sympathetic nervous system.

It is highly improbable that all of the sites listed in Table 1 are affected by atriopeptin under normal conditions. It is well known that hormonal concentrations that are above physiological levels may affect the function of organs other than those classically assumed to be their target tissues (see References 92 and 93). The problem for the investigator is to deal with the redundancy of experimental information and to determine which responses are of physiological significance.

### Plasma Atriopeptin During Hemodynamic Alterations

Acute changes in plasma atriopeptin occur in response to transient changes in atrial filling pressures. Consequently, it is not surprising that changes in systemic hemodynamics have been demonstrated to alter circulating atriopeptin levels. For example, an abrupt increase in arterial blood pressure, such as that induced by intense exercise or by the infusion of vasoconstrictor agents, is accompanied by acute increases in plasma atriopeptin that correlate with the changes in atrial pressures. Spontaneous changes in arterial blood pressure also are accompanied by changes in plasma atriopeptin. An interesting example of this was described in a patient with Landry-Gullain-Barré syndrome and autonomic dysfunction. The patient had a labile blood pressure; plasma atrial peptide also was labile and tended to correlate quite well with the changes in arterial blood pressure (Figure 8). Plasma samples were obtained 5 minutes after each blood pressure measurement. Because the acute hemodynamic changes, not changes in body fluid balance, appeared to cause the fluctuations in plasma atriopeptin, it may be argued that any adjustments induced by changes in circulating atrial peptide appropriately might be directed toward the cardiovascular system, not toward the kidneys. The conjecture here is that the physio-
logical importance of atriopeptin lies in its ability to modulate cardiovascular performance.

In conclusion, despite intense research efforts and thousands of published reports, it is not yet possible to describe clearly the physiological relevance of the atrial peptides. Although a large volume of data in the literature is consistent with the view that atriopeptin serves primarily as a natriuretic hormone involved in the regulation of body fluid homeostasis, considerable data to the contrary also are available. The divergent data and opinions have provided fuel for this debate. The goal here has been to gather some of those data and to focus on three lines of evidence that imply that atriopeptin does not serve as a physiological regulator of sodium excretion.

Infusions of the peptide into conscious animals and normal human subjects that resulted in plasma concentrations of atriopeptin within and slightly above the physiological range have produced only a slowly developing and relatively modest natriuresis. Estimates indicate that a doubling of circulating atriopeptin in these subjects would have increased sodium excretion by less than 10%, a rather trivial response. This information takes on added significance when it is taken into account that most relevant evidence indicates that the ingestion of food (the route by which virtually all sodium enters the body under ordinary living conditions) does not increase circulating atriopeptin. Nevertheless, a natriuresis routinely occurs postprandially. In other words, physiological regulation of sodium excretion occurs postprandially without any evidence for a contribution from atriopeptin. Finally, the many situations in which circulating atriopeptin has been found to correlate with renal sodium excretion suggest, but do not establish, a cause-and-effect relation. On the other hand, there are numerous situations, several intimately related to daily living conditions, in which such a correlation does not exist. The lack of correlation in these situations provides evidence against a cause-and-effect relation between atriopeptin and renal sodium excretion.

Acknowledgments

It is a pleasure to acknowledge the contributions of my colleagues Dr. Peter Bie, Pamela Geer, Robert Leadley Jr., Dr. Jeffrey Madwed, Mark Saville, Dr. Bin Wang, and Professor Jia Long Zhu and the technical contributions of Gloria Flora-Ginter and Barbara Roberts to the work performed in our laboratory. Ramona Bailey provided excellent secretarial support.

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KEY WORDS • atrial natriuretic factor • fluid volume • natriuresis • sodium excretion
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Hypertension. 1990;15:9-19
doi: 10.1161/01.HYP.15.1.9

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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