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The Vogue in Renal Physiology

A Review Article

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The three main functions of the million and a quarter nephrons in each kidney have been known for well over 50 years:[24] ultrafiltration at the glomerulus, followed by a selective re-absorption from filtrate to blood, and secretion from blood to filtrate, in the convulated tubules. For a considerable time the peculiar morphology of the loop of Henle remained a mystery. As long ago as 1942, Kuhn[64] suggested that the loops and their accompanying blood vessels formed a counter current multiplying system, but the leading nephrologist of that era, Homer Smitth,[101] dismissed the loop as merely a section of the nephron where the tubule fluid became isotonic before entering the distal convolution. It was another nine years before Kuhn[118] could prove his point; indeed, his theory was not generally accepted until 1960.

The loop of Henle has two functions: the inner papillary segment actively transports sodium into the interstitial fluid of the papilla to produce a high osmotic gradient that can later be used to concentrate the urine by osmotic absorption of water from the collecting ducts and ducts of Bellini. The second function of the loop is to dilute the urine by continuing to absorb sodium from the tubular fluid in the cortical segment, so that only water remains. These two aspects of the loop's activity can be estimated from the T/cw and the Cw,[97, 101] the free water re-absorption and clearance respectively. The T/cw is a measure of the kidney's power to concentrate the urine during an osmotic diuresis whereas the Cw is the rate at which the kidney can excrete water, in excess of solute, during a water diuresis.

$T/cw = Cosm - V$; $Cw = V - Cosm$.

$Cosm = \frac{V\,[Osm]u}{[Osm]p}$; V = rate of urine flow [Osm]p [Osm]u = osmolality of plasma and urine respectively.

How the counter current multiplier sets up the osmotic gradient and concentrates the urine is now clearly understood; it is no longer a subject for argument.[48, 49, 60] More recently, interest has shifted to another peculiarity of the kidney's micro-anatomy: the two populations of nephrons. In man only 15 per cent. of the nephrons have the long thin segments that are essential if the loops of Henle are to reach down into the medulla.[87] The remaining 85 per cent. have very short thin segments, the descending thick limb (straight part of the proximal tubule) merging, almost at once, with the ascending thick limb (straight part of the distal tubule). Strictly speaking, there are not two entirely distinct populations: there is a gradual transition from the subcapsular to the juxta-medullary nephrons, the loops developing progressively longer thin segments that dip further into the medulla. There is also a gradation in the size of the glomeruli and in the length of the convoluted tubules: both are larger in the deeper nephrons.[58, 81, 85] The amount of renin in the epithelioid cells of the afferent arteriole in the polar cushion of the juxta-glomerular apparatus steadily decreases from the renal capsule to the cortico-medullary junction.[16] Finally, the two types of nephron differ in their blood supply: the juxta-medullary efferent arterioles form the vasa recta that accompany the loops of Henle into the medulla.[119]

The two varieties of nephron have different functions: only the deep nephrons with long loops can contribute to the counter current multiplier and concentrate the urine, whereas the superficial nephrons produce a dilute urine by removing sodium from the tubular fluid as it passes through their distal segments. Goodyer and Jaeger[47] in 1955 suggested that the conservation of salt by the kidney, which follows haemorrhage, is due to a shift of glomerular filtration to the large juxta-medullary nephrons, where more effective re-absorption could minimise the loss of sodium in the urine. Their idea seems to have been ignored and it was not revived for another 11 years, when Barger[7] proposed that the function of the kidney as a whole could be regulated by shifting glomerular filtration from one group of nephrons to the other. This has

proved to be one of the most exciting and productive ideas in renal physiology and has been extensively developed by the German nephrologists, particularly Thurau.[58, 107, 108] Reduced to its simplest and most extreme form, Barger's theory holds that the kidney comprises two populations of nephrons: cortical nephrons which are active when there is an adequate supply of salt and water, and juxta-medullary nephrons which are only used in an emergency (such as a haemorrhage),[47] when there is a need to conserve either salt or water. The short cortical nephrons are usually preferred because they are more efficient in eliminating waste materials; their short length and small surface area minimise the back-diffusion of filtered or secreted waste matter into the bloodstream. Urea, for example, is excreted by filtration; urea clearance (Cu) is greater in the cortical nephrons, and if urea formation (U) is constant, the plasma urea concentration [U]pl is lower when filtration is restricted to the superficial glomeruli $[U]pl = \frac{U}{Cu}$. In the same way, there is less back-diffusion of secreted uric acid in the cortical nephrons and a correspondingly higher clearance.

Although the cortical nephrons are more effective for excreting waste metabolites, they suffer from a serious disadvantage: they are unable to retain salt and water. The short length of their tubules is insufficient for complete sodium resorption, and since their loops of Henle do not extend into the medulla they cannot contribute to the counter current system to concentrate the urine. When there is a lack of either salt or water, renal function is transferred to the juxta-medullary nephrons.[58] Inevitably there is a retention of urea and similar waste materials, but the more complete re-absorption of salt and water is, on balance, an advantage. Under conditions of stress, waste products are allowed to accumulate in the body to obviate the loss of salt and water that would otherwise be associated with their more complete elimination.

The interesting question is the mechanism that can divert filtration and function from one group of nephrons to the other. Three factors seem to be involved: a hormone, an enzyme and a neurohormone. The hormone, vasopressin, constricts the efferent arteriole of the juxta-medullary glomeruli[39, 40, 109] so that their filtration pressure and filtration rate are increased. Since total filtration is unaltered,[107, 108] there must be a reduction in superficial cortical filtration, due perhaps to a constriction of superficial afferent arterioles. The proteolytic enzyme, renin, splits angiotensinogen to produce angiotensin I, which is converted by a plasma enzyme to angiotensin II. Angiotensin II constricts the afferent arterioles of the subcapsular glomeruli so that a greater proportion of the total filtration can occur in the juxta-medullary region.[19] Noradrenaline is the neurohormone released by the sympathetic vasomotor nerves to constrict the cortical arterioles. When the renal vasomotor nerves are stimulated there is an increase in the blood flow through the medulla,[88] suggesting that there is also a dilator component. Histochemistry shows that the vasa recta have a cholinergic innervation,[116, 119] which suggests that these blood vessels are dilated by sympathetic activity.[102]

The following conditions release vasopressin and renin and increase sympathetic vasomotor activity so that filtration and function can be diverted from the superficial to the deep nephrons. The main factor controlling vasopressin secretion is the concentration of sodium[82] in the plasma; it is measured by receptors in the supra-optic nuclei of the anterior hypothalamus[30, 92] and in the liver.[54] A rise in plasma sodium concentration releases vasopressin and diverts renal function to the deep nephrons where water can be re-absorbed more effectively. The second parameter that controls vasopressin is the volume of blood in the circulation. When the volume is reduced there is a fall in blood pressure which reflexly causes vasopressin release. The pressure receptors concerned are mainly in the left atrium,[45, 55, 56, 61, 62, 86, 121] but they can also be found in the arterial side of the circulation, especially in the carotid sinuses.[20, 53, 86, 98]

There is considerable disagreement about the control of renin; the following hypothesis seems to fit the experimental data. The amount of renin *contained* in the afferent arteriole is inversely proportional to the concentration of sodium in the tubular fluid at the macula densa, a group of columnar cells at the origin of the distal convolution, which are connected to the polar cushion by the lacis. When the filtered sodium is reduced by a low filtration pressure or by a low plasma sodium concentration, a greater proportion is absorbed as the filtrate passes through the proximal segment and the loop of Henle.[80] The concentration of sodium at the macula densa is lowered, renin accumulates in the afferent arteriole and produces angiotensin which makes the arteriole contract.[106, 110, 111] Renin is only found in the superficial glomeruli, so that this mechanism will arrest cortical filtration and shift renal function to the deeper salt conserving population of nephrons. In all proba-

bility the reason for the greater superficial renin content is that these glomeruli are further from the renal artery,[85] they have a lower filtration pressure and a lower sodium concentration at the macula densa.

Sympathetic renal vasomotor activity is reciprocally related to baro-receptor activity, particularly from the carotid sinuses[57] and aortic arch. A fall in either mean or pulse pressure leads to the release of noradrenaline in the renal cortex and a shift of function from the cortical to the juxta-medullary nephrons.

Let us consider the change in the kidney that follows a decrease in blood volume due to haemorrhage. There is a reduction in baro-receptor activity leading to a reflex secretion of vasopressin and also to an increase in sympathetic vaso-constrictor activity. The fall in blood pressure and reflex afferent arteriole constriction lowers the filtration pressure, less sodium reaches the macula densa and more renin is produced. All three of these changes summate; they all tend to divert filtration and function to the deep nephrons where the more effective resorption of salt and water can help to restore the blood volume. Conversely, overtransfusion produces the opposite effects so that the superficial cortical nephrons can rid the body of the surplus salt and water.

The effects of a change in the plasma sodium concentration are more complex: a rise in sodium, due to an excessive quantity in the diet, initially stimulates vasopressin secretion; it diverts renal function to the deep nephrons where the counter current system can produce a concentrated urine and restore the plasma osmotic pressure. A delayed effect, coming into play when there is a sustained positive sodium balance, is a decrease in the amount of renin in the superficial glomeruli, their filtration rate is increased so as to excrete the excessive quantity of salt in the urine.[122] The opposite changes ensure when the plasma sodium concentration is reduced by a salt deficient diet. At first vasopressin secretion is suppressed, renal function moves to the cortex to produce a dilute urine and restore plasma tonicity. After a time the low concentration of sodium at the macula densa stimulates renin formation in the superficial glomeruli, filtration into the superficial salt losing nephrons stops and renal function is eventually restricted to the salt conserving juxta-glomerular nephrons.

Up to this point I have confined the discussion to the way the kidney can be controlled by diverting blood flow and filtration from one group of glomeruli to another. However, both vasopressin and renin have other important effects on the kidney; indeed, the prime action of vasopressin is not on the renal vasculature, but on the cells lining the collecting ducts. So long as cortisol[51, 63, 103] is in the blood, but no vasopressin, these cells are impervious to water and the kidney excretes a large volume (up to 20 l./day) of dilute urine. Vasopressin activates adenyl cyclase to produce 3′ 5′ cyclic adenosine monophosphate,[83] which makes these cells permeable and allows water[43, 78, 79] to pass down the osmotic gradient from the hypotonic tubular fluid in the cortical collecting ducts[11] to the blood plasma in the peritubular capillary plexuses, and from the isotonic (and eventually hypertonic) tubular fluid in the papillary collecting ducts and ducts of Bellini to the hypertonic plasma in the vasa recta.[48]

Juxta-medullary efferent arteriole constriction by vasopressin has already been described; it reduces the rate of blood flow through the vasa recta and helps to sustain the osmotic gradient in the papilla which might otherwise be flushed away.[33, 67] It is a common mistake to believe that the vasa recta contribute to the counter current multiplier and augment the concentration gradient in the medulla.[8, 67] In fact, they form a counter current exchanger:[12, 48] they cannot increase the gradient, but by their hairpin configuration they minimise its dispersion; they carry away the water osmotically absorbed from the collecting ducts during their passage through the medulla to open as the ducts of Bellini, at the apex of the papillae.

A very important action of vasopressin is to increase urea permeability[59, 70, 79, 95, 112] (and possibly transport) from the collecting duct and allow urea in the urine to equilibrate with urea in the papilla. Consequently the final concentration of the non-urea solutes in the urine can become equal to the concentration of sodium and chloride set up by the multiplier and sequestrated in the papilla. This process allows the kidney to excrete a far more concentrated urine than would otherwise be possible;[93, 94] in effect, urea, which is the main urinary solute, is concentrated without expenditure of energy; the work done by the kidney to conserve water is limited to overcoming the osmotic force due to the non-urea solute.[69] This ability to use urea as a means of concentrating the urine without wasting energy explains how the concentrating power of the kidney is increased by a high protein diet and is reduced by protein starvation.[76] At first sight it might seem that a high protein diet is beneficial, but this is not really the case. A more concentrated

urine is excreted, but only at the expense of a back-diffusion of urea from the urine into the medulla and its unavoidable escape through the vasa recta. On a high protein diet the urine may be more concentrated, but urea clearance is reduced and there is a rise in the plasma urea concentration.

Another renal effect of vasopressin is far more dubious: the stimulation of sodium transport in the loop of Henle to increase the effectiveness of the counter current multiplier[23, 44, 117] and produce a greater osmotic gradient at the papilla. The absorption of sodium is probably increased by vasopressin, but it is more likely to be due to the greater flow through the loops of the deep nephrons rather than to a direct action on sodium transport itself.

Apart from redistributing the blood flow and filtration according to the requirements of the sodium balance, the renin-angiotensin system plays a most important rôle in controlling the secretion of aldosterone. When the concentration of sodium at the macula densa is lowered, renin is synthetised and enters the general circulation, where it produces the angiotensins. Angiotensin II is carried to the zona glomerulosa of the adrenal cortex and converts cholesterol to pregnenolone for aldosterone synthesis.[17] Aldosterone passes to the distal segment of the nephrons, where it induces an enzyme called permease,[32, 73, 89, 99, 100] which allows sodium ions to diffuse through the luminal surface of the distal segment cells from the urine. The sodium ions are, in part, accompanied by chloride ions and the remainder are exchanged for intra-cellular potassium or hydrogen ions. As soon as the sodium enters the cell it is pumped into the bloodstream through the outer and lateral surfaces of the tubule cell.[32, 46] Aldosterone may also enhance sodium absorption at the loop of Henle and in the collecting duct.[4, 65, 104] An increase in potassium or a fall in sodium concentration in the plasma passing through the adrenal cortex can also stimulate aldosterone[13, 52] formation from corticosterone[17] and it may be released by a reflex from circulatory baro-receptors,[2, 9, 10, 34] possibly mediated by a pineal trophic hormone[35, 36] or by corticotrophin.[41, 42, 52] These changes reinforce the renin-angiotensin effect when there is a decrease in plasma sodium concentration, in blood volume or in blood pressure. Ross[91] goes so far as to suggest that the normal physiological rate of aldosterone secretion (30μg/day)[5] is too small to be of any importance in controlling normal renal function, and that it forms an emergency system to combat a severe deficiency of salt or the loss of blood.

Renin has another important function: it controls the glomerulo-tubular balance; it matches the quantity of fluid filtered at the glomerulus with the amount that is re-absorbed in the proximal segment of the nephron so as to ensure that the correct proportion (about 33 per cent. of the filtrate)[11] reaches the distal segment and collecting duct. If for any reason the filtration rate in one particular nephron is increased, the greater rate of flow through the proximal segment and loop will raise the sodium concentration at its macula densa and automatically cause a renin-dependent constriction of the corresponding afferent arteriole, so as to reduce the filtration to the normal level.[106, 110, 111] Conversely, a reduced filtration in an individual nephron decreases the sodium concentration in the tubular fluid at its macula densa and its afferent arteriole relaxes. Britton[15] suggests that a high concentration of sodium at the macula densa, acting through the lacis, causes the local formation of angiotensin in the afferent arteriole and makes it contract.[106] It is only when the sodium concentration remains high over a prolonged period that the synthesis of renin is depressed so that less enters the general circulation. The renin-angiotension system appears to have two distinct functions: an intra-glomerular effect through the local action of angiotensin to control the minute to minute balance between filtration and proximal absorption in individual nephrons, and a long term effect (one hour or more) that depends on the formation and general systemic release of renin, and the redistribution of function between superficial and deep nephrons. A transitory increase in sodium concentration at the macula densa causes the local release of renin and afferent arteriole constriction, whereas a sustained increase in sodium concentration depresses renin synthesis so that eventually the renin in the afferent arteriole is exhausted,[21] the arteriole opens and filtration is increased so that the cortical nephrons of the kidney can excrete the surplus salt. Similarly, a short-term decrease in sodium at the macula densa prevents the local release of renin, the afferent arteriole dilates and the increased filtration restores the quantity of sodium reaching the distal segment. When there is a protracted sodium deficiency at the macula densa, renin synthesis is stimulated, renin accumulates in the afferent arteriole until angiotensin formation closes the arteriole to turn off the superficial salt-losing nephrons. Moreover, the increased synthesis of renin allows the enzyme to spill over into the general circulation, where it produces angiotensin. Angiotensin has three extrarenal actions: the synthesis and release of aldosterone;[52]

arteriolar constriction[1, 29] and a rise in arterial blood pressure; and the stimulation of the thirst centres in the hypothalamus.[37, 38]

In the last few years there has been great interest in the possibility of another hormone to control sodium transport from the proximal segment. There have been numerous reports[22, 27, 28, 74, 75, 90, 96, 123] of a "third factor" that regulates sodium balance; third is used in the sense that filtration and aldosterone are the first and second.[14] In my opinion this is a mistake: I regard renin and angiotensin as being far more important than aldosterone in controlling the body's sodium and that a natriuretic hormone, if indeed it exists, is a very poor fourth in comparison with the other factors. No doubt an increased blood volume can depress sodium transport in the proximal segment, but the main reason is that there is a rise in the peritubular capillary pressure[6, 31, 72, 77] which opposes the movement of the sodium ions from the interstitial fluid and from the inter-cellular channels[25] to the bloodstream. Furthermore, a shift of renal function to the superficial cortical nephrons with their short length and limited absorptive area inevitably reduces proximal sodium transport; there is no need to postulate a change in proximal segment function in individual nephrons.

The possibility of a natriuretic hormone cannot be ruled out entirely; the injection of hypertonic saline into either the third ventricle[3, 68] or the hepatic portal circulation[26, 71] promotes a rapid excretion of sodium in the urine. These two sites[30, 54, 92] are already known to control vasopressin secretion; it is possible that they can also direct the release of a hypothalamic salt-losing hormone, possibly vasotocin.[113]

Medullin is another candidate for the rôle of natriuretic hormone;[114] it is prostaglandin A_2 and appears to be concerned in regulating blood flow and sodium transport in the renal medulla.[66] The loss of its vasodilator effect is probably the explanation for renoprival hypertension.[66] Related prostaglandins (PGA_1, PGE_1) modulate the action of vasopressin to provide a more delicate local control of water resorption.[18, 50, 84, 115, 120]

CONCLUSION

Salt and water balance are controlled by three factors:

(a) Vasopressin is mainly concerned with the conservation of water.

(b) The renin-angiotensin-aldosterone system regulates sodium excretion.

(c) The sympathetic vasomotor nerves can prevent the loss of both sodium and water.

All three factors operate, in part at least, by changing the proportion of superficial cortical to deep juxta-medullary nephrons that are functioning at any one time. A shift of activity from the superficial to the deep nephrons can be a very effective means of avoiding an unnecessary loss of salt and water in the urine.

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