Peptide Hormones and the Regulation of Sodium Excretion

MICHAEL H. HUMPHREYS AND SHAN-YAN LIN

KEY WORDS • peptide hormones • hormone receptors • intracellular messengers • glomerular filtration rate • sodium reabsorption • sodium excretion

TWENTY years ago, intensive research led to the delineation of the role played by alterations in blood composition in mediating the natriuresis that resulted from the infusion of colloid-free isotonic saline solutions into humans and experimental animals. Results of this research indicated that changes in renal hemodynamics (glomerular filtration rate [GFR], renal blood flow, renal vascular resistance, filtration fraction) and hematocrit and plasma protein concentration occurring in response to saline infusion led to inhibition of tubular sodium reabsorption through changes in hydrostatic and oncotic pressures in the peritubular capillary circulation, the so-called physical factor effects.1 Because of these findings, the view emerged that, regardless of the extrarenal consequences of saline expansion, the natriuresis resulted from strictly intrarenal mechanisms.2,3 This viewpoint was later strengthened by in vitro studies on isolated perfused rabbit proximal convoluted tubule segments that demonstrated a direct effect of bath protein concentration on fluid transport.4

Subsequent research, however, has indicated that the regulation of sodium excretion is more complex. The model of saline expansion natriuresis is clearly unphysiological, and although it has provided important insights into mechanisms regulating tubular sodium reabsorption, their relevance to the day-to-day maintenance of salt balance through changes in sodium excretion may be questioned. Moreover, recent theoretical considerations have drawn attention to the difficulty in attributing an observed change in tubular reabsorption to an alteration in the peritubular Starling forces thought to regulate fluid uptake.5 Finally, the quest has never ended for a natriuretic hormone. Indeed, current attention has focused on the control of sodium excretion by several such humoral agents, acting directly through adjustments in tubular reabsorption of sodium or more indirectly through changes in renal hemodynamics and peritubular physical factors. This review will attempt to summarize the vast amount of work that has emerged in this area in the past decade. Emphasis will be confined to a consideration only of the effects of peptide hormones to alter renal hemodynamics and sodium excretion; where possible, certain subjects will be mentioned briefly and the reader referred to several more detailed recent reviews.

Mechanisms of Peptide Hormone Action

For a peptide hormone to exert its actions in target tissues, it must bind to a receptor on the cell surface. This binding exhibits several characteristics that are true of all hormones,6 including a high affinity and stereospecificity of the receptor for the ligand, rapid and reversible binding, a low capacity (i.e., a small number of receptor sites per cell that can be occupied by the peptide), and activation by binding of the hormone to the receptor of a second messenger, to culminate in the physiological evidence of hormone action (e.g., increased cell membrane permeability, increased Na⁺-H⁺ exchange). With respect to the kidney, the second messengers mediating the action of many peptide hormones are known, although for many others there is no definite information available (Table 1). One of the best defined second messenger systems involves the activation of an adenylate cyclase coupled to the peptide receptor that catalyzes the synthesis of cyclic adenosine 3',5'-monophosphate (cAMP) from adenosine 5'-triphosphate (ATP); this hormone-dependent cAMP production is involved in the action of many peptide hormones in the kidney.7 The participation of cAMP in volume expansion natriuresis has been

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### TABLE 1. Characterization of Certain Peptide Hormone Actions on the Kidney

<table>
<thead>
<tr>
<th>Peptide</th>
<th>Localization of receptors</th>
<th>Intracellular messenger</th>
<th>Physiological effects</th>
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<tbody>
<tr>
<td>Atrial natriuretic factor</td>
<td>Mesangium; efferent arteriole</td>
<td>cGMP</td>
<td>↑ GFR</td>
</tr>
<tr>
<td></td>
<td>Inner medullary collecting duct</td>
<td>cGMP</td>
<td>↓ Na reabsorption</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>Mesangium; efferent arteriole</td>
<td>↑ [Ca²⁺],</td>
<td>↓ GFR; ↑ glomerular capillary hydrostatic pressure; complex effect on GFR</td>
</tr>
<tr>
<td></td>
<td>Proximal tubule</td>
<td>? ↑ [Ca²⁺],</td>
<td>Stimulates NaHCO₃ reabsorption</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>V₁ — mesangium, renomedullary interstitial cells</td>
<td>↑ [Ca²⁺],</td>
<td>↑ NaCl reabsorption; ↓ HCO₃ reabsorption</td>
</tr>
<tr>
<td></td>
<td>V₂ — medullary thick ascending limb, cortical and medullary collecting duct</td>
<td>cAMP</td>
<td>↑ Water permeability; ↑ K secretion</td>
</tr>
<tr>
<td>y-MSH</td>
<td>(?) Proximal tubule</td>
<td>?</td>
<td>↓ Na reabsorption; natriuresis</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>Renal tubule</td>
<td>?</td>
<td>Postulated role in GFR, renal blood flow</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Renal tubule</td>
<td>?</td>
<td>Probably no function in mammals</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Mesangium</td>
<td>cAMP</td>
<td>↓ Kᵦ; extracellular fluid volume–related effects on GFR</td>
</tr>
<tr>
<td></td>
<td>Proximal tubule</td>
<td>cAMP; [Ca²⁺]</td>
<td>↓ NaHCO₃ reabsorption; trivial effect on Na excretion</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thick ascending limb of Henle's loop; distal convolution</td>
<td>cAMP</td>
<td>↑ Ca reabsorption; no major effect on Na reabsorption</td>
</tr>
<tr>
<td>Insulin</td>
<td>Proximal convoluted tubule</td>
<td>?</td>
<td>↑ proximal reabsorption;</td>
</tr>
<tr>
<td></td>
<td>?</td>
<td>↑ distal reabsorption;  ↓ Na excretion</td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>(?) Mesangium</td>
<td>? cAMP</td>
<td>↑ GFR</td>
</tr>
<tr>
<td></td>
<td>Thick ascending limb of Henle's loop; distal convolution</td>
<td>cAMP</td>
<td>↑ Ca, Mg reabsorption; ↓ HCO₃ reabsorption; no effect on Na excretion other than that related to increases in GFR</td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate; cGMP, cyclic guanosine 3',5'-monophosphate; cAMP = cyclic adenosine 3',5'-monophosphate; Kᵦ = glomerular ultrafiltration coefficient; [Ca²⁺]ᵢ = intracellular free cytosolic calcium concentration; γ-MSH = γ-melanocyte stimulating hormone; ↑ = increased; ↓ = decreased.

inferred from studies demonstrating an increase in nephrogenous cAMP production during extracellular fluid volume expansion. Cholera toxin, which causes diarrhea by a cAMP-mediated intestinal secretory process, also leads to increased cAMP production and natriuresis when infused into a renal artery, and cAMP and its synthetic analogue dibutyryl-cAMP increase the permeability of the isolated perfused proximal tubule. These observations are all consistent with the possibility that volume expansion natriuresis could result in part from peptide hormone–mediated activation of cAMP production and a resultant decrease in tubular sodium reabsorption in addition to any physical factor effects. As will be discussed, just such a sequence has been argued to occur from enhanced parathyroid hormone (PTH) secretion after volume expansion, even though this peptide is usually viewed in the context of regulating calcium and phosphate reabsorption. Other second messenger systems of peptide hormone action identified in the kidney include guanylate cyclase activation and an increase in intracellular calcium concentration from influx of extracellular calcium or mobilization of intracellular calcium stores. These systems participate in volume expansion natriuresis to the extent that the peptides whose actions they mediate are regulated by volume changes, for example, increased atrial natriuretic factor (ANF) secretion, leading to increased cyclic guanosine 3',5'-monophosphate (cGMP) production, and decreased angiotensin II (Ang II) production, leading to a decrease in cytosolic calcium in its target cells, each of which occurs in response to volume expansion. A striking characteristic of renal hormone–dependent second messenger systems is their localization to defined nephron segments. Such localization of peptide-stimulated enzyme activity argues for a physio-
logical role of the peptide in that nephron segment, as well as an integrated nephronal response to the peptide in determining its effects on the composition of the final urine, since the effects of hormone action in one nephron segment may be adjusted by intrinsic or hormonally mediated transport in a downstream segment. In the discussion that follows, the renal actions of the peptide hormones covered in this review will be related to the nephron segments in which receptors for the peptide or hormone-coupled second messenger activation (or both) have been described, focusing on the effect of such receptor activation on the regulation of sodium excretion.

**Atrial Natriuretic Factor**

The growth of information concerning ANF, the recently discovered peptide synthesized and secreted by cardiac atrial myocytes, has outstripped a clear understanding of its role in body fluid homeostasis. We shall discuss only a small number of its biological effects; more intensive reviews describe its renal and extrarenal actions, regulation of its biosynthesis, and control of its secretion in great detail. Numerous biologically active peptides have been isolated from plasma and atria of different species or have been synthesized; these different peptides vary somewhat in potency in different assay systems, but they share in basic structure and in producing their actions through activation of guanylate cyclase and the production of cGMP. Consequently, we shall refer to them in aggregate as ANF.

The renal actions of ANF include effects on the vasculature, the mesangium, renin secretion, and sodium excretion. More indirect effects on renal function may be attributed to systemic vasodilatation and reduced arterial pressure produced by ANF infusions and to direct inhibition of aldosterone production and secretion by the adrenal gland. Evidence now is virtually uniform in indicating that ANF exerts its actions in all target tissues through stimulation of cGMP production. Renal receptors for ANF are located in three regions: renal vasculature, glomerular mesangium, and medullary collecting duct; ANF also stimulates cGMP production in mesangium and inner medullary collecting duct, indicating that these are the nephron segments likely involved in the peptide’s actions. The most striking of these actions are an increase in GFR and a natriuresis, usually without kaliuresis. The increase in GFR occurs as a result of an increase in GFR and a natriuresis, usually without kaliuresis. Acute volume expansion increases plasma ANF concentration in addition to causing natriuresis and to account for the increased sodium excretion per nephron in experimental chronic renal failure. ANF may also ameliorate the severity of ischemic acute renal failure in the rat. Patients with congestive heart failure have elevated levels of ANF in plasma and blunted responsiveness to infused ANF, suggesting that it may play a reactive or compensatory role in this state of sodium retention. Similarly, levels in some patients with liver disease are elevated. A potentially important role of the renal nerves in the blunted response to infused ANF has been reported: In salt-retaining rats with bile duct ligation or experimental nephrotic syndrome, renal denervation corrected the impaired natriuretic effect of infused ANF. In patients with nephrotic edema, basal levels of ANF in plasma have been reported as normal or low; volume expansion with albumin infusion or head-out water immersion elevates plasma ANF concentration and leads to natriuresis, although in the latter study the natriuretic response was less than that observed in normal controls. Future studies will define more precisely the role that ANF plays in body fluid homeostasis, particularly once specific receptor antagonists become available such as already exist for Ang II and vasopressin.

One comment should be made about the regulation demonstrating natriuresis without change in GFR. On the other hand, other studies suggest that only a negligible portion of ANF-stimulated natriuresis persists when GFR is controlled by aortic clamping. Furthermore, the natriuresis resulting from glucagon infusion, which also increases GFR, is comparable in magnitude to that seen with ANF infusion, despite the markedly different tubular effects of the two peptides. These studies would suggest that the rise in GFR caused by ANF is the critical factor in ANF natriuresis. This conclusion should be tempered, however, since the reduction in perfusion pressure used to control ANF hyperfiltration in these studies itself lead to alterations in tubular reabsorption so as to obscure a tubular action of the peptide. Moreover, infusion studies in anesthetized animals may yield different results than those observed in conscious animals.
of ANF secretion. The relationship between atrial pressure and ANF levels in vivo and in vitro have led to the conclusion that atrial stretch or distention is the primary factor leading to ANF secretion. However, neural or hormonal regulation may also exist. In particular, a role of the pituitary in mediating the increased ANF secretion following volume expansion has recently been reported: in hypophysectomized animals, volume expansion failed to increase plasma ANF concentration, but responsiveness of peptide secretion was restored when pituitary tissue was implanted under the renal capsule. Observations such as this suggest that complex interactions may exist in determining the role of ANF in integrated volume regulation.

Angiotensin II

Ang II, like ANF, has a wealth of renal and extrarenal actions and is an important humoral regulator of renal function. Direct renal actions include constriction of the renal vasculature, particularly the efferent arteriole of the glomerulus, contraction of glomerular mesangial cells, and regulation of tubular reabsorption, most notably in the proximal convoluted tubule. Indirect actions are mediated by increases in perfusion pressure brought about by its peripheral vasconstrictor activity, by enhancement of cortical collecting duct sodium reabsorption and potassium secretion resulting from its stimulation of aldosterone secretion, and possibly by neuroendocrine consequences of its actions in the central nervous system. The physiological effects and biochemical events resulting from Ang II have been the subjects of numerous recent reviews, and only brief highlights will be covered here. Although some ambiguity still exists about the biological role of the heptapeptide angiotensin III (Ang III), the bulk of evidence supports a major if not sole role of the parent octapeptide Ang II in the actions attributed to this compound, and that viewpoint will be taken here.

Receptors for Ang II have been localized to glomeruli, renal cortex, and outer stripe of inner medulla overlying the vasa recta. In glomeruli, the receptors are located on mesangial cells, and Ang II may function in this cell to induce contraction, thereby altering GFR (see next paragraph). The intracellular event leading to mesangial cell contraction by Ang II is an increase in cytosolic calcium concentration resulting from activation of phospholipase C and release of calcium from intracellular stores, as also occurs in vascular smooth muscle. Ang II receptors have also been identified in various regions of the tubule, with greatest binding capacity in the proximal convolution. However, these receptors appear to differ from those in glomerular mesangium with respect to binding of Ang III, affinity for Ang II, regulatory response to variations in sodium intake, and intracellular events activated by Ang II (reviewed in Reference 55). Although functional studies indicate an action of Ang II on the efferent arteriole, receptors in this vessel have not been characterized, nor have those in the inner medulla.

The response of GFR to Ang II is the result of at least three separate actions of the peptide on the determinants of GFR. Efferent arteriolar constriction reduces glomerular plasma flow, a change leading to a decrease in GFR. At the same time, efferent constriction raises hydrostatic pressure in the glomerular capillary, enhancing filtration. Ang II also decreases the glomerular ultrafiltration coefficient (Kf) through mesangial cell contraction, a change again associated with a reduction in GFR. Finally, chronic Ang II infusion also diminished prostaglandin-mediated cAMP production of mesangial cells, an effect that also serves to promote contraction of these cells. The net effect on overall GFR is therefore determined by the balance of these individual actions. Alterations in tubular function appear confined largely to the proximal convolution, although effects on distal nephron absorption have been suggested (reviewed in Reference 59). In the proximal tubule, a bimodal action of Ang II has been observed: At low concentrations, sodium reabsorption is stimulated, whereas higher concentrations inhibit it. This effect on reabsorption has recently been shown by Liu and Cogan to be most pronounced in the S1 segment and to involve chiefly the reabsorption of sodium bicarbonate (Figure 1). In accord with this finding, the binding capacity for Ang II was greatest in the overall proximal tubule compared with other nephron segments, and within the proximal convolution, binding was 10-fold greater in S1 compared with S2 segments.

![Figure 1. Bicarbonate reabsorption rates from early and late segments of rat proximal convoluted tubules (PCT) studied by in vivo microperfusion. Intravenous infusion of Ang II (O, •), 20 µg/kg/min, increased bicarbonate reabsorption, while saralasin (SAR; O, •), 1 µg/kg/min, decreased it. These effects were much more pronounced in early (S1) than in late (S2) proximal convoluted segments. No change in reabsorption occurred in time control (CON) experiments in either segment (O, •). Reprinted from Liu and Cogan with permission of the American Society for Clinical Investigation.](http://hyper.ahajournals.org/doi/figure/1)
Given this panoply of renal actions, numerous physiological and pathophysiological roles in the regulation of sodium excretion have been advanced for Ang II. A fundamental, and largely unresolved, issue is the pathway by which Ang II gains access to its renal receptors. The enzyme renin is secreted into renal venous blood, and subsequent generation of Ang II in the pulmonary circulation means that arterial flow to all organs, including the kidney, delivers this peptide, which could explain its vascular, glomerular, and tubular actions. On the other hand, all the components of the renin-angiotensin system are found within the kidney itself, causing a number of groups to argue that intrarenal Ang II mediates tubuloglomerular feedback and perhaps other physiological events. This latter possibility is further supported by the recent observation that rat renal cortical, but not hepatic, angiotensinogen messenger RNA increased 3.5-fold on a low sodium diet, suggesting physiological regulation of the intrarenal renin-angiotensin system. Much of the information concerning the renal actions of Ang II has come from studies of infused peptide on the one hand or observations during blockade of endogenous peptide by receptor blockers or converting enzyme inhibitors on the other. These approaches do not allow a clear definition of the roles of intrarenal and extrarenal Ang II in its actions, since these maneuvers will influence local renal as well as systemic Ang II levels.

The predominant action of Ang II on the efferent arteriole suggests that it may function to preserve GFR during states of renal hyperperfusion by increasing glomerular capillary hydrostatic pressure to offset the decrease in glomerular plasma flow. Although the tubular action of Ang II to stimulate proximal bicarbonate reabsorption may have an important impact on renal acid excretion, it is likely that the most important consequence of this proximal action is to influence sodium chloride delivery to the distal nephron by altering the proximal chloride concentration profile in luminal fluid that drives passive sodium chloride reabsorption. It also seems evident that Ang II is one among numerous redundant and offsetting contributors to the regulation of sodium excretion. The contrasts between the actions of ANF and Ang II on their renal and extrarenal targets are obvious, and hormone action at these sites is mediated by the V1 receptor. The V2 receptor mediates the vasoconstrictor and prostaglandin synthesis stimulating actions of the peptide, whereas the V3 receptor is responsible for its diuretic effect. AVP induces contraction of glomerular mesangial cells in vitro in association with a rise in intracellular free calcium concentration that is blocked by a specific V1 receptor antagonist. In vivo, AVP reduces the Kf of the glomerular capillary, leading to the possibility that it could be another humoral regulator of GFR. The V1 receptor also is responsible for stimulation of prostaglandin synthesis in both mesangial cell and renal tubule cells; this action modulates the glomerular effect of AVP by opposing AVP-induced mesangial contraction and the tubular effect by counteracting the increase in water permeability of the collecting duct caused by the peptide.

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Arginine vasopressin (AVP) also has multiple renal and extrarenal actions. Regulation of its secretion, the biochemistry of its actions in various cells, and its physiological effects have been the subjects of numerous detailed reviews. Although this peptide is critical in the regulation of water balance by increasing the water permeability of the distal nephron to permit the elaboration of a concentrated urine, and also plays a role in distal nephron potassium secretion and bicarbonate reabsorption, we shall limit our discussion to brief considerations of AVP's receptors and the peptide's effects on GFR and sodium excretion.

Two classes of vasopressin receptors have been identified. V1 receptors are found in glomerular mesangium, renal vasculature, and medullary interstitial cells, and hormone action at these sites is mediated by an increase in intracellular calcium. V2 receptors are located along the renal tubule, notably the thick ascending limb of Henle's loop and the cortical and medullary collecting duct; hormone action in these regions is linked to activation of adenylate cyclase and the generation of cAMP. The basis for this discrimination of AVP receptors is functional as well as biochemical; the V1 receptor mediates the vasoconstrictor and prostaglandin synthesis stimulating actions of the peptide, whereas the V2 receptor is responsible for its diuretic effects. AVP induces contraction of glomerular mesangial cells in vitro in association with a rise in intracellular free calcium concentration that is blocked by a specific V1 receptor antagonist. In vivo, AVP reduces the Kf of the glomerular capillary, leading to the possibility that it could be another humoral regulator of GFR. The V1 receptor also is responsible for stimulation of prostaglandin synthesis in both mesangial cell and renal tubule cells; this action modulates the glomerular effect of AVP by opposing AVP-induced mesangial contraction and the tubular effect by counteracting the increase in water permeability of the collecting duct caused by the peptide.

The effect of AVP on sodium excretion has remained controversial. Infusion studies have generally indicated that AVP produces a natriuresis, but usually in the setting of an increase in blood pressure, GFR, or both (reviewed in Reference 87). A specific natriuretic action of the hormone has been related to its diuretic effect: In hydrated, conscious dogs excreting a dilute urine, AVP infusion increased sodium excretion as water diuresis converted to antiurea. Natriuresis was also observed when water diuresis was terminated by stimulation of endogenous AVP release by nonhypotensive hemorrhage, when hemodynamic changes were clearly inadequate to account for the increase in sodium excretion. Subsequently, this natriuretic property of AVP was related to its activation of V1 receptors, since infusion of the synthetic analogue 1-deamino-8-D-arginine vasopressin, which possesses marked antidiuretic potency but is nearly devoid of vasopressor activity, produced equivalently concentrated urine but no natriuresis. This relation was further strengthened by the observation that AVP infusions did not increase sodium excretion in animals with inhibited prostaglandin synthesis. Thus, the par-
Tercipitation of AVP in the regulation of sodium excretion may be through activation of renal \( V_1 \) receptors to stimulate prostaglandin synthesis; the prostaglandins may then act locally to decrease tubular sodium reabsorption and produce natriuresis.91 On the other hand, in vitro studies have convincingly shown an ability of AVP to stimulate sodium chloride reabsorption from medullary thick limb of the mouse and rat.92,93 This action facilitates the excretion of a concentrated urine by increasing the hypertonicity of the medullary interstitium,94 but it is clearly antinatriuretic. The recent availability of analogues with agonist and antagonist properties for the \( V_1 \) receptor should permit a more precise definition of the intrarenal mechanism(s) by which AVP influences sodium excretion.77

The role of AVP in physiological alterations of fluid balance and in pathophysiological states has been a subject of keen interest. Animals undergoing dehydration exhibit an increased rate of sodium excretion, and AVP may participate in this response as a means of protecting against hyperosmolality as dehydration develops.95 AVP has also been suggested to mediate the natriuresis resulting from cerebral ventriculocisternal perfusion with hypertonic sodium chloride artificial cerebrospinal fluid,96 although the Brattleboro rat exhibits a similar response despite congenital absence of AVP.97 Finally, a growing literature attests to the interest in determining if AVP plays a major role in the development and maintenance of experimental and clinical hypertension. At present, no consensus has emerged about this possibility, although there have been numerous intriguing observations.98

Anterior Pituitary Peptides

Many peptides synthesized and secreted by the anterior pituitary have effects on kidney function. Earlier studies for the most part demonstrated these effects through hormone infusion experiments in normal or hypophysectomized animals, and conclusions were necessarily limited. More recent techniques, however, have permitted more rigorous definitions of the effects of some of these peptides on renal function.

Peptides Derived from Pro-opiomelanocortin

Pro-opiomelanocortin (POMC) is a large precursor protein found in pituitary corticotrophs and in other brain regions.99 Its structure is depicted schematically in Figure 2. It gives rise to a number of peptides in the peripheral circulation, the most prominent of which is adrenocorticotropic hormone (ACTH), but including \( \beta \)-endorphin and \( \alpha \)-melanocyte stimulating hormone (MSH), \( \beta \)-MSH, and \( \gamma \)-MSH; the initial N-terminal sequence bears structural similarity to calcitonin. ACTH influences renal function only indirectly through its regulation of adrenal steroid synthesis, and \( \beta \)-endorphin has no known direct renal functional ef-

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**Figure 2.** A. Schematic representation of the pro-opiomelanocortin molecule indicating the sites of dibasic amino acid pairs that represent potential sites for posttranslational processing. Also shown are the derived peptides. (Reprinted from Krieger DT, Martin JB. Brain peptides. N Engl J Med 1981;304:876–885 with permission of The New England Journal of Medicine.) B. Structure of melanocyte stimulating hormone (MSH) peptides. At least three species of \( \gamma \)-MSH exist: \( \gamma_1 \)-MSH is a des-Gly\(_{12} \), C-terminal amide derivative of \( \gamma_2 \)-MSH, whereas \( \gamma_2 \)-MSH is a 15 amino acid C-terminal extension of \( \gamma_1 \)-MSH in the rat because of a proline substitution at position 13. Close homology within a core heptapeptide sequence exists for all MSH peptides, as indicated by the solid and dotted lines. LPH = lipotropin; CLIP = corticotropinlike intermediate peptide.
fect, although it stimulates the enzyme ornithine decarboxylase. However, MSH peptides of α, β, and γ primary structure all exhibit natriuretic activity. These peptides exist as free peptides in pituitary and plasma; they bear considerable amino acid homology among themselves and are flanked on the parent POMC molecule by pairs of dibasic amino acids, which may serve as proteolytic cleavage sites to yield the component peptides (see Figure 2). At least three species of γ-MSH exist (termed γ1-MSH, γ2-MSH, and γ3-MSH; see Figure 2; they differ in total length and in amida
tion at the carboxy terminus. Since the POMC mole
cule has been strongly conserved across species lines, the possibility seems real that its component peptides serve important biological functions. Certain POMC peptides, including those related to γ-MSH, possess potent aldosterone-stimulating capability in vivo and in vitro, and high affinity binding sites for Lys-γ-MSH have been demonstrated in rat adrenal cortical tissue. Thus, MSH peptides may have a role in the regulation of aldosterone secretion.

All three classes of MSH peptides cause natriuresis when injected intraperitoneally or given intravenously, although the presence of specific receptors in renal tissue has not yet been reported, the natriuretic effect at least of γ-MSH seems likely to occur through intrarenal mechanisms, since infusion of a low dose of this peptide directly into a renal artery of anesthetized rats led to ipsilateral natriuresis without any effect on the contralateral kidney (Figure 3). The natriuresis occurs without an increase in blood pressure or whole kidney GFR, suggesting an inhibition of tubular sodium reabsorption. Indirect evidence suggests that the natriuretic action may be related to decreased reab-
sorption in the proximal tubule. Higher doses of this peptide elevate blood pressure through stimulation of sympathetic nervous outflow, apparently mediated by centrally acting vasopressin.

The function of MSH-related peptides in volume homeostasis is not established. The possibility that γ-MSH or a similar peptide could participate in the reflex control of sodium excretion has been suggested on the basis of studies of the natriuresis that occurs from the remaining kidney shortly after acute unilateral nephrectomy (AUN). This maneuver increases sodium excretion within an hour without raising GFR; the natriuresis occurs in the presence of exogenous mineralocorticoid hormone. We suggested that the postnephrectomy natriuresis resulted from a neurocirculatory reflex: AUN causes a transient, immediate increase in arterial pressure, the sensing of which by carotid sinus baroreceptors is key to the natriuresis and constitutes the afferent limb of the reflex. The efferent limb involves the pituitary gland, since the postnephrectomy natriuresis did not occur in hypophysectomized rats, and a relationship to POMC was suggested by the observation that pretreatment of rats with high dose of glucocorticoid, sufficient to suppress the pituitary content of ACTH and β-endorphin, also abolished the natriuresis following AUN. This study also showed that AUN led to an increase in plasma immunoreactiv-
ity to an antibody raised against an epitope on the N-terminal region of POMC immediately adjacent to the γ-MSH sequence, and the increase in immunoreactiv-
ity correlated with the increment in sodium excretion that occurred after AUN. We found that immunoreactive γ-MSH concentration was elevated after AUN compared with values in sham-operated control rats, and the magnitude of this elevation also correlated with the increment in sodium excretion that resulted from AUN. That this elevation was important in the natriuresis was indicated by the effectiveness of antibodies to γ-MSH, given before the acute experiment, in blocking the postnephrectomy natriuresis. In aggregate, these studies suggest the operation of a neurohumoral reflex, activated in response to AUN, that stimulates sodium excretion through increased secretion of a γ-MSH-like peptide from the anterior pituitary. Presumably, such a reflex should be activated in response to other stimuli as well; in this regard, we have shown in preliminary studies that traction on a carotid artery, known to produce natriuresis, is accompanied by an increase in plasma immunoreactive γ-MSH concentration and that the
traction-induced natriuresis again is abolished in the presence of anti-γ-MSH antiserum. Thus, this reflex system may have a broader role that includes regulation of sodium excretion in response to carotid sinus baroreceptor input and, possibly, to other afferent stimuli.

At present, there is no information concerning the participation of this γ-MSH system in chronic alterations in sodium balance or in pathophysiological states. Circumstantial reasoning has led to the suggestion that it could serve as the natriuretic hormone incriminated in the pathogenesis of hypertension and could be the mediator of central nervous system natriuresis in response to sodium loads. We must await further studies to evaluate these and other possibilities.

Growth Hormone and Prolactin

Specific binding sites for the anterior pituitary peptides growth hormone (GH) and prolactin have been demonstrated in membrane fractions of whole kidney homogenates in several species, and complex interactions in receptor regulation exist between the two hormones. Nevertheless, their roles, if any, in the regulation of renal function have remained ambiguous. GH may be necessary for maintenance of baseline GFR and renal blood flow: Hypophysectomized animals and humans have reduced hemodynamics, whereas GH administration inactivates the hormone's effects on cAMP and intracellular calcium. This concept has reappeared recently in the kidney. Recent interest has centered on the possibility that GH could participate in the increased GFR observed after a protein meal or following amino acid infusions. In four GH-deficient adults, GFR failed to increase after a large protein meal compared with the rise seen in four normal subjects. However, plasma GH concentration did not increase in three of the four normal subjects after feeding, indicating that some abnormality other than impaired GH secretion accounted for the lack of effect of protein feeding in the GH-deficient subjects. In another study, GH stimulation was achieved by arginine infusion in normal and GH-deficient subjects. Both GFR and renal plasma flow increased in each group, but plasma GH concentration rose only in the normal subjects. These studies consequently suggest that factors other than increased GH secretion mediate the rise in renal hemodynamics seen after protein feeding or amino acid infusion. One such factor could be elevated plasma glucagon concentration, and this possibility will be discussed. Moreover, a recent preliminary report indicates that GH effects on GFR may be mediated through stimulation of insulinlike growth factor I, which then causes GFR to rise. It seems certain that future studies will clarify these interesting relationships.

The role of prolactin in the regulation of renal hemodynamics and sodium excretion also remains ambiguous. Data for prolactin receptors are strongest for amphibian tissue, but localization of putative receptors to discrete nephron segments and identification of an intracellular second messenger are not available. Binding studies have identified receptors in membrane fractions of tissue homogenates where they could serve a function in metabolic clearance rather than endocrine stimulation. Functional consequences of prolactin administration have been clouded by pharmacological doses of impure preparations. Effects of the peptide to increase renal hemodynamics, impair volume expansion natriuresis, and act as an antidiuretic agent have been reported in some animal studies but not observed in humans. It would seem that the renal actions, if any, of prolactin are minor at best.

Calcium-Regulating Peptides

Parathyroid Hormone

Parathyroid hormone (PTH) exerts a number of renal actions related to the regulation of normal calcium and phosphorus balance; these have been extensively reviewed and will not be further discussed here. PTH administration is known to influence the glomerular capillary and has been suggested to play a role in the regulation of urinary sodium and net acid excretion. The latter has been recently reviewed, we shall consider only PTH's effect on GFR and on sodium excretion. Receptors for PTH have been recognized in plasma membrane fractions of kidney homogenates in numerous species, and the nephron loci have been identified by means of specific hormone-sensitive adenylate cyclase stimulation. PTH-responsive adenylate cyclase and cAMP generation have been demonstrated in rat and human glomeruli and various tubular segments, including proximal convolution, cortical thick ascending limb, and distal convolution and connecting tubule, although species variations exist with respect to these last two segments. Hormone action has generally been attributed to the consequences of cAMP stimulation; numerous in vivo and in vitro studies show that the glomerular and proximal tubular actions of the peptide are mimicked by cAMP analogues, and PTH administration increases not only renal tissue cAMP content but also cAMP in renal vein and urine. Despite the wealth of such data, however, evidence has also accrued to suggest that the hypocalciuric and phosphaturic actions of PTH may be mediated by a different second messenger, an increase in intracellular calcium. This concept has received experimental support: In primary cultures of canine proximal tubule cells, physiological concentrations of PTH caused an increase in intracellular free calcium concentration in a manner distinguished from the hormone's effects on cAMP production. Future work should clarify the nature of the interactions of these two intracellular messengers in producing the actions of PTH on tubular transport and metabolism. Clinical states of hyperparathyroidism have long been associated with reduced GFR, and the effects of the peptide on the determinants of single nephron GFR have been determined in rat and dog. Single nephron GFR was the same in thyroparathyroidectomized...
animals. However, the determinants were markedly altered: $K_w$ was reduced in PTH-replaced thyroparathyroidectomized rats and dogs by 25 to 50%; constancy of single nephron GFR was achieved by offsetting increases in effective filtration pressure. These results suggest that PTH may play a role in the physiological regulation of GFR, presumably through its activation of glomerular adenylate cyclase and cAMP production. The effect of PTH on overall sodium excretion is complex. PTH infusions decrease proximal sodium bicarbonate reabsorption by inhibiting the sodium-proton antiporter in the brush border membrane. The peptide also decreases bicarbonate reabsorption from rat isolated perfused medullary thick ascending limb. However, any increase in sodium excretion that occurs is minimal, indicating reabsorption of proximally rejected filtrate by more distal nephron segments. A role for PTH in the decrease in proximal reabsorption occurring with volume expansion has been advocated: Infusion of hyperoncotic albumin caused plasma volume expansion and decreased proximal reabsorption; it also resulted in a decrease in plasma ionized calcium concentration and an increase in serum PTH. If the albumin was preincubated with calcium, or infused into thyroparathyroidectomized animals, no decrease in proximal reabsorption occurred despite similar degrees of plasma volume expansion. A similar mechanism has been advanced to account for the natriuresis following colloid-free expansion, which also decreases plasma ionized calcium concentration and increases nephrogenous cAMP; the decrease in proximal reabsorption after volume expansion was less in thyroparathyroidectomized rats than in normal controls. Although these studies are of interest, it is difficult to assign a major role of PTH in the regulation of sodium excretion and extracellular volume. As mentioned earlier, the volume expansion protocols employed in these studies are unphysiological perturbations of volume control systems, and a role for PTH in other circumstances of altered sodium homeostasis has not been identified.

**Calcitonin**

Receptors for calcitonin in the kidney have also been identified and in the distal nephron are linked to adenylate cyclase in the thick ascending limb of Henle's loop and distal convoluted tubule. No receptors exist in glomeruli or proximal convoluted tubule, and no effect of the peptide on GFR has been reported. Its major tubular actions appear to be promotion of phosphaturia and, in the rabbit, stimulation of calcium reabsorption in the medullary thick limb. Acutely, calcitonin administration causes natriuresis in a variety of species including humans, but this effect in humans is transient. At present there is no reason to invoke a role for calcitonin in volume homeostasis.

**Glucoregulatory Hormones**

Renal actions of both insulin and glucagon have been clearly demonstrated, yet ambiguity persists concerning the importance of these actions in the regulation of extracellular fluid volume.

**Insulin**

Although receptors for insulin have been identified in the glomerulus and effects of the peptide observed in both the proximal and distal nephron, the importance of these findings has remained unclear. The mechanism of action of insulin does not appear to involve the classic second messengers discussed earlier. Since the kidneys account for the degradation of a considerable fraction of circulating insulin, binding and uptake could represent catabolism of the peptide rather than initiation of a hormone-stimulated effect on the cell. These comments notwithstanding, it seems clear that insulin decreases urinary sodium excretion acutely. Micro puncture studies in the dog indicate that this effect occurs despite a decrease in proximal tubular reabsorption, by inference suggesting an appreciable ability of insulin to stimulate sodium transport in the distal nephron. However, a more recent study has convincingly shown that insulin stimulates fluid reabsorption from isolated perfused rabbit proximal convoluted segments. If this is true in the intact animal, then the decrease in sodium excretion caused by insulin may be adequately explained by increased reabsorption in the proximal tubule. The transport-related effects of insulin may be due to its inhibition of renal cortical gluconeogenesis.

Another unanswered question concerns the possibility that somatomedins (insulinlike growth factors I and II) could mediate some of the renal actions attributed to insulin. Insulinlike growth factors I and II bear close structural similarity to insulin, and their actions are also similar in many target tissues. Insulinlike growth factor I has recently been implicated as the mediator of GH-related increases in GFR and renal plasma flow, and further studies will be needed to clarify the effects of these peptides as well as insulin itself on renal hemodynamics and sodium excretion.

**Glucagon**

Glucagon-responsive adenylate cyclase and cAMP generation have been observed in the thick ascending limb of Henle's loop and early distal convoluted tubule. The tubular actions of this peptide in these segments is chiefly to stimulate calcium and magnesium reabsorption, with little if any effect on sodium handling. A recent study has shown that it inhibits bicarbonate reabsorption in isolated perfused rat medullary thick ascending limb. The peptide also has effects on renal and extrarenal phosphate metabolism.

Major interest surrounds the possible role of glucagon in the regulation of renal hemodynamics. Infusions of the peptide cause increases in GFR, and the argument has been advanced that the stimulation of glucagon secretion postprandially or by amino acid infusion mediates the increase in GFR observed in these settings. However, infusion studies have by and large used doses that achieve pharmacological
concentrations of the peptide in plasma, and data on the intrarenal mechanisms by which GFR is increased are not available. Considerable evidence also suggests that glucagon's effects on renal hemodynamics may be indirect.158,159 Infusion of a low dose of glucagon into the portal vein increased GFR and renal blood flow in the dog, whereas the same dose in the renal artery was without effect.159 and intraportal infusion of the peptide also exerted a more profound effect on renal hemodynamics than infusion into a peripheral vein.160 These studies suggest that glucagon's effects on GFR are indirectly mediated through the liver. Regardless of the mechanism, the increase in GFR results in an increase in sodium excretion.31

Gastrointestinal Peptides

Numerous peptides with interesting biological properties have been identified in brain and gastrointestinal tract. In the brain, they are thought to serve as neurotransmitters or neuromodulators, while in the gastrointestinal tract they may act as neurotransmitters, circulating hormones, or both.161-163 Some of these peptides have been shown to have direct renal effects, although their importance awaits elucidation. Secretin shares structural similarity with vasoactive intestinal polypeptide, and both are natriuretic when infused directly into the renal artery.164,165 However, they produce different effects on renal hemodynamics, secretin being a vasodilator while vasoactive intestinal polypeptide constricts the renal vasculature. Somatostatin has a widespread effect of inhibiting release of many peptide hormones, but it may also have a direct renal action independent of inhibition of secretion of other renally acting hormones. It stimulates renal gluconeogenesis, a metabolic effect that could be accompanied by changes in tubular transport166; in addition, it antagonizes the effect of AVP on urinary concentrating ability, apparently by inhibiting AVP-induced increases in cAMP production.167 Neurotensin is another peptide that may have a renal action: When infused into conscious rabbits, it was antinatriuretic.168 In view of the structural similarities among many of these gastrointestinal peptides161,162 and their presence in plasma, it seems likely that others will subsequently be shown to have effects on renal function. The importance of such observations must be questioned, since these peptides function largely as neurotransmitters or in a paracrine manner and may not have a role outside the gastrointestinal tract. On the other hand, changes in circulating levels of gut hormones in response to feeding may participate in the postprandial response of the kidney.

Integration of Hormonal Effects

The hormonal controls of GFR and sodium excretion are regulated in a complex manner, with different peptides exerting competing or offsetting effects. The net result is a remarkable collection of redundant and overlapping systems, which in aggregate serve as checks and balances to regulate these vital aspects of the body economy. Although integration occurs at a variety of levels, we call attention to four levels of integration that are evident from the material covered in this review.

First, a peptide may have multiple effects that counterbalance each other to result in only a small net change. For example, vasoconstrictor hormones such as Ang II and AVP constrict the efferent arteriole of the glomerulus to raise filtration pressure while at the same time decreasing Kf. As a result, the net effect on GFR may be minimal. AVP increases the water permeability of the collecting duct while at the same time stimulating the production of prostaglandins that oppose its hydroosmotic actions. y-MSH decreases tubular sodium reabsorption on the one hand, but it may stimulate aldosterone secretion on the other and thereby promote sodium reabsorption. Second, some peptides oppose the actions of others. Most obvious perhaps is the almost exact balance between the actions of ANF and Ang II on blood vessels, GFR, and sodium excretion, not to mention aldosterone synthesis. Other examples of hormonal antagonism are likely to emerge with further study.

Third, within the nephron itself resides the capacity to buffer abrupt changes in function. Intrinsic to the nephron is the ability to couple reabsorption to load. Large increases in GFR are accompanied by increases in proximal tubular reabsorption, so that the volume of fluid delivered out of the proximal tubule is less than the full increment in GFR—so-called glomerulotubular balance. Similarly, the distal nephron segments can absorb large fractions of fluid delivered out of the proximal tubule, so that changes in sodium excretion are only modest. To some extent these adjustments may be mediated by hormones: The localization of receptors to discrete nephron segments, coupled with their known actions in these segments, suggests that this may be so, although further research is required to establish this more firmly.

Finally, integration also occurs in the regulation of the secretion of many of these peptides, an area not covered by this review. Ang II stimulates AVP release, while AVP suppresses renin secretion by the kidneys. A growing literature attests to an ability of ANF to inhibit AVP secretion, possibly through a central action,169 and other evidence raises the possibility of neural and humoral regulation of ANF secretion.53 The effects of y-MSH on blood pressure and peripheral resistance appear mediated by centrally acting AVP.109 It seems likely that multiple interactions among these peptide hormones occur at both the secretory and target organ levels.

The integrated renal response in the intact animal is the result of all these interactions plus the effects of neural and nonpeptide humoral inputs. Recent research advances have allowed the design of experiments demonstrating the specific actions of peptides in discrete nephron segments, as well as the intracellular events mediating hormone action, so that we have gained a much more detailed analysis of the control of GFR and tubular sodium reabsorption. With this information, we can expect even greater insight into the
integrated control of extracellular fluid volume in the intact organism.

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