Pathophysiology of Renal Concentrating Defects

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ABSTRACT

A number of advances which took place during the last decade have increased our understanding of the physiology and pathophysiology of urinary concentrating defects. The development of a highly sensitive radioimmunoassay for plasma vasopressin concentration has shed new light on vasopressin control mechanisms. The cellular action of vasopressin in biological membranes has been studied by various techniques. The role of adenylate cyclase, cyclic adenosine monophosphate (cAMP), microtubules, and microfilaments, in the response of vasopressin-sensitive membranes is now partially understood. New models of countercurrent multiplication systems, in which urea plays a prominent role, offer a better explanation of certain experimental facts. Such advances have permitted a better understanding of clinical conditions characterized by concentrating defects, including hyperkalemia, hypercalcemia, parenchymal renal disease, obstructive renal disease, and polyuria induced by certain drugs.

Introduction

Our understanding of renal concentrating defects has gained considerably from the many advances in the physiology of urinary concentration that took place during the last decade. It is appropriate to review briefly the basic concepts in areas such as control of vasopressin secretion, cellular action of vasopressin, and the new countercurrent models.

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laboratories* were successful in developing a highly sensitive radioimmunoassay\textsuperscript{24} that made possible the correlation of plasma VP concentrations with a variety of stimuli.

Robertson demonstrated an excellent correlation between POsm and plasma VP concentration \((\text{VP} = 0.38 \times [\text{POsm}-280]^{0.25})\). This equation indicates that at 280 mOsm per kg, VP begins to be detected in the blood and that for every mOsm per kg, plasma VP increases approximately 0.38 pg per ml.

The same authors\textsuperscript{25} have measured plasma VP concentration and urinary osmolality (UOsm) in a group of healthy adults. A correlation was found described by the equation, \(\text{UOsm} = 250 \times (\text{VP}-0.25)\), indicating that for every pg per ml of increase in plasma VP, urine concentration rises approximately 200 mOsm per kg. This is consistent with the observation that many individuals achieve maximal urinary concentrations at plasma VP concentrations of about 5 pg per ml. Because of the exquisite sensitivity of the response, very small changes in POsm result in large variations in UOsm. From the equations of Robertson, a change of one mOsm per kg in POsm results in a mean change of 95 mOsm per kg in UOsm.

Vernay had concluded, from his original studies, that the hypothalamic osmoreceptors responded with VP release to an increase in osmolality, regardless of the nature of the solute. However, it is now recognized that the VP response to solutes other than sodium chloride (NaCl) may be quite different. In general, VP release seems to depend, for reasons still unclear, on the facility with which the solute crosses the blood-brain barrier. The response to mannitol and NaCl are essentially identical. Urea, which is very difusible across cell membranes, has only a slight effect whereas glucose paradoxically depresses rather than stimulates VP release, at least under certain experimental conditions.\textsuperscript{25}

The importance of non-osmotic stimulatory factors has also been clarified. Hypovolemia and hypotension can stimulate the secretion of VP, even to the point of overriding the osmotic stimulus. Robertson and Athar showed in man that variations in volume changed the threshold but not the slope of the POsm-VP regression curve. Hypovolemia lowers the threshold and expansion with saline increases it.\textsuperscript{23} These findings are confirmed in rats by entirely different experimental approaches.\textsuperscript{6}

However, small degrees of hypovolemia or hypervolemia do not alter the VP response to osmolality. Removal of small amounts of blood up to nine percent of the total blood volume had no effect on plasma VP in normal volunteers or rats.\textsuperscript{6} However, when 10 to 15 percent of the blood volume is removed, the threshold for VP secretion is lowered.\textsuperscript{6} The result is a new steady state attained at a lower level of osmolality and is manifested as hyponatremia. Whether this is the only or even the major mechanism of hyponatremia in hypovolemic states is not known. The hyponatremia associated with cirrhosis and congestive heart failure may be due in part to the same mechanism. In the elderly, there is an exaggerated response in terms of VP release to increased osmolality, but the response to hypovolemia is decreased.

Hypervolemia and hypertension appear to increase the threshold for VP release.\textsuperscript{20} This effect is not as well established as the opposite effect of hypovolemia but may explain the hypernatremia observed in hyperaldosteronism.\textsuperscript{8}

Vasopressin Action on the Kidney

Significant advances have been made in the understanding of the mechanism of
action of VP on the renal tubular epithelium. VP binds reversibly to receptors located on the basolateral surface of the luminal epithelia in distal and collecting tubules. The saturation of binding sites with VP is a function of VP concentration in plasma. Thus, Bockaert\(^1\) found that the binding sites become saturated when VP concentration is between $10^{-7}$ and $10^{-10} \text{ M}$; as the concentration falls, the hormone leaves receptor sites. At $5 \times 10^{-10} \text{ M}$, the receptors are essentially hormone-free.

Vasopressin enhances osmotic flow more than diffusion of water. This observation led to a model consisting of a diffusion barrier and a barrier with "pores" presumably enlarged by VP. This model has been challenged because it fails to take into account the "unstirred layers" effect. This effect means, in essence, that layers of unstirred water surrounding the membrane can retard the diffusion process much more than the membrane itself. Recognition of this effect explains the low rate of water diffusion and eliminates the need for a "pore" theory. At present, it appears that the movement of water in response to VP is mostly diffusional and that large "pores" or channels are not a theoretical necessity.

The mechanism whereby VP enhances water diffusion is still unclear. Whereas VP binds to the peritubular membrane, it increases the permeability of the luminal and perhaps the intercellular membranes. Therefore a great deal of work has been devoted to the problem of how the message is transmitted across the cell body. The evidence indicates that VP binds to receptors located mainly in the basal or lateral membranes. These receptors are believed to be closely associated with the enzyme adenylate cyclase. Vasopressin-responsive adenylate cyclase is found in the VP-sensitive membranes of all mammals. In the kidney, the highest concentration of adenylate cyclase is found in the medulla,\(^2\) corresponding to the highest density of collecting ducts.

Many studies have demonstrated a striking relationship between the ability of VP to stimulate adenylate cyclase and the induction of antidiuresis. In animals whose native antidiuretic hormone is 8-arginine-vasopressin, adenylate cyclase is more responsive to that polypeptide; however, in the pig, adenylate cyclase responds more effectively to 8-lysine-vasopressin, which is the natural hormone in that animal.

Activation of adenylate cyclase leads to increased formation of cyclic adenosine monophosphate (cAMP). A good correlation has been found between the dose of VP and the concentration of cAMP in several in vitro preparations of renal medulla.\(^3\) The other important enzyme that affects the concentration of cAMP in the cell, phosphodiesterase, does not seem to be influenced by VP.

A great deal of evidence supports the concept that cAMP is responsible for increased permeability of the luminal membrane to water.\(^4\) Addition of cAMP to appropriate preparations results in effects similar to those of VP.\(^5\) The mechanism by which cAMP enhances permeability to water is under active study. Several hypotheses have been proposed; none of them are confirmed. Strong experimental evidence suggests that cAMP permits the synthesis of a protein kinase which facilitates the formation of a phosphorylated protein which acts on the luminal membrane to increase its permeability to water.

There is strong evidence that the cytoplasmic structures, microtubules and microfilaments, are somehow involved in the action of VP. Microtubules are tubular structures with a diameter of about 250 Å. Toxic substances such as colchicine, which disrupt the microtubular structure, also prevent the response to VP or to cAMP in the toad bladder and in the intact rat kidney.\(^6\) These facts point toward some role of the microtubules in the response to VP, but the nature of that role remains unknown.
The microfilaments are organelles found in many cells, including collecting duct cells, which are composed of a contractile protein similar to muscle actin. They seem to be attached to cell membranes particularly to the membrane in the lateral spaces. The exact role of the microfilaments is unclear; they may widen the lateral spaces, perhaps by their contractile action, facilitating the flow of water through the lateral spaces. The addition of cytochalasin B prevents widening of the lateral spaces; instead, cell swelling, vacuolization, and disruption of microfilaments take place and also interfere with the response to VP or to cAMP. Although these changes in amphibian membranes are accompanied by reduced water flow, cytochalasin B does not impair the antidiuretic effect of VP in rats.

Many other ultrastructural changes induced by VP in the luminal cell membrane have been described. However, the exact meaning of these changes, their relationship to alterations in microtubules and microfilaments and to increased permeability to water remain unclear.

**The Countercurrent Mechanism**

A hyperosmolar environment in the renal medulla is an indispensable element of the concentrating mechanism. It has been known for a number of years that the tonicity of the interstitial fluid increases progressively from cortex to deep medulla, reaching a maximum of about 1400 mOs per kg in the papilla. In the classical countercurrent model, the hyperosmolar milieu results from shift of salt from the thick segment of the ascending limb of Henle’s loop to the interstitium, without simultaneous transfer of water. As a result the fluid in the ascending limb becomes hypotonic and the interstitial fluid hypertonic. The vasa recta were envisioned as countercurrent exchangers which prevented dissipation of the hypertonicity of the interstitium.

Although the classical model greatly facilitated our understanding of the concentrating mechanism, it could not explain several facts. Particularly, it could not explain the genesis of the high osmolality found in the deep medulla and papilla, since these structures are not located in the vicinity of the thick section of the ascending limb. Also, the fluid in the thin ascending limb is hypotonic with relation to the blood in the vasa recta and the fluid in the thin descending limb. However, it is felt that the thin segment does not possess the structural characteristics commonly associated with an epithelium capable of active transport. These observations have not been easy to reconcile.

Kokko and Rector and Stephenson have proposed alternate models. In these models, salt leaves the thick segment of the ascending limb as in the classical model, leaving behind a hypotonic fluid. In the presence of VP, free water moves passively from the distal convoluted tubule and from the cortical and outer medullary segments of the collecting duct, but urea does not. The poor permeability of these segments to urea results in progressive concentration of urea as well as salt in the collecting duct up to the limit between the outer and inner medulla. At this level, however, the inner medullary and papillary collecting duct become permeable to urea which diffuses out and accumulates in the interstitium surrounding these deep structures.

The thin ascending limb in this model has to be impermeable to water, very permeable to NaCl, and only moderately permeable to urea. The concentration of salt inside the thin segment is higher than in the interstitium whose osmolality is, to a large extent, due to urea. In consequence, salt will diffuse out of the thin ascending limb faster than urea can move in, and the fluid will be hypotonic with respect to the surrounding interstitium but, at the same time, relatively richer in urea. In the thick ascending limb, salt is actively removed as the fluid ascends toward the cortex while the urine delivered to the distal convoluted tubule will be hypotonic and
TABLE I
Mechanisms of Concentrating Defects

<table>
<thead>
<tr>
<th>Central Mechanism</th>
<th>Renal Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective vasopressin secretion (central diabetes insipidus)</td>
<td>Reduced number of functioning nephrons.</td>
</tr>
<tr>
<td></td>
<td>Decreased salt delivery to diluting segment</td>
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<tr>
<td></td>
<td>Inhibition of salt transport in diluting segment</td>
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<tr>
<td></td>
<td>A defect in urea recycling mechanism</td>
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<td></td>
<td>Utilization of osmotic gradient</td>
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<td></td>
<td>Reduced blood flow in vasa recta</td>
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<tr>
<td></td>
<td>Lack of response of collecting tubules to vasopressin (nephrogenic diabetes insipidus)</td>
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<tr>
<td></td>
<td>Poor generation of cAMP</td>
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<td></td>
<td>Poor response to cAMP</td>
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From the previous discussion, it follows that the concentrating ability of the kidney can be impaired at many levels (table I). Concentrating defects occur in three general types of disturbances: electrolyte disorders, structural renal disease, and by the action of certain drugs (table II).

Hypokalemia and hypercalcemia have been known for many years to impair concentrating ability. Although several mechanisms are probably involved, the major one seems to be a poor osmotic gradient in the medullary interstitium. In hypokalemic rats, sodium concentration in medulla and papilla is diminished. This may be due to impaired sodium transport in the thick segment in analogy with the transport defect found in other membranes when potassium concentration in the medium is decreased. Some authors have also suggested an impaired response to vasopressin in hypokalemic rats. Whether the concentrating defect is due to hypokalemic or to intracellular potassium depletion is not clear, but clinical studies in patients with surreptitious vomiting seem to implicate depleted intracellular stores rather than low extracellular potassium concentration in the genesis of the defect.

Hypercalcemia also causes a concentrating defect and the mechanism may be multifactorial. In chronic hypercalcemia, tissue calcification affects predominantly the medulla, particularly the ascending limb of Henle's loop and medullary collecting ducts. Disruption of these structures interferes with generation of a high osmotic gradient and, indeed, the content of the medullary interstitium has been found reduced in hypercalcemia. Also, calcium impairs the response of toad bladder to VP. Since there is experimental evidence that calcium impairs the activation of adenylate cyclase by VP and the formation of cAMP in the rat, a defective response of the collecting tubule to alcohol dehydrogenase (ADH) is entirely possible. In addition, the concentrating defect associated with hypercalcemia is often found in patients who already have...
reduced glomerular function. If renal failure has occurred, the isostenuria of chronic renal disease may be a dominant factor.

**Large Water Intake**

It is commonly observed that continuous ingestion of large volumes of water causes a partial loss of concentrating ability. After 16 to 20 hrs of water abstention, a normal individual should have urine concentrated to > 850 mOsm per kg. In psychogenic polydypsia, the urine osmolality may not exceed 450 mOsm per kg. This fact creates a problem in the differential diagnosis of diabetes insipidus and psychogenic polydypsia. The concentrating defect secondary to polydypsia has been interpreted as owing to diminished interstitial tonicity (wash-out of the medulla) by the high urine flow. High urine output, if prolonged, reduces sodium and urea concentrations in the medulla.\(^{15}\) In addition, the activation of adenylate cyclase seems impaired.\(^5\) If polyuria is curtailed by restriction of water intake, the ability to concentrate is regained, while at the same time the responsiveness of adenylate cyclase to VP and the tonicity of the medulla are normalized.\(^5\)

**Nephrogenic Diabetes Insipidus**

In a broad sense, all concentrating defects with normal ADH secretion are forms of nephrogenic diabetes insipidus (NDI). However, the term as used here is restricted to the hereditary defect characterized by poor response of the collecting duct to normal concentrations of VP. It is a rare disease of unknown mechanism. In mice with hereditary NDI, there is a deficit in the activation of adenylate cyclase by VP. It has been postulated that the same mechanism may be present in the human form.\(^8\) Patients with total lack of response to VP are usually male, whereas the incomplete form of the disease has been described only in women. Children born with this defect have constant polyuria and repeated episodes of dehydration and fever which may lead to mental retardation. Management of NDI was most frustrating until the discovery that thiazides and sodium restriction reduce the severity of polyuria in many cases.\(^7\) They do so by inducing a moderate volume contraction. Indomethacin also ameliorates the polyuria by an unknown mechanism.

**Parenchymal Renal Disease**

Patients with chronic renal insufficiency lose their ability to concentrate urine early in the course of the disease. When glomerular filtration rate (GFR) has fallen to about 50 percent of normal (or serum creatinine is > 2.0 µg per dl), there is already a significant concentrating defect. This deficit is not necessarily accompanied by polyuria because of the simultaneous decline in GFR. Later, the ability to dilute is also lost and, eventually, only isostenuric urine can be formed. The defect occurs earlier and is more severe in diseases affecting the medulla such as medullary cystic disease, polycystic kidney, amyloidosis, obstructive nephropathy, and a variety of interstitial diseases.

The mechanism is multiple. Disruption of medullary structures involved in the generation and maintenance of the interstitial osmotic gradient is probably a factor. Cysts in medullary cystic disease and polycystic kidney, papillary necrosis, hydronephrosis and interstitial diseases all affect the anatomical organization of Henle’s loop, vasa recta, and collecting ducts. In addition, osmotic diuresis in the remaining functioning nephrons also impairs the ability to concentrate. In post-obstructive diuresis there is a significant loss of concentrating ability which may or may not become permanent, depending on the duration of obstruction. There is a suggestion that prostaglandins may be in-
involved in the immediate post-obstructive diuresis.

**Drug-Induced Concentrating Defects**

A number of drugs can impair concentration, but the most important ones are lithium and demeclocycline, methoxyflurane, and certain sulfonylureas.

**Lithium**

A significant number of patients receiving therapeutic doses of lithium carbonate develop polyuria and polydypsia.16 A primary stimulation of thirst by lithium has been suggested but the overwhelming evidence points to a renal defect. This form of polyuria is resistant to dehydration and, at least partially, to vasopressin administration, but it responds to treatment with thiazides in a manner analogous to nephrogenic diabetes insipidus.16 Lithium does not interfere with the generation of a high osmotic gradient in the kidney and there is no evidence that lithium inhibits sodium reabsorption in the ascending limb of Henle’s loop. Studies done in Brattleboro rats (rats with congenital absence of ADH) suggest, however, that lithium inhibits sodium reabsorption in the proximal tubule. This could be a contributory factor.

The chief mechanism of lithium-induced concentrating defect seems to be a defect in the response of the collecting duct to vasopressin, probably at two levels, owing to reduced activation of adenylate cyclase by VP and also after formation of cAMP. On the other hand, some patients have shown a partial restoration of concentrating ability with vasopressin, indicating that a defect of ADH release may be partially responsible. The concentrating defect caused by lithium usually disappears within a few weeks after therapy is stopped.

**Demeclocycline**

Most tetracyclines appear to have the potential to cause a minor concentration defect, but demethylchlortetracycline (demeclocycline) is the only member of the group that can produce a profound impairment of renal concentration.26 In fact, this property has been utilized in the treatment of the syndrome of inappropriate ADH secretion. The effect is dose-dependent, begins to be observed at 600 mg per day, and is invariably present at 1200 mg per day.

The defect is not due to impaired formation of an osmotic gradient in the interstitium. Demeclocycline prevents the response of the tubules to VP. Studies done in toad bladders show that, as with lithium, the water flow in response to VP is inhibited. However, in contrast to lithium, the main action of demeclocycline seems to take place after the formation of the cAMP step, although at higher doses formation of cAMP is impaired as well.

**Methoxyflurane**

Many cases of acute renal failure following administration of the anesthetic methoxyflurane have been described.19 In most although not all cases, polyuria was a significant feature; in other cases, polyuria without renal failure has occurred. It has been postulated that renal damage is due to the products of methoxyflurane metabolism, oxalic acid and fluoride. Oxalate has been implicated in oliguric cases and fluoride in the genesis of polyuria. Serum fluoride is found increased in patients who develop polyuria after methoxyflurane. Also, administration of sodium fluoride has caused polyuria in rats and dogs.

**Glyburide**

Glyburide is a relatively new sulfonylurea. In contrast to other sulfonylureas such as chlorpropamide and tolbutamide
which impair free water excretion, glyburide impairs the concentrating ability of the kidney and causes polyuria. The mechanism is almost certainly at the level of the kidney, but it has not been definitely delineated.

References


