invited review

Physiology and pathophysiology of atrial peptides

GOETZ, KENNETH L. *Physiology and pathophysiology of atrial peptides.* Am. J. Physiol. 254 (Endocrinol. Metab. 17): E1–E15, 1988.—The atria secrete atrial peptides (atriopeptins) that are capable of producing dramatic alterations in a number of body processes. Secretion of atriopeptin appears to be regulated primarily by the prevailing pressure within the atria. In pharmacological doses, atriopeptin rapidly elicits a natriuresis when administered to experimental animals or humans. In contrast, infusion rates that increase plasma atriopeptin only by about three- to fivefold tend to produce a slowly developing and modest diuresis. Evidence examined in this review suggests that the atrial peptides are not potent natriuretic substances under normal physiological conditions, although it is likely that they exert a modulating influence on sodium excretion. The atrial peptides are vasoactive and induce a number of cardiovascular changes including decreases in arterial blood pressure, cardiac filling pressure, and cardiac output and a translocation of fluid from plasma to the interstitial fluid space. They also interact with other hormones, particularly the renin-angiotensin-aldosterone system. Finally, atriopeptin is distributed throughout many regions of the brain where it may serve as a neuromodulator or neurotransmitter. Atriopeptin circulating in the bloodstream also may influence cerebral mechanisms by acting on receptors in the circumventricular organs. A more complete understanding of the diverse effects of this cardiac endocrine system is expected to provide further insight into a spectrum of physiological and pathophysiological processes.

atriopeptin; blood volume; aldosterone; vasopressin; sodium balance; blood pressure; vascular reactivity; cardiac output; hypothalamus

OVER THE PAST SEVERAL YEARS a unique hormonal system has been discovered and delineated in considerable detail. The endocrine gland that secretes the peptide hormone is the heart, primarily the cardiac atria, but cells in the cardiac ventricles as well as the brain and other sites also are capable of synthesizing the peptide.

Although evidence compatible with the existence of a cardiac hormone had been accumulating slowly for over 30 years, the recent explosion of work in this field can be traced directly to the classic experiments of de Bold, Borenstein, Veress, and Sonnenberg (37). These investigators reported in 1981 that an intravenous injection of extracts of rat atria given to anesthetized rats caused a marked increase in the renal excretion of sodium and chloride and a substantial increase in urine flow. The dramatic renal response to atrial extracts was accompanied by a decrease in arterial blood pressure and an increase in hematocrit, changes that de Bold and his colleagues surmised might be secondary to the associated urinary fluid loss. It is now clear, however, that the atrial peptides can decrease blood pressure and increase hematocrit in the absence of any urinary fluid losses (193). In contrast to the remarkable effects of atrial extracts, ventricular extracts caused essentially no change in any of the measured variables (37). Focusing on the powerful natriuretic effect of the atrial extract, de Bold and his colleagues referred to the unknown substance as atrial natriuretic factor.

Intense efforts by several groups of investigators, utilizing modern biochemical techniques, resulted in the extraction, purification, and complete chemical identification of the atrial factor (52) within three years of the initial report of de Bold and his colleagues. The circulating form in the human is a 28 amino acid peptide (109) with a cysteine-cysteine disulfide cross-link forming a 17-residue ring (Fig. 1). The circulating form of the peptide in the dog appears to be identical to that in the human (150), whereas the peptide in rodents differs slightly; isoleucine rather than methionine is present at position 12 (52).

Following the pattern established by de Bold et al. (37) many investigators refer to the cardiac hormone as atrial natriuretic factor or atrial natriuretic peptide. Another term that carries the same connotation, cardionatrin (52), has been suggested for the circulating form of atrial peptide in the rat. Other investigators have coined terms that do not imply a specific physiological role for the hormone. These include auriculin (130) and perhaps the

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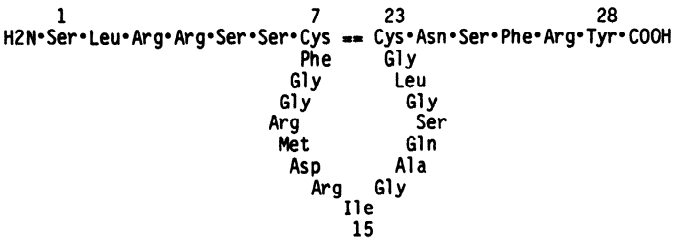

FIG. 1. Amino acid sequence of circulating form of human atrial peptide.

most widely used, atriopeptin (33). These latter terms have merit because the atrial peptides are capable of causing a broad spectrum of responses throughout the body. Moreover, it is not yet unequivocally established that the atrial peptides exert an important influence on sodium excretion under normal physiological conditions. Accordingly, in this review the atrial hormone will be referred to as atriopeptin or atrial peptide to avoid the implication that the atrial hormone is solely or primarily a natriuretic hormone. Furthermore, because close attention will not be given either to dose-response relationships or structure-activity relationships in the studies to be described, the specific chemical identity of the various analogues of atriopeptin used in each study will not be identified. Although the analogues used have differed somewhat in amino acid chain length, nearly all have contained the 17-residue ring and the sequence, Phe-Arg-Tyr, at the carboxyterminus; such compounds exhibit appreciable vasoactive and natriuretic activity (112).

Scope of Review

The large volume of literature pertaining to the atrial peptides precludes a definitive review in the limited space available. Accordingly, after a brief section sketching the historical events leading to the discovery of the cardiac hormone, five areas will be considered in greater detail. These include *1*) factors affecting atriopeptin secretion, *2*) effects of atriopeptin on renal function, *3*) effects on the cardiovascular system, *4*) effects on other hormones, and *5*) effects on the central nervous system. The focus will be on selected studies that may provide clues for identifying specific physiological and pathophysiological roles for the atrial peptides. Unfortunately, many excellent studies directly pertinent to these areas could not be cited because of space limitations. Also excluded from this review is a description of the tremendous achievements of biochemists and molecular biologists who have identified the 126 amino acid prohormone that is stored in the atrial granules, sequenced and cloned the entire atrial peptide gene, and identified atrial peptide messenger RNA in large quantities in the atria and in smaller quantities in the brain and other sites. Reviews covering a variety of aspects of the atrial peptides may be consulted for further information (11, 13, 21, 52, 67, 96, 127, 139, 140).

Background

Atrial neural reflexes. An association between the cardiac atria and renal function was suggested over 30 years ago when Henry, Gauer, and Reeves (86) discovered that distension of the left atrium of anesthetized dogs usually produced an increase in urine flow. The renal response to atrial distension could not be elicited after neural traffic in the cervical vagi had been blocked. Accordingly, Henry and his colleagues concluded that stretch receptors in the left atrium served as part of a reflex mechanism that linked changes in blood volume with homeostatic responses of the kidney. They postulated that atrial distension caused a reflex inhibition of the secretion of antidiuretic hormone and thereby evoked a water diuresis. They did not suggest, however, that the atria might influence the excretion of sodium. Their report generated a modest but steady stream of investigative work, much of it consistent with the original hypothesis of the authors as illustrated by a number of comprehensive reviews (e.g., Ref. 64). There were, however, inconsistencies that also have been reviewed in detail (e.g., Ref. 72). By the mid 1970s "volume control" by atrial reflexes was considered to be mediated primarily by regulation of water excretion through reflex changes in circulating antidiuretic hormone. Although effects of atrial stretch on the excretion of sodium had been noted occasionally (e.g., Ref. 129), these observations generated little interest until Reinhardt and his colleagues (156) demonstrated that distension of the left atrium in conscious dogs consistently evoked a natriuresis. In contrast, most of the data available indicate that distension of the right atrium of the dog does not produce a natriuretic response (12, 86, 174, 188), but Kappagoda (110) did report that a small increase (16%) in renal sodium excretion occurred in response to distension of the right atrial appendage in anesthetized dogs. Comparable studies are not available for other species, but data to be discussed subsequently suggest that the right atrium of the rat may play an appreciable role in regulating renal function in that species. Left atrial distension in conscious dogs with chronically denervated hearts does not elicit increases in urine flow or sodium excretion (49, 108), thus implying that these responses depended on neural reflexes originating within the heart. These cardiac reflexes may augment renal sodium excretion either by a reduction in renal sympathetic neural activity (41) or by an inhibition of the renin-angiotensin system (157).

Third factor or natriuretic hormone. In 1961 de Wardener and his colleagues (40) demonstrated that infusion of saline produced an increase in urine flow and sodium excretion in anesthetized dogs even in the presence of high circulating levels of aldosterone and vasopressin and a reduced glomerular filtration rate. These experiments gave rise to the popular concept that an unidentified "third factor" affected sodium excretion. The search for this third factor soon focused on a possible hormonal mediator that came to be known as natriuretic hormone. Although this mediator (or mediators) remains chemically unidentified at this time, there is considerable evidence that at least one hormone (or class of hormones) acts by inhibiting sodium-potassium ATPase. Thus it clearly is different from the atrial peptides that do not inhibit ATPase. The anatomic source of the natriuretic hormone or hormones that act on sodium-potassium

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ATPase has not been identified. Recent reviews dealing largely with this natriuretic hormone are available (39, 82).

Atrial specific granules and atrial peptides. Shortly before Henry and his colleagues (86) reported their observations regarding left atrial distension, Kisch (116), utilizing electron microscopy, described dense granules that were located in the atria but not the ventricles of mammals. These granules subsequently were described in detail by Jamieson and Palade (102). Surprisingly, these early reports generated relatively little interest in the atrial granules, even though their morphology clearly suggested a secretory function (102). Moreover, the work of Henry and Gauer (86) concerning the effects of atrial distension on the kidney was well known.

In the 1970s changes in salt and water balance were found to cause changes in the morphology of the atrial granules (e.g., Ref. 36), thus raising the possibility that the granules were involved in the regulation of salt and water balance. Shortly afterward de Bold and his colleagues discovered the remarkable natriuretic and hypotensive effects of atrial extracts and naturally suspected that the active factor was derived from the atrial granules (37).

The work of de Bold and his colleagues created tremendous interest and touched off intense research activity in this area. The active substance soon was shown to be a peptide that originated in the atrial granules. Identification of the complete amino acid sequence of the hormone (53, 109) led rapidly to the synthesis of the peptide (178), thus paving the way for the development of radioimmunoassays for atriopeptin (79). Radioimmunoassays were used to detect atrial peptides in plasma and establish that they are circulating substances (190).

The availability of synthetic atrial peptides for administration to experimental animals and human subjects, along with radioimmunoassays capable of detecting changes in the concentration of atrial peptides in blood and other tissues, provided the requisite tools to investigate the physiological and pharmacological effects of the atriopeptins. Most of the early work was performed with extremely large doses of the hormone, which produced massive increases in plasma concentration and thereby led to distorted conclusions concerning the potency and possible biological roles of the atriopeptins. Recent studies employing far smaller amounts of the peptide have had a tendency to modify earlier concepts, but the results continue to suggest that atriopeptin can elicit a broad range of biological effects.

Factors Regulating Secretion of Atrial Peptides

The concentration of atriopeptin in the plasma of normal individuals appears to vary relatively little under most physiological conditions. Radioimmunoassay values in a population of normal standing or sitting human subjects may range from 3 to 25 pmol/l in various laboratories that assay plasma after it has been extracted to minimize interference from other plasma components. Atriopeptin has a molecular weight of ~3,000; thus the above values are equivalent to 9 to 75 pg/ml. In our laboratory, samples of venous blood drawn from laboratory personnel average ~30 pg/ml or if corrected for extraction losses, 45 pg/ml. Plasma values reported for laboratory animals tend to be somewhat higher, most normal values reported are under 100 pg/ml but some may reach as high as 150 pg/ml. This difference is explained in part by the fact that blood samples from animals are often obtained from an arterial source, whereas samples from normal human subjects are usually obtained from a venous source. Venous blood may contain up to a 50% lower concentration of atriopeptin than arterial blood (175), and the concentration of atriopeptin in samples obtained from a forearm vein showed considerable variation when compared with values from samples obtained simultaneously from a femoral artery (175). It was suggested that local factors such as the rate of cutaneous blood flow and skin temperature may influence this extraction ratio. Although age generally has relatively little effect on the concentration of circulating atriopeptin, newborn infants have appreciably elevated plasma levels during the first few days of life (e.g., Ref. 182).

A number of factors reportedly affect the secretion of atriopeptin into the bloodstream, but only one, atrial distension, has been established with certainty. The effect of atrial distension was demonstrated in vitro first by bioassay measurements of natriuretic activity in samples of perfusate obtained from a rat heart-lung preparation before and after the atria were distended (42) and later by radioimmunoassay of the fluid perfusing an isolated rat heart in a modified Langendorff preparation (124). Subsequently, distension of isolated atria was shown to elicit an increase in the release of atrial peptides (18, 173).

Left atrial distension in anesthetized dogs (128) and distension of either the right or the left atrium in conscious dogs (73, 132) causes an increase in circulating atriopeptin. For each 1-mmHg increase in atrial pressure (either right or left), plasma atriopeptin increases acutely by ~10–15 pmol/l (73). This effect is not dependent on cardiac nerves because distension of the left atrium in conscious dogs with chronic cardiac denervation elicits an increase in plasma atriopeptin that does not differ from the response obtained in normal dogs with intact cardiac nerves (73).

The above observations have been supplemented by numerous reports indicating that intravascular volume expansion in experimental animals (124) or human subjects (149, 205) increases the concentration of atrial peptide in plasma; presumably the elevation of right and left atrial pressures during the infusion stimulates atriopeptin secretion. The rise in plasma atriopeptin under these conditions, however, may be relatively small. For example, administration of two liters of saline intravenously to supine human subjects over 2 h increased mean plasma atriopeptin levels only by ~30% (212). Maneuvers that do not increase the volume of circulating blood, but rather simply redistribute a quantity of blood to the thorax, also elevate plasma atrial peptide levels. For example, immersion of seated human subjects in water to neck level increases the volume of blood within the

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chest and also elevates plasma atrial peptide levels approximately twofold (6, 47, 147). A change from standing to the supine position also slightly increases plasma atriopeptin (91, 146, 184).

A unique method of demonstrating that distension of the human atria enhances the secretion of atrial peptides was reported by Schwab and his colleagues (176). These investigators studied two patients with implanted Jarvik-7 artificial hearts; these patients depend entirely on the artificial heart for their cardiac output, but a major portion of the native atrial tissue remains in place after implantation of the mechanical heart. The atrial tissue was distended in each of these two patients by reducing the rate of the artificial heart. As right atrial pressure increased in response to the reduced cardiac output, a corresponding increase in the circulating concentration of atrial peptide occurred.

Acute physical exercise stimulates the secretion of atriopeptin in direct proportion to the intensity of exercise (189). The increase in circulating atriopeptin correlates with an increase in pulmonary wedge pressure during exercise on a bicycle ergometer in supine subjects (143); this finding suggests that the presumed increase in secretion of the peptide during exercise is attributable to atrial distension. The increase in heart rate during exercise also may increase the secretion of atriopeptin because isolated atrial tissue increases its rate of hormone release as the rate of repetitive stretch is increased (18) or as electrical pacing of the tissue is accelerated (172).

One might predict, on the basis of the above data, that pathophysiological conditions that produce an expanded blood volume would be accompanied by elevations in plasma atriopeptin. Indeed abnormally high levels of circulating atriopeptin have been found in patients with the syndrome of inappropriate secretion of antidiuretic hormone (29, 164), primary aldosteronism (195, 210), congestive heart failure (24, 154), and chronic renal failure (144, 155). Furthermore, abnormally high plasma atriopeptin levels decline in patients as their congestive heart failure is treated (111) and as the excess fluid accumulated during renal failure is removed by hemodialysis (7, 194, 211). Patients with paroxysmal atrial tachycardia often develop an increase in atrial pressure during the tachycardia as well as an increase in plasma atriopeptin (119, 141, 142). Similarly, the increase in cardiac filling pressure that occurs after the injection of a contrast agent into the left ventricle of human subjects is accompanied by an increase in circulating atriopeptin (153, 170). This response occurs within less than a minute and appears to be caused by an increase in cardiac filling pressure induced by the negative inotropic effect of the contrast agent rather than by a direct effect of the agent itself (153).

An intriguing exception to the general observation that circulating atriopeptin levels vary directly with changes in blood volume has been noted in patients with Bartter's syndrome, a condition characterized by inappropriate renal salt loss, hypokalemic and hypochloremic alkalosis, high plasma renin and aldosterone levels, and a reduced blood volume; patients with Bartter's syndrome have elevated concentrations of atriopeptin in their plasma (169, 195, 209). Although this finding is compatible with the possibility that the primary cause of Bartter's syndrome is an excessive production and secretion of atriopeptin, it would be premature to draw this conclusion on the basis of data now available.

Results from several investigations indicate that deficits in body fluids induce decreases in plasma atrial peptide levels. A progressive reduction of body fluids accomplished by 3 days of water restriction decreased circulating atriopeptin to below detectable levels in Sprague-Dawley rats (106). In similar experiments, 5 days of water restriction also caused plasma atriopeptin to decrease substantially; there was a concomitant reduction in the relative levels of atriopeptin mRNA, but the amount of peptide stored in the atria increased, implying that a decrease in the secretion of atriopeptin had occurred (216). Mechanical ventilation with positive end-expiratory pressure, a procedure that reduces atrial transmural pressure as well as altering a number of other cardiovascular variables (72), has been reported to reduce the concentration of atriopeptin in the plasma of patients with acute respiratory failure and healthy human volunteers (152). Presumably the decrease in atrial transmural pressure reduced atriopeptin secretion in these experiments.

A number of studies suggest that factors other than atrial stretch have the capability to affect the secretion of atriopeptin. Exposure of isolated rat atria or isolated rat hearts to a variety of agents including α_1-adrenergic agonists (34, 185) and vasopressin (185) elicits an increase in the rate of atriopeptin secretion. Because these agonists activate the phosphoinositol system, it was suggested that inositol triphosphate is the second messenger of stimulus-secretion coupling in atrial cells (185). This second messenger system provides a mechanism for mobilization of calcium and also activates protein kinase C. Data consistent with the concept that this system is involved in atriopeptin secretion comes from other experiments indicating that calcium activation by an ionophore and protein kinase C activation by a phorbol ester increase the release rate of atrial peptides from isolated rat hearts (160). The precise role of the phosphoinositol system in modulating atriopeptin secretion by receptor-mediated (34, 185) or stretch-mediated (160) stimuli remains to be elucidated. One should keep in mind, however, that the effects on atriopeptin secretion by agents such as vasopressin may be mediated by other mechanisms under in vivo conditions. For example, pharmacological doses of vasopressin increase right atrial pressure in anesthetized rats, and the time course of the associated release of atriopeptin parallels the change in right atrial pressure (140). Thus increases in atrial pressure apparently stimulate atriopeptin secretion under these conditions.

Renal Effects of Atrial Peptides

The atrial peptides may influence renal function in several different ways. They have been shown to increase glomerular filtration rate (e.g., Ref. 130). The increase in filtration may be caused by an increase in the glomer-

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ular capillary ultrafiltration coefficient (55) and by a reduction in afferent arteriolar resistance and an increase in efferent arteriolar resistance (214). It should be noted, however, that atriopeptin apparently has no effect on isolated afferent or efferent renal arterioles of the rabbit (45). Although atriopeptins reduce renal arteriolar resistance in preconstricted isolated kidneys (26) and increase renal blood flow acutely in response to bolus doses in conscious dogs (88), a constant infusion of atriopeptin often decreases renal blood flow in conscious animals (74, 126). This decrease in flow apparently is caused by a reflex increase in renal sympathetic nerve activity (126); thus effects of the atrial peptides on renal blood flow are complex. The atrial peptides can affect sodium transport in the medullary collecting duct (214). There is little evidence to suggest that atriopeptin affects sodium transport in the proximal tubule; however, a recent report indicates that even though atriopeptin has no direct effect on proximal sodium and water reabsorption under basal conditions, it does markedly inhibit the stimulatory effects of angiotensin II on fluid reabsorption in the proximal tubule (83). Atriopeptin also may directly affect renal water excretion by inhibiting vasopressin-stimulated water reabsorption from the renal collecting ducts (43). A review of the actions of the atrial peptides on the kidney provides an up-to-date summary of this field (214). In the remainder of this section, the emphasis will be on the effects of atriopeptin on renal sodium excretion rather than on specific renal mechanisms.

By grouping the results of various experiments arbitrarily according to whether high (>500 $ng \cdot kg^{-1} \cdot min^{-1}$), intermediate (50–500 $ng \cdot kg^{-1} \cdot min^{-1}$), or low (<50 $ng \cdot kg^{-1} \cdot min^{-1}$) amounts of synthetic peptides were administered intravenously, it is evident that high infusion rates produce extremely high plasma levels of the hormone and rapidly elicit a sizable natriuresis (30, 44, 180). Intermediate doses usually evoke a similar renal response in experimental animals (107, 180, 186) and human subjects (19, 28, 192, 203, 204). When infusions near the low end of the intermediate range are given, the natriuretic response is not particularly brisk. For example when plasma atriopeptin is increased to roughly 10–25 times above basal levels in humans by intravenous infusion, sodium excretion increases only by about threefold (4, 32, 203). When low amounts of atrial peptide are infused intravenously to produce plasma concentrations in the physiological or pathophysiological range, the renal response may be delayed for the better part of an hour or more (5, 17, 20), even in subjects given daily sodium chloride supplements for 5 days before receiving the infusion (19). In other experiments no renal response was detectable (35, 99). It should be noted that low infusion rates usually elevate plasma atrial peptide to levels at least as high as those produced by intravenous volume expansion or left atrial distension; however, these latter interventions produce a substantially greater natriuretic effect than that elicited by administration of the peptides alone. Thus the atrial peptides may contribute to the natriuresis and diuresis elicited by these stimuli, but they do not appear to be the primary causal mechanism.

The renal responses induced by low infusion rates of atrial peptides in dogs have varied in different laboratories. For example, Bie and his colleagues (17) found that infusion of 12.5 $ng \cdot kg^{-1} \cdot min^{-1}$ of α-human atrial peptide to conscious dogs elicited a threefold increase in the concentration of atrial peptide in plasma. Renal sodium excretion before the infusion was 29 ± 10 μeq/min and became significantly increased (50 ± 13 μeq/min, $P < 0.05$) only after 40–60 min of continuous infusion. The authors concluded that small fluctuations in circulating atrial peptides that occur under normal conditions have little effect on sodium excretion, although it was recognized that the atrial peptides might act synergistically with other natriuretic mechanisms that were not activated during the conditions of these experiments. In contrast, Zimmerman and his colleagues (215) infused α-human atrial peptide at a slower rate (2.5 $ng \cdot kg^{-1} \cdot min^{-1}$) to anesthetized dogs after acute surgery. The concentration of atriopeptin in plasma increased 47%, and sodium excretion (single kidney) increased significantly from 22 ± 6 to 66 ± 15 μeq/min before the end of a 35-min infusion. These authors concluded that atriopeptin was natriuretic at physiological concentrations. Aside from the obvious difference between conscious and anesthetized animals, it is difficult to find a reason for the different sensitivity of the kidneys to the atrial peptides in these two studies. It is possible, however, that progressive saline loading in the anesthetized dogs (2 ml/min) may have contributed to the natriuretic response elicited in these animals. The effects of infusion of saline not containing atrial peptide were not reported by these authors.

Garcia and his colleagues chronically infused very low doses of atrial peptide (35 pM/h or ~5–8 $ng \cdot kg^{-1} \cdot min^{-1}$) into several types of hypertensive and normotensive conscious rats (59–61). Arterial blood pressure decreased significantly in each group of hypertensive rats, but only one of the hypertensive groups (59) and none of the control groups increased their sodium excretion during the week-long infusion period. Unfortunately, sodium intake was not monitored in any of these experiments, so sodium excretion in each group may simply have reflected sodium intake rather than any specific effect of atriopeptin.

Granger and his colleagues (76) avoided potential problems with sodium intake in conscious dogs by feeding them a sodium-deficient diet and providing sodium via an intravenous infusion of isotonic saline at a constant rate. Chronic infusion of atrial peptide at 50 $ng \cdot kg^{-1} \cdot min^{-1}$ for 5 days produced no significant change in daily sodium excretion even though circulating atriopeptin levels increased 10-fold. Mean blood pressure, however, declined from 90 to 75 mmHg, a change the authors believed might have counteracted any natriuretic effect of atriopeptin.

Marked changes in daily sodium intake in human subjects have caused modest changes in plasma atriopeptin concentration in some studies (32, 78, 163), although Weidmann and his co-workers (204) did not detect statistically significant alterations in normal subjects with sodium intakes ranging from 10 to 310 mmol/day. It

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remains to be established that the 1.4- to 3.5-fold changes in circulating atrial peptides elicited by rather extreme changes in dietary intake (32, 78, 163) were responsible for the rather marked adjustments in renal sodium excretion that necessarily accompanied the dietary changes. In an effort to investigate acute changes elicited by a single high-sodium meal in human subjects, we (171) determined the effects on urinary sodium excretion and circulating atriopeptin of eating a breakfast containing 100 mM sodium. Fluid intake was limited to 500 ml with the meal and 2 $ml \cdot kg^{-1} \cdot h^{-1}$ thereafter. Sodium excretion increased ~3.5-fold after the high-sodium meal, peaking at 3 h, but the plasma concentration of atriopeptin did not increase. In fact, there was a tendency for plasma atriopeptin to decline during the 7 h after the meal. These results are in conflict with a brief report (94) indicating that ingestion of 90 g of salted potato chips caused an acute increase in the concentration of atriopeptin in plasma from 19 to 31 pg/ml; any associated fluid intake was not reported.

Verburg and his associates (196) fed dogs a meal containing a considerably higher sodium load (~5 mmol/kg body wt) and provided water ad libitum. This provoked a 45% increase in circulating atrial peptides that was accompanied by approximately a 10-fold increase in sodium excretion (196). The difference between these results and those obtained in humans after a high-sodium breakfast could be attributable to the amount of salt consumed, to species differences, or more likely to the presumably greater water intake in the canine experiments and the probability that the fluid intake significantly increased atrial pressures.

The natriuretic response induced by atrial distension in the conscious dog does not appear to depend on an associated release of atrial peptides. When left atrial pressure was increased in normal conscious dogs by partially occluding the mitral valve, the resulting increase in urine flow and sodium excretion was accompanied by an increase in circulating atriopeptin levels (73). From these results alone one might assume that the rise in plasma atriopeptin was responsible for the natriuretic response. However, in parallel experiments performed in conscious dogs with surgically denervated hearts, a comparable increase in left atrial pressure caused similar increases in plasma atriopeptin, but urine flow and sodium excretion did not increase during the period of atrial distension. These results implied that the renal response elicited by atrial distension in the dog is mediated by reflex effects from cardiac nerves rather than the release of atriopeptin.

On the other hand, several lines of evidence suggest that the atrial peptides may be of considerable importance in modulating sodium excretion in the rat. For example, urine flow and sodium excretion decreased and plasma renin increased in anesthetized rats after administration of antiserum containing antibodies raised against atriopeptin, thus suggesting that endogenous atriopeptin plays a role in regulating these variables in the rat (137). Moreover, anesthetized rats immunized with monoclonal antibodies raised against atriopeptin lacked the ability to increase urine flow and sodium excretion during the first 20–40 min after intravenous volume expansion with homologous blood (89). This rather surprising result implies that the atrial peptides are totally responsible for the early natriuresis and diuresis elicited by blood volume expansion and that other known regulatory mechanisms including atrial neural reflexes (72), renal sympathetic nerve activity (41), peritubular physical factors (118), the renin-angiotensin system (157), and other putative natriuretic hormones (82) are unable to increase urine flow and sodium excretion appreciably during the first 20–40 min after volume expansion with whole blood in the rat.

Veress and Sonnenberg (197) reported that removal of the right atrial appendage attenuated the natriuretic response to volume expansion in anesthetized rats, and Kobrin et al. (120) observed that removal of both atrial appendages attenuated sodium and water excretion after volume expansion in conscious rats. These studies implied that atrial appendectomy reduced the amount of atriopeptin released during volume expansion. This was verified by Villarreal et al. (198) and Schwab et al. (177) who demonstrated that removal of either the right (177) or both (198) atrial appendages does not affect basal levels of atrial peptides in plasma but does attenuate the rise in plasma atriopeptin levels as well as the increase in urinary sodium excretion induced by intravascular volume expansion in rats. Bilateral atrial appendectomy does not, however, attenuate the increase in sodium excretion after volume expansion in the dog (15, 115). Moreover, although the increase in mean plasma atriopeptin levels after volume expansion in dogs with the atrial appendages removed was comparable to that observed in sham-appendectomized dogs, no correlation between the changes in plasma atriopeptin and sodium excretion could be found (15). The above data suggest that the renal response to intravascular volume expansion in the rat may be more dependent on atriopeptin than it is in the dog.

Immersion of seated human subjects to the neck in thermoneutral water elicits a natriuresis and an approximate doubling of circulating atriopeptin (6, 47, 147). A direct cause and effect relationship between the change in plasma atriopeptin and the associated natriuresis, however, was not established in these experiments. Natriuretic responses also were observed when trained conscious dogs were immersed in a water bath for 100 min (133); there was, however, a lack of correlation between the natriuresis elicited by water immersion and changes in plasma atrial peptide levels in this study.

Similarly, supraventricular tachycardia in human subjects consistently elevates plasma atriopeptin levels (119, 141, 142), even though only half or fewer of the patients with this condition experience an increase in urinary output during the attack (141, 142). A striking lack of correlation between a rise in atrial peptide concentration and renal sodium excretion was noted in the two patients with paroxysmal supraventricular tachycardia studied by Kojima et al. (119). A 60-min period of provoked tachycardia increased the concentration of plasma atriopeptin 12- and 24-fold above basal levels in the two patients and also increased urine flow and free water excretion;

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urinary sodium excretion, however, decreased substantially in each patient. The increase in free water clearance may have been caused by an inhibition of vasopressin secretion mediated by an increase in the discharge rate of atrial receptors during the tachycardia (72, 119) or by a direct inhibitory effect of the elevated atriopeptin levels on vasopressin-stimulated water reabsorption from the renal collecting ducts (43). However, the observation that sodium excretion declined during a period when plasma atriopeptin levels were substantially elevated demonstrates again that a substantial rise in plasma atriopeptin levels does not consistently cause a natriuresis in human subjects.

Cardiovascular Effects of Atrial Peptides

Pharmacological doses of the atrial peptides are capable of producing major alterations in systemic hemodynamics, but it is not yet clear whether physiological concentrations of atriopeptin exert appreciable cardiovascular effects. For example, large doses of atrial peptides given as a bolus injection consistently produce an acute decrease in arterial blood pressure but smaller amounts usually do not. Nevertheless, a small gradual decline in arterial blood pressure often occurs during the course of a low-dose infusion; in fact, a statistically significant decrease in blood pressure may occur only after administration of the peptide has been stopped (17). A prolonged hypotensive response that persists after administration of atriopeptin has ended is not uncommon (17, 19, 23, 25). In view of the short half-life of the circulating peptide hormone (estimates range from <1 min to 2–3 min), the persistent hypotensive response conceivably could be caused by a prolonged production of cGMP in vascular smooth muscle cells after plasma atrial peptide levels declined (81) or by other unidentified effects on the central nervous system or other endocrine systems that influence blood pressure. Evidence that chronic infusions of the peptides can lower blood pressure in hypertensive rats (59–61) and normotensive dogs (76) without producing significant alterations in renal sodium excretion suggests that hemodynamic effects of the atrial peptides, at least in some circumstances, may be more potent than the renal effects. It may be relevant to note that atrial extracts from the chicken apparently do not induce natriuresis in that species, but they do lower blood pressure (77).

Isolated vessels or vascular preparations partially constricted with a variety of pressor agents relax in the presence of the atrial peptides (1, 48, 66, 97, 206). The vascular actions of atriopeptin do not require the presence of the endothelium (207). Atriopeptin stimulates particulate guanylate cyclase and increases intracellular cGMP (57, 81, 206, 207). Atriopeptin also decreases cytosolic free calcium, possibly by inhibiting calcium influx, inhibiting calcium release from intracellular stores, and accelerating calcium extrusion (57, 206). There is some disagreement concerning the relative susceptibility of various vessels to the vasodilator action of the atrial peptides. Although the aorta and renal vessels in vitro dilate in the presence of the atrial peptides, conflicting data have been obtained for other arteries, veins, and resistance-sized vessels (1, 48, 97, 151, 202, 206).

Vasodilation does not necessarily occur when atriopeptin is given to intact animals. A number of studies on conscious experimental animals have demonstrated that total peripheral resistance either remains constant (168, 200) or increases (23, 74) when atrial peptides are infused intravenously; associated decreases in arterial blood pressure in the latter experiments were caused by decreases in cardiac output. Although a comprehensive explanation for the difference in results from isolated vessels and intact animals is not yet possible, two points may be considered. First, it has been reported that the atrial peptides may cause vasoconstriction in isolated perfused kidneys if the renal vessels are not preconstricted with other vasoactive agents (26), and it is likely that the constrictor tone of renal vessels in the conscious animal would be low. Second, arterial baroreceptors appear to respond to the hypotensive effects of the atrial peptides and elicit reflex increases in sympathetic neural traffic to resistance vessels, thereby offsetting any vasodilation induced directly by the peptides (93). Although it is likely that arterial baroreceptors cause a reflex increase in vascular smooth muscle tone during the administration of atriopeptin, it is worth noting that a decrease in arterial pressure in dogs and rats during atriopeptin administration is not accompanied by a reflex tachycardia (14, 17, 65, 74, 117, 179). This implies that under these conditions the arterial baroreceptors selectively adjust efferent neural traffic to resistance vessels without altering efferent traffic to the heart. Another possible link between the atrial peptides and the arterial baroreceptors was suggested by Gardner and his colleagues (62), who reported that the atrial peptide gene is expressed in the aortic arch; considerably more atrial peptide mRNA was identified in the arch of the aorta than in the distal thoracic aorta. Although the amount of immunoreactive atriopeptin detected in the aortic arch was considerably less than that in the atria per milligram of protein, dense immunoreactivity was detected in the adventitia of the arch, especially in the areas where the baroreceptors are known to be distributed. It was suggested that the atriopeptin in the aortic arch may serve a paracrine or autocrine role in mediating or modulating the baroreceptor reflex (62); this is reminiscent of speculation by others that atriopeptins may chemically stimulate cardiac reflexes (191). It is conceivable, therefore, that atriopeptin may modulate the discharge pattern of mechanoreceptors located at various sites within the cardiovascular system.

Human subjects respond somewhat differently than experimental animals when given intravenous infusions of the atrial peptides. Intravenously administered atriopeptin causes cutaneous vasodilation in human volunteers (25), and infusion of human atriopeptin into the brachial artery causes a reduction in human forearm vascular resistance (22). In addition, human subjects occasionally develop facial flushing and hypotension (19, 25, 158, 201) with the decrease in blood pressure being severe in some cases. These results obviously imply that the atrial peptides are potent vasodilators in normal

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human subjects, perhaps more so than in experimental animals. Nearly all reports indicate that a decrease in blood pressure elicited by atrial peptides in humans is accompanied by an increase in heart rate (19, 58, 70, 103, 158, 203, 204). Presumably the increase in heart rate is mediated via a reflex initiated by the arterial baroreceptors. The only exception is that large decreases in arterial pressure in humans have been accompanied by a vagal reaction and bradycardia (19, 25, 103).

The atrial peptides are capable of decreasing plasma volume (51, 203), an effect that was anticipated by the original observation that hematocrit increased in anesthetized rats after they were given atrial extracts (37). Although a reduction in plasma volume obviously would be expected in response to urinary fluid losses, plasma volume also diminishes in anephric animals that are given atrial peptides (2, 51, 193). Comparable results have been obtained after removal of both kidneys and spleen (51). A shift in circulating fluid to the interstitial space may be caused by an increase in capillary hydraulic conductivity (95) and by an increase in postcapillary resistance (193). The ability of atriopeptin to cause a net transfer of fluid from plasma to interstitial space raises the possibility that edema formation in congestive heart failure and other conditions associated with abnormally high plasma atriopeptin levels may be attributable in part to the effects of the atrial peptide.

Infusions of atrial peptide that raised the plasma concentration of atriopeptin 3-, 7-, and 12-fold in conscious dogs caused progressive decreases in right and left atrial pressures (17). Further work is needed to establish that the effects of atriopeptin on atrial pressures are of physiological importance. However, because an increase in atrial pressure increases the release of atriopeptin, which in turn may decrease cardiac filling pressure, the atrial peptides may serve as part of a negative feedback system that enables the heart to influence its own filling pressure (71, 153).

The decrease in cardiac filling pressure, or preload, appears to be primarily responsible for the decrease in cardiac output that may be induced by the atrial peptides (71). The peptides also conceivably could reduce myocardial contractility and thereby reduce cardiac output. Consistent with this possibility is the observation that atriopeptin inhibits adenylate cyclase activity and reduces the amount of cAMP in heart tissue (3). Extremely large doses of atriopeptin decrease the peak rate of pressure rise (dP/dt) in the left ventricle in anesthetized rats (44). Small negative inotropic effects of the atrial peptides on ventricular contractility have been noted in other studies in anesthetized rats (181), whereas no effects on contractility were detected in isolated atria (16) or isolated guinea pig hearts (90) on exposure to atriopeptin. In view of the overwhelming evidence that atrial peptides are released in response to atrial distention, teleological considerations suggest that any substantial negative inotropic effect of the atrial peptides on an already distended heart would be an undesirable physiological response.

Effects of Atrial Peptides on Other Hormonal Systems

It is clear that the atrial peptides can influence a number of other hormonal systems, but results obtained thus far have been inconsistent. For example, when atriopeptin is administered to intact experimental animals or humans, plasma renin activity and aldosterone often decrease simultaneously (28, 32, 54, 130). Nevertheless, it is not uncommon for the acute administration of atrial peptides to cause no decrease in either plasma renin activity or aldosterone, especially if the basal levels of these substances are normal or low (19, 20, 74, 76, 114, 192). Finally, plasma aldosterone may be suppressed following administration of atriopeptin even when plasma renin activity is unchanged (148, 187, 201) or increased (99, 199). Similarly, plasma cortisol has been decreased significantly in normal humans after administration of atrial peptides in some (99, 148) but not all (28, 32) studies.

Investigation of the effect of atrial peptides on renin secretion in vitro also has produced conflicting results. Some investigators found no effect of atriopeptin on renin release from isolated renal glomeruli (159); others observed an exquisitely sensitive inhibitory effect on renin release from cultured juxtaglomerular cells (123). Finally, when atriopeptin was infused into isolated rat kidneys, renin secretion increased (80).

In contrast to the conflicting data regarding the effect of atriopeptin on renin secretion in vitro, there is essentially unanimous agreement that the atrial peptides have a direct inhibitory effect on aldosterone secretion in isolated adrenal cortex preparations. This has been demonstrated in isolated adrenal glomerulosa cells and isolated preparations of adrenal cortex taken from the human (87, 138), rat (10, 27, 98, 122), and cow (38, 46, 75). Increases in the intracellular concentration of cGMP (87, 98, 138) and decreases in intracellular cAMP (98, 138) appear to contribute to the suppression of aldosterone secretion by atriopeptin. Other evidence suggests that atriopeptin may inhibit aldosterone secretion partly by inhibiting calcium influx into the glomerulosa cells (27), but this is controversial (75). Aldosterone secretion in isolated zona glomerulosa cells may be inhibited by picomolar concentrations of the atrial peptides (10), i.e., in concentrations that circulate normally in plasma, thus suggesting that aldosterone secretion may be modulated by physiological concentrations of the atrial peptides.

Atriopeptin reduces the rate of release of vasopressin from hypothalamic-hypophysial preparations (31, 105), but the atrial peptides may either stimulate (104) or inhibit (145) vasopressin secretion from the isolated posterior pituitary. Also, high levels of circulating vasopressin induced either by osmotic stimulation or hemorrhage in rats were reduced by intravenous administration of atriopeptin (165). These findings have led to the hypothesis that the atrial peptides modulate the secretion of vasopressin. In a study on hydrated human volunteers, plasma vasopressin fell to undetectable levels after an intravenous infusion of atriopeptin, but plasma values were quite low before atriopeptin was administered (58), and the authors concluded that the vasopressin response probably was not of physiological significance because the infusion of peptide had produced a supraphysiological plasma concentration. Furthermore, other investigations on human subjects or anesthetized

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dogs (19, 20, 32, 70, 114, 192) have not detected changes in plasma vasopressin during intravenous infusion of atriopeptin. The data available at this point suggest that atriopeptin within the brain may modulate the secretion of vasopressin, but it is doubtful that atriopeptin circulating in the blood significantly affects vasopressin secretion.

Several lines of evidence suggest that the atrial peptides may influence the sympathetic nervous system. Low infusion rates of atriopeptin given to conscious dogs lower blood pressure slightly and decrease the calculated release rate of catecholamines; higher doses tend to reverse this effect (92). These data imply that low infusion rates of atriopeptin inhibit the release of epinephrine from the adrenal medulla and also inhibit baroreceptor reflexes that normally increase norepinephrine release as blood pressure decreases. However, as larger doses of atrial peptide are given, the more prominent hypotensive effects elicit a more powerful reflex stimulation of the sympathetic nervous system by the arterial baroreceptors. Thus baroreceptor reflexes probably are responsible for the increases in circulating norepinephrine that have been detected after intravenous infusion of atriopeptin to human subjects (32, 99) and for the tachycardia that commonly occurs in human subjects in response to the atrial peptides (see *Cardiovascular Effects of Atrial Peptides*). A brief review (121) summarizes current data indicating that atrial peptides may inhibit the sympathetic nervous system.

Central Nervous System Effects

The atrial peptides are distributed widely throughout the brain (69, 134, 167, 190, 213), and the presence of atrial peptide mRNA transcripts within the hypothalamus and other brain sites (63) provides convincing evidence that these peptides are synthesized locally within the brain. Furthermore, abundant binding sites have been demonstrated on both sides of the blood-brain barrier (68, 131, 162). These anatomical observations imply that the atrial peptides serve a functional role within the central nervous system. Pharmacological experiments have produced compatible evidence. Atrial peptides have been shown to increase the concentration of cGMP in neural tumor cell lines (56) and in the anterior pituitary (85). When administered into the lateral ventricles, the peptides decrease the amount of dopamine and its metabolites in the rat brain, a response opposite to that produced by angiotensin II (136). Also, direct application of atrial peptides to hypothalamic neurons by pressure injection or iontophoresis alters the discharge rate of approximately one-third of the responsive hypothalamic cells tested (84, 208); in most cases, the firing rate of the cells decreased after administration of the peptides.

The highest concentrations of atriopeptins in the brain appear to be located in the hypothalamus (113, 134), a distribution consistent with the notion that these agents may participate in the central regulation of the cardiovascular system and body fluid balance. Indeed, centrally administered (lateral ventricle) atrial peptides attenuate blood pressure increases elicited by centrally administered angiotensin II (101, 183). Furthermore, binding sites for atriopeptin in the subfornical organ are less numerous in spontaneously hypertensive rats than in Wistar-Kyoto rats (131, 161), whereas binding sites for angiotensin II are increased in the hypertensive strain (161); these latter observations are consistent with the possibility that each of these peptides may be involved in the pathogenesis of this form of hypertension.

Intracerebroventricular administration of atriopeptin also may alter renal function. Heavily hydrated rats, some also salt loaded, increased urine flow and sodium excretion in response to the injection of atrial peptide into a lateral ventricle (100). Relatively low infusion rates of atriopeptin (30 or 60 pM/h) into the lateral ventricles stimulated urine flow in normally hydrated and sodium-depleted rats when compared with vehicle-infused rats, but sodium excretion did not increase (50). The increase in urine flow appeared to be elicited by central mechanisms because atriopeptin infused intravenously at the same rate had no effect on renal function (50).

Salt and water intake can be influenced by atrial peptides. Sodium consumption was reduced by administration of atrial peptides into the third (9) or lateral ventricles (50) of sodium-depleted rats. Similarly, water intake was inhibited by atriopeptin in rats whose thirst was stimulated by mild dehydration or centrally administered angiotensin II (8, 125, 135). Possibly related results come from experiments in which the brains of dehydrated rats were examined. Atriopeptin-like immunoreactivity in dehydrated rats was decreased in the neural lobe, organum vasculosum of the lateral terminalis, and the suprachiasmatic and supraoptic nuclei (166), and the number of binding sites for atriopeptin in the subfornical organ was higher in dehydrated rats than in normally hydrated controls (162).

CONCLUDING DISCUSSION

The frequent inclusion of "natriuretic" as part of the designation for the atrial peptides has focused considerable attention on the effects of these peptides on the kidney. There is agreement that large pharmacological doses of atriopeptin cause prompt and substantial increases in urine flow and sodium excretion. Accumulating evidence, however, indicates that infusion rates that increase plasma atriopeptin only by perhaps three- to fivefold may produce only a delayed and modest natriuresis or in some cases no response at all. Although a number of natriuretic stimuli, e.g., intravascular volume expansion, elevate plasma atrial peptide levels with a time course similar to the accompanying natriuretic response, it is unlikely that the small increase in circulating atriopeptin alone accounts for the brisk increase in urine flow and sodium excretion induced by these stimuli. There are a number of circumstances, unexplained at the moment, in which substantial increases in circulating atriopeptin occur without any change in the renal excretion of sodium. Until these are clarified, and until a more definitive understanding of possible interactions between atriopeptin and other well-delineated factors that regulate sodium excretion is available, a precise role of the

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atrial peptides in modulating renal sodium excretion will remain elusive.

The observation that chronic administration of low doses of atrial peptide are potent hypotensive agents in animals with high blood pressure and the observation that chronic low-dose infusions into normal animals also may lower blood pressure without affecting renal sodium excretion raise the possibility that the cardiac hormone may play a role in blood pressure regulation either by acting directly on receptors within the cardiovascular system or by acting indirectly through effects on other hormonal systems or on the brain. Other possible physiological actions of the atrial hormone include regulation of the distribution of fluid between plasma and the interstitial compartment and regulation of cardiac filling pressure independently of renal actions.

Atriopeptin interacts with several endocrine systems. Much evidence indicates that the atrial peptides interact with the renin-angiotensin-aldosterone system in several ways. The ability of atriopeptin to antagonize the actions of angiotensin II at several sites including the blood vessels, proximal renal tubule, adrenal cortex, and the brain may have considerable functional significance. Atriopeptin may inhibit the secretion of vasopressin by central mechanisms.

Current evidence suggests that atriopeptin synthesized within the brain may serve as a neuromodulator or neurotransmitter, and circulating atriopeptin may influence cerebral function by acting on receptors in the circumventricular organs, which lack a blood-brain barrier. Although a number of lines of evidence suggest that atriopeptin acting on the brain may affect cardiovascular and renal function as well as the intake of salt and water, it should be stressed that most of the experiments performed thus far have employed large doses of the atrial peptides. It would be premature to consider that the effects elicited in those experiments necessarily occur during normal physiological conditions.

The diverse effects of atriopeptin on cardiovascular, renal, endocrine, and neural mechanisms as well as other effects not considered in this review imply that this cardiac hormone is an important physiological regulator of bodily processes. Evidence currently available suggests that atriopeptin acts in an integrative manner on a number of target organs to modulate cardiovascular function and fluid balance.

NOTE ADDED IN PROOF

This review essentially was completed by mid-1987. The temptation to summarize developments that have occurred in this fast-moving field during the intervening six months was overridden by the realization that about 300 papers concerning the atrial peptides were published in this interval. This massive literature could not be summarized adequately in a few additional paragraphs.

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