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PROXIMAL TUBULAR REABSORPTION AND ITS REGULATION

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INTRODUCTION

The early micropuncture studies of Walker et al (1) first documented that (*a*) proximal tubular reabsorption is isosmotic, and (*b*) the percentage of the filtered load reabsorbed proximally remains relatively constant, a concept referred to as proximal glomerulotubular (GT) balance. Subsequently, it was shown that proximal GT balance was not fixed but could be reset in response to factors that altered effective arterial blood volume, expansion serving to lower and contraction to enhance the fraction of filtrate reabsorbed proximally (2–5).

The present review examines the anatomic and physiologic features determining proximal reabsorption of sodium and water. Toward this end the anatomy of the proximal tubule is briefly reviewed and the concept of proximal tubule heterogeneity introduced. Next the factors determining reabsorption are divided into two major categories: (*a*) outward transport, comprised of active and passive components and (*b*) passive back-leak of reabsorbate. Net reabsorption thus represents outward transport (active plus passive) minus back-leak. Finally, some remarks are made about the regulatory factors modulating these reabsorptive processes.

PROXIMAL TUBULE HETEROGENEITY

For approximately 70 years it has been known that in most mammals, including man, two nephron populations, termed *superficial* and *deep* (or *juxtamedullary*), exist (6). The proximal tubules of both these nephron populations consist of both a convoluted and straight portion (pars recta). The superficial proximal tubules, though shorter than those of the deep nephrons, have a longer pars recta (6). It also has been shown that a gradual transition of cell types exists along the length of each proximal tubule resulting in the division of the tubule into two or three regions based

on cell size, height of the luminal brush border, histochemical staining, and quantity and type of intracellular organelles (7–12). Thus, it was recognized early that on a structural basis the proximal tubule exhibited two types of structural heterogeneity —intranephron and internephron heterogeneity. However, the functional significance of these structural differences was unknown.

Until recently, virtually all direct information about proximal reabsorption has been obtained from studies of the superficial proximal convolutions, owing to the inaccessibility of both the superficial pars recta and the entire deep proximal tubule to micropuncture. However, early studies of glomerular filtration rate and blood flow suggested, on the basis of highly inferential data, that superficial and deep nephrons may differ in their contribution to total kidney reabsorption (13–19). These early studies stressed that heterogeneity between nephron populations may exist with respect to glomerular filtration rate and renal plasma flow. Under various physiological circumstances, glomerular filtration and consequently the load of salt and water presented to the proximal tubule for reabsorption, may differ between superficial and deep cortical nephrons. Even though these studies served to point out possible intrarenal hemodynamic heterogeneity, they could not directly disclose whether intrinsic differences existed between tubules located in the superficial and deep cortex. *Hemodynamic heterogeneity* is not discussed further in this review. However, it is now evident that *structural heterogeneity* on a tubular level exists both within (intranephron heterogeneity) and between (internephron heterogeneity) nephron populations (20–25).

INTRANEPHRON HETEROGENEITY

In both superficial and deep nephron populations the convoluted portion has transport properties different from those of the straight portion. Kawamura et al (24) and Schafer et al (21) have studied the pars recta utilizing in vitro microperfusion of rabbit nephron segments. The former authors demonstrated, in pars recta from both superficial and deep nephrons, that net volume reabsorption in these segments is about one third to one half that of the convoluted portion. However, these studies were performed with ultrafiltrate of serum as perfusate. When the pars recta was perfused with a solution simulating in vivo conditions (perfusate without glucose and amino acids and with a bicarbonate concentration of 5 mM and a chloride concentration of 140 mM), net reabsorption was reduced to one fourth to one third of the convoluted portion. In addition to net reabsorptive differences, pars recta from both nephron populations exhibited active electrogenic[1] Na transport without

[1]By electrogenic sodium transport we mean the generation of a transepithelial potential difference owing to sodium movement mediated by either of two processes: 1. A rheogenic sodium-potassium exchange pump in the peritubular cell membrane may directly separate charges and generate a potential difference if the coupling is not 1:1. 2. Passive sodium transport may generate a transepithelial potential difference if the movement of sodium is coupled to substances (such as glucose or amino acids) which are actively transported; the mechanism generating the transepithelial potential difference is partial depolarization of the luminal cell membrane by the passive (though coupled) movement of sodium.

the requirement of glucose and amino acids in the perfusate, as opposed to the convoluted portions which have been shown to require these organic solutes to transport Na actively and to develop a lumen negative potential (25, 26). Finally, the superficial pars recta was shown to be more permeable to Cl than to Na as opposed to the superficial convoluted segment, which at least in its early portion is more permeable to sodium (25, 27). In these studies (24) the deep pars recta exhibited greater Na than Cl permeability similar to the subsequent demonstration of greater relative Na permeability in the deep convolution (25). The observations of Kawamura et al (24) with respect to the superficial pars recta confirmed the studies of Shafer et al (21) who had originally examined this segment and found the same reabsorptive and permeability properties.

In addition to these differences between straight and convoluted portions of the proximal tubule, functional differences exist within the superficial proximal convolution. Seely (20) first showed that the transepithelial electrical resistance varied along the length of the rat superficial proximal convolution. He postulated that this variation in resistance could reflect varying electrolyte permeabilities. Recently the superficial proximal convolution of the rabbit, studied in vitro, demonstrated varying relative Na and Cl permeabilities along its length from glomerulus to pars recta (25). In an in vivo micropuncture study, Le Grimellec (23) has demonstrated differences in electrolyte reabsorption between early and late superficial proximal convolutions. Finally, Hamburger et al (22) in another in vitro study have demonstrated differing reabsorptive rates between early and late superficial convolutions. It has thus been clearly demonstrated in both superficial and deep proximal tubules that intranephron functional heterogeneity exists. What role such intranephron heterogeneity plays in functional differences remains to be elucidated.

INTERNEPHRON HETEROGENEITY

The second major type of structural heterogeneity is internephron heterogeneity. Both the convoluted and straight portions of the superficial proximal tubule differ from their respective counterparts in the deep nephron. The superficial convolution has a varying relative Cl to Na permeability along its length, with Na being more permeant in the early portion and Cl in the later. In contrast, the deep convolution has a constant relative Na to Cl permeability along its length, with Na being more permeant (25). Similarly, the superficial pars recta has a greater Cl than Na permeability, while the deep pars recta has a greater Na than Cl permeability (24). When the later portions of the superficial convolution and pars recta are perfused in vitro with solutions simulating in vivo conditions (no glucose, no amino acids, high Cl, low HCO_3) a lumen-positive transepithelial potential is present. Similar experiments with the same segments from deep nephrons result in negative potentials (24, 25). These differences are secondary to the differing relative Na to Cl permeabilities found in these segments. In vivo micropuncture studies have confirmed the role of these permeability differences in the transepithelial potential profile of the superficial proximal tubule (28–30). To date such an in vivo study on deep nephrons has been technically impossible.

Clearly, both inter- and intranephron structural heterogeneity will influence overall proximal tubular activity. In consequence, the behavior of the renal proximal tubule cannot be reliably inferred from data obtained by a study of the convoluted portion of the superficial nephrons alone. Results from micropuncture at the end of the superficial proximal convolution cannot be automatically extrapolated to the pars recta of the same nephron. The volume and composition of fluid delivered to the thin descending limb will be changed by the transport properties of the pars recta. Moreover, even if attention is restricted to the superficial convolution, the results, whether obtained by micropuncture or microperfusion, cannot be generalized to the kidney as a whole, since the transport characteristics of similar segments differ between superficial and deep nephrons. Much of the information concerning the volume and composition of fluid delivered to the loop of Henle has been derived from micropuncture studies of superficial nephrons at the end of the accessible portion of the proximal tubule. Such studies may be seriously incomplete in the sense that (*a*) the reabsorptive activity of the superficial pars recta is not included; (*b*) if different physiologic stimuli are imposed, it cannot be assumed that the reabsorptive activity of the pars recta will change in the same manner as the convoluted portion; (*c*) the reabsorptive behavior of the juxtamedullary nephrons is not taken into account; (*d*) the response of the juxtamedullary proximal tubules to varying physiologic stimuli is uncertain.

OUTWARD TRANSPORT: ACTIVE AND PASSIVE

The proximal tubule is an example of a leaky epithelium. This conclusion is based on three distinct types of experimental evidence: (*a*) electrophysiological studies; (*b*) studies using extracellular markers; and (*c*) electron microscopic studies. All suggest that the proximal tubule contains a low resistance paracellular pathway that plays an important role in salt and water transport.

Windhager, Boulpaep & Giebisch (31) showed in the necturus that the transepithelial electrical resistance of the proximal tubule was at least two orders of magnitude less than the sum of the luminal and peritubular cell membranes in series. The necturus, as opposed to other species, lent itself particularly well to this type of study because its proximal tubular cells are large enough to measure directly both individual cell membrane resistances as well as transepithelial resistance. Boulpaep & Seely (32), employing micropuncture in the autoperfused dog kidney, also showed that the transepithelial resistance of the proximal tubule was quite low. Utilizing salt gradient experiments and monitoring resistance changes during bulk flow induced by osmotic gradients enabled these authors to suggest that a paracellular pathway existed for fluid and electrolyte transport. Boulpaep (33), in a series of electrophysiological and split-drop experiments on the necturus, observed the effects of saline infusion on transepithelial resistance and permeability to NaCl. During inhibition of net reabsorption caused by saline infusion, the transepithelial resistance decreased without a change in peritubular cell membrane resistance while tubular permeability to electrolytes increased. He concluded from these observations that depression of proximal sodium reabsorption during saline infusion occurred via back-leak

through a low resistance paracellular shunt. In addition to these studies on the necturus and dog, Hegel et al (34) have demonstrated a low transepithelial resistance in rat proximal tubule, while Lutz et al (35), utilizing in vitro microperfusion of rabbit proximal tubules, have also demonstrated a low electrical resistance. Finally, Fromter and his collaborators (36), in a series of electrophysiological studies on the rat, have shown that (*a*) rat proximal tubular epithelium has the lowest electrical resistance of any known epithelium; (*b*) the epithelial permeabilities to K, Na, Cl, and HCO_3 are entirely different from the peritubular cell membrane permeabilities; and (*c*) the permeability properties of the epithelium are determined by paracellular channels.

Further support for the concept that a paracellular pathway plays an important role in proximal tubule transport is offered by several studies that have shown, under various physiological conditions, increased tubular permeability to substances normally confined to the extracellular space. Bank et al (37) showed in a micropuncture study on the rat that the inhibition of proximal reabsorption caused by renal vein constriction was associated with an increased permeability to sucrose. Lorentz et al (38) demonstrated increased proximal permeability to mannitol during elevation of ureteral pressure, partial renal venous constriction, and massive saline diuresis. In the proximal tubule of the necturus, Boulpaep (33) observed increased permeability to the extracellular marker, raffinose, during volume expansion with saline. Imai & Kokko (39) showed increased sucrose permeability in the in vitro rabbit tubule when proximal reabsorption was inhibited by hypooncotic peritubular fluid. In addition, Lorentz (40) demonstrated increased proximal permeability to mannitol in rats undergoing infusion of cyclic AMP and dibutyryl cyclic AMP. Finally, Berry & Boulpaep (41), conducting micropuncture studies in the necturus, showed that changes in proximal tubule permeability to sucrose were secondary to alteration of tight junctions and paracellular pathways and that under normal conditions a portion of lumen to peritubular volume reabsorption occurs via the paracellular space. The demonstration that three extracellular markers, mannitol, sucrose, and raffinose, which normally do not penetrate the proximal tubule to any significant degree, do penetrate the tubule under various conditions associated with decreased reabsorption constitutes strong evidence for a paracellular pathway.

The final group of studies supporting a significant role for the paracellular pathway in proximal reabsorption are morphological studies of this pathway itself. Early studies on the gall bladder, another example of a leaky epithelium, revealed widened intercellular spaces during reabsorption (42, 43). Subsequently, Whittembury & Rawlins (44), studying the doubly perfused toad kidney, demonstrated that lanthanum, an electron-dense extracellular marker, precipitated only in the paracellular space and tight junction. Bentzel (45), studying the proximal tubule of the necturus during control and volume expansion, observed a relationship between morphology and the state of net reabsorption. During volume expansion and decreased net reabsorption, the paracellular space was dilated and the zonula occludens widened. Under control conditions both the paracellular space and zonula occludens were narrowed. Bentzel correlated both the differing reabsorptive rates and morphological changes with simultaneously measured transepithelial pressure

measurements. Tisher & Yarger (46) and Martinez-Palomo & Erlij (47) studied the rat and demonstrated lanthanum precipitation in the paracellular space as well as lanthanum penetration of the tight junctions in the proximal tubule. Bulger et al (48) observed widening at the tight junction in the proximal tubules of rats in which intratubular pressure had been elevated by partial renal venous constriction or elevation of ureteral pressure. More recently Rawlins et al (50) examined the width of the paracellular pathway and the movement of lanthanum through this pathway in the proximal tubule of the toad. When the tubular fluid was made hyperosmotic by the addition of urea or mannitol, the paracellular pathway and tight junction widened, allowing more lanthanum to cross the epithelium through the extracellular route. Finally, Humbert et al (51) observed widening of the tight junctions of necturus proximal tubules undergoing saline diuresis.

The exact anatomical nature of the paracellular pathway is a matter of considerable uncertainty. Tisher & Kokko (49) have recently studied the morphology of the paracellular pathway in isolated proximal tubules perfused in vitro. Alteration of the peritubular oncotic pressure, which had been shown to alter net reabsorption and permeability of the paracellular pathway to sucrose (39), was associated with changes in the morphology of the paracellular space. Specifically, widening of the paracellular pathway was observed when net reabsorption was increased by a hyperoncotic bath, while a narrowed pathway was observed when reabsorption was decreased by a hypooncotic bath. These authors, utilizing autoradiography, demonstrated significant entrance of albumin into the paracellular pathway. Because of this latter finding, they proposed that in vivo protein may exert a significant oncotic pressure effect across the lateral plasma membranes forming the boundary of the paracellular pathway, presumably affecting solute and water entry into the paracellular space from intracytoplasmic channels.

Lewy & Windhager (52), in a series of micropuncture studies that are discussed later, using the evidence for an important role of the paracellular pathway in reabsorption and combining this evidence with the model for transepithelial transport postulated by Curran & MacIntosh (53), proposed a model for proximal transport, the critical features of which are outlined in Figure 1. Adjacent proximal tubule cells are linked by a tight junction (*A*) which has finite permeability properties with respect to salt and water. Between cells is the lateral intercellular space (paracellular pathway) which is represented by a simple compartment (*B*), although in reality it exists as a complex space composed of invaginations of adjacent lateral cell membranes. Finally, at the antiluminal border of the tubule the paracellular space is separated from the blood compartment by the tubular basement membrane (*C*). Solutes and water are transported into the paracellular compartment by active and passive processes. This reabsorbate can meet one of two fates: first, it may be picked up by the peritubular capillaries and to this extent constitute net reabsorbate; second, it may reflux back into the luminal compartment—a process termed *back-leak*. The apportionment of reabsorbate between peritubular capillary uptake and back-leak is regulated, at least in part, by the effective hydraulic and oncotic forces acting in the peritubular environment.

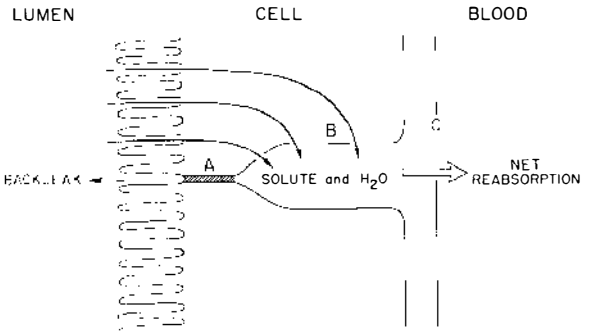

Figure 1 Simplified model to represent the role of the paracellular pathway in net reabsorption in the proximal renal tubule. *A* refers to the zonula occludens or tight junction between adjacent proximal tubular cells, *B* refers to the intercellular space, and *C* refers to the basement membrane. The *solid arrows* depict outward transport of solute and water into the paracellular space while the interrupted and *open arrows* refer to the ultimate fate of this solute and water—back-leak and net reabsorption respectively.

Movement of salt and water into the paracellular space, a process called *outward transport*, can occur by active and passive transport. Controversy still exists over the relative magnitude of each. For our purpose, transport is active if it requires energy and cannot be wholly attributed to electrochemical driving forces and bulk flow. Transport is passive if it is secondary to chemical concentration gradients, electrical driving forces, or solvent drag secondary to bulk movement of fluid.

Two major types of observation support the existence of active Na transport in the proximal tubule: (*a*) the observation of net transport in the presence of a transepithelial potential difference that is lumen negative (32, 54–59) and (*b*) the demonstration that the proximal tubule can generate and maintain a sodium concentration gradient in the presence of a nonreabsorbable solute in the lumen (27, 60, 61). The latter studies include the implicit assumption that the net electrochemical driving forces oppose passive transport. While these studies document active Na transport in a portion of the superficial proximal convoluted tubule, they clearly do not demonstrate that all the salt and water transported into the paracellular spaces of the proximal tubule is necessarily mediated by an active Na transport process. Indeed, several recent studies indicate that a significant fraction of Na transport may be passive. Moreover, the component that is active may not represent a simple direct transport of Na ions, but a complex coupling of Na and organic solute reabsorption. Finally, studies on superficial proximal convolutions cannot be extrapolated to other segments of the proximal tubule in either superficial or deep nephrons.

Micropuncture studies have shown that the majority of the filtered bicarbonate (62, 63) is reabsorbed in the early (first 25%) portion of the proximal convolution. In addition, both micropuncture (64–67) and in vitro microperfusion (68) have demonstrated that glucose reabsorption is mostly accomplished by the early proxi-

mal tubule. Finally, in vivo micropuncture studies have demonstrated that amino acids are also reabsorbed early in the proximal tubule (69–73). Knowledge of this alteration in the intraluminal fluid constituents led to studies examining the roles these substances play in the generation of the proximal tubule potential difference and volume reabsorption.

Kokko & Rector (59) first showed that the transtubular potential difference in isolated perfused segments of rabbit proximal convoluted tubules was flow dependent, the lumen negative potential approaching zero as perfusion rate was progressively decreased below 10 nl/min. They postulated transport depletion of some essential substance(s) as a possible explanation for the decline in the potential as perfusion rates were reduced. Subsequently, Kokko (26) showed that the potential in the superficial proximal convolution depended in a major way on the presence of glucose and amino acids in the lumen; indeed, the potential difference could reverse in polarity to a lumen-positive value if glucose and amino acids were removed from the luminal fluid and the majority of the bicarbonate replaced with chloride. This latter alteration of the perfusate simulates the in vivo composition of tubular fluid beyond the first quarter of the proximal convolution.

On the basis of this in vitro study the following sequence of events was proposed. Early in the proximal tubule the reabsorption of Na coupled with glucose and amino acids generates a lumen-negative potential. At the same time the bulk of the $NaHCO_3$ is reabsorbed by a process that was shown to be nonelectrogenic. This active outward transport of solute results in the osmotic flow of water into the paracellular pathway, thus reducing tubule fluid volume and maintaining isotonicity. The net result is a constant Na but elevated chloride concentration in the tubular fluid. At this point (roughly beyond 25% of the proximal convolution) the substrates for active sodium transport, the process responsible for a negative potential, have been largely depleted. The resultant high luminal Cl concentration is a force for outward diffusion of chloride down its concentration gradient, thus generating a positive potential in the remaining superficial proximal tubule. Subsequently, in vivo micropuncture studies have supported the in vitro study by showing a potential profile along the length of the superficial proximal convolution with approximately the first 25% of the tubule exhibiting a lumen-negative potential and the remainder a lumen-positive potential (28–30, 57).

The existence of this potential profile and its relationship to alteration of luminal fluid constituents have popularized one theory of proximal tubular transport originally proposed in part by Rector et al (74) and subsequently supported by Barratt (28), Maude (75), and Fromter et al (76). In essence this theory states that early in the proximal convolution, outward transport of sodium is active and coupled electrogenically to glucose, amino acids, and possibly other organic solutes and nonelectrogenically to HCO_3. These early active processes establish the conditions for two driving forces for subsequent passive outward transport: (*a*) electrochemical forces and (*b*) effective osmotic pressure forces. Luminal fluid in the later proximal tubules contains a higher Cl concentration than peritubular blood. The lumen to blood Cl concentration gradient results in Cl diffusion out of the tubule lumen. This Cl

diffusion generates a lumen-positive potential which serves as a driving force for passive Na efflux.

In addition to electrochemical forces, a second type of passive driving force in the later portions of the proximal tubule is the presence of an effective osmotic gradient. The early removal of glucose, amino acids, and $NaHCO_3$ with their osmotic equivalent of water results in later luminal fluid that, from the point of freezing point depression, is in osmotic equilibrium with peritubular fluid. However, the effective osmotic pressure in the lumen may be lower. This stems from the fact that the principal solute in late proximal tubule fluid is NaCl whereas peritubular fluid has, in addition, $NaHCO_3$, glucose, and amino acids. As first pointed out by Staverman (77), the osmotic pressure that a molecule can generate across a given membrane is affected by how permeable the membrane is to the molecule. If the membrane exhibits finite permeability to the molecule, the molecule will not exert its theoretical osmotic pressure as predicted by the Van't Hoff relationship $\pi = nRTC$. Staverman (77) introduced the concept of reflection coefficient which is defined as the ratio of observed osmotic pressure to osmotic pressure predicted by the Van't Hoff relationship. The reflection coefficient for NaCl has been determined for the proximal convolution (27, 76) and is in the range of 0.7. Recently the reflection coefficients for glucose, alanine, and $NaHCO_3$ have been determined in the in vitro proximal tubule and were found to be essentially one (78). Thus, in the last two thirds to three fourths of the proximal tubule, even though luminal and peritubular fluid may have the same osmolality as determined by freezing point depression, the presence of glucose, amino acids, and bicarbonate in peritubular (presumably also in paracellular pathway) fluid generates an effective osmotic driving force for water movement. Hierholzer et al (78) have postulated that osmotic water flow generated by this process can account for at least 20% of proximal tubule NaCl reabsorption on the basis of solvent drag. Fromter, Rumrich & Ullrich (76) earlier predicted that approximately one third of proximal tubule Na transport is via solvent drag partly secondary to the effective osmotic driving force of peritubular bicarbonate.

Although the aforementioned passive driving (PD) forces (chloride concentration gradient, positive PD, and effective osmotic pressure gradients) for reabsorption in the latter two thirds of the proximal tubule could theoretically account for a large fraction of the outward transport of NaCl, actual measurements have thus far failed to demonstrate uniformly significant passive salt transport. Green & Giebisch (79), performing simultaneous perfusion of peritubular capillaries and proximal convoluted tubules in the rat, studied the ionic requirements of proximal tubular sodium transport. The authors perfused the tubules and capillaries with solutions designed to examine the role of bicarbonate, Na removal, and chloride gradients in proximal reabsorption. In addition, they examined the effect of cyanide on volume reabsorption when the chloride gradient favored passive reabsorption. They found that even in the presence of a favorable chloride gradient, cyanide inhibited the major portion of sodium and fluid reabsorption. They concluded (*a*) that active sodium transport accounts for the majority of proximal tubule volume reabsorption, (*b*) that a lumen to peritubular Cl gradient accounts for at most 20% of net transport, and (*c*) that

normal peritubular bicarbonate concentration is essential to maintain a normal rate of volume reabsorption. Although these studies document the existence of some passive reabsorptive phenomena, they predict only a minor passive contribution. There are several difficulties with these experiments. First, no potential measurements were recorded and thus the question of a relationship between a lumen-positive potential and net reabsorption could not be examined. Second, Green & Giebisch found no effect of glucose on volume and Na flux as opposed to the findings of Burg (80) and Imai et al (81) in the isolated perfused rabbit tubule. Furthermore, Weinman and his associates (82) have demonstrated, in free-flow micropuncture studies in the rat, that glucose enhances sodium and fluid reabsorption, but the segment responsible for the glucose effect was not identified. However, in a subsequent study utilizing in vivo microperfusion of the Sprague-Dawley rat, Weinman et al (82a) demonstrated the enhancing effect of glucose on sodium and fluid reabsorption throughout the accessible portion of the proximal convolution, an effect which could be inhibited by phloridzin. Third, Green & Giebisch found that acetate, whether substituted for or added to, bicarbonate in perfusion solutions did not promote net reabsorption. This is in disagreement with the findings of Shafer and co-workers (21, 83) who found a significant component of volume reabsorption linked to acetate transport. In addition, Neumann & Rector (83a) found in the rat that acetate is capable of supporting volume reabsorption almost to the same degree as HCO_3. Although acetate was substituted for bicarbonate only in the perfusion solution, not in the peritubular fluid, it is unlikely that the amount of peritubular bicarbonate that could leak back into the tubular fluid would be sufficient to sustain normal rates of net reabsorption. Finally, Green & Giebisch did not examine directly those circumstances that pertain in vivo, specifically low HCO_3, high Cl, and no organic solutes in the tubular perfusate with normal plasma constituents in peritubular perfusate.

These latter circumstances were evaluated in a study by Cardinal et al (84). Utilizing in vitro microperfusion, these authors investigated the role of bicarbonate, organic substrates, and Cl gradients on proximal reabsorption. They observed that net volume reabsorption was two thirds normal when organic substrates were absent from tubular fluid and when a chloride concentration gradient existed from lumen to peritubular side. Under these circumstances a lumen-positive potential was observed. However, the addition of ouabain 10^{-5} M to the peritubular side inhibited net volume reabsorption without affecting the PD. This finding was interpreted to mean that despite the presence of passive driving forces, active transport, as manifested by complete inhibition of volume reabsorption by ouabain, is still responsible for all net volume reabsorption. There are three major difficulties with this group of experiments. First, whereas fluid that simulates in vivo late proximal tubule fluid was used as perfusate, no attempt was made to perfuse the late proximal tubule. With the aforementioned intranephron heterogeneity in mind, it is evident that experiments examining the effects of the composition of luminal fluid must be done in the appropriate region of the tubule. Second, in the group of experiments designed to examine the role of passive forces a significant amount of acetate was present in the perfusion fluid. This acetate may have served as a substrate for active Na transport.

Finally, these authors found no effect of HCO_3 removal from perfusate and bath on net volume reabsorption. This latter finding is in conflict with the observations of several investigators (75, 79, 85) who find a significant role for HCO_3 in proximal tubule volume reabsorption. Clearly, the type of study performed by Cardinal et al (84) should be repeated in vitro and in vivo in several species and in the appropriate nephron segments before the role of bicarbonate, chloride gradients, and chloride diffusion potentials can be defined with confidence. One study has documented significant passive reabsorption in the proximal tubule. Shafer, Patlak & Andreoli (86) perfused the superficial pars recta with fluid that simulates in vivo conditions. When active reabsorption was inhibited by ouabain, reabsorption continued at 40% the control rate. The authors attributed a major portion of this passive transport to the Cl concentration gradient, lumen-positive potential, and effective osmotic pressure of peritubular HCO_3.

In attempting to delineate the relative contributions of active and passive transport to net proximal salt and water reabsorption, proximal tubule heterogeneity must be considered. First, in vitro studies have suggested that a significant lumen-positive potential may not exist in the later portion of the deep proximal tubule because of its lower Cl permeability. This no doubt would affect the magnitude of reabsorption attributed to the passive forces of Cl concentration gradient and Cl diffusion potential. Second, net reabsorptive capacity has not been examined directly in the convoluted portion of the deep nephron. Third, various other properties of the deep convolution have not been directly quantitated. The osmotic water permeability and the reflection coefficients for NaCl, glucose, amino acid, and $NaHCO_3$ have not been determined. Knowledge of these parameters will be required to evaluate the role of passive driving forces in the deep convolution. It is clear that, coupled with as yet missing information about the deep nephron, the inter- and intranephron heterogeneity already documented (differing permeabilities to Na and Cl, differing transepithelial potentials, differing requirements for organic solutes in active Na transport) makes it premature to propose a unitary hypothesis for the mechanism of outward transport in the proximal nephron.

REGULATORY FACTORS: PASSIVE BACK-LEAK

The foregoing discussion advanced evidence that outward transport of reabsorbate had two components: (*a*) active outward transport accompanying the transport of HCO_3, glucose, amino acids, and possibly other organic solutes and (*b*) passive outward transport driven by the high luminal Cl concentration and effective osmotic gradients in the peritubular environment. Although there is admittedly great uncertainty concerning the quantitative contribution of each of these processes to outward reabsorption it is highly likely that both are operative. However, outward transport is not equivalent to net reabsorption. Indeed, several studies have demonstrated that under normal circumstances net Na reabsorption is only a fraction of outward Na transport (21, 27, 33, 87). Roughly 20% of the Na transported out of the tubular lumen is actually taken up by the peritubular capillary. The return of approximately 80% of the outward transported Na to the tubular lumen is termed *back-leak*.

Several studies have shown that a site of regulation of proximal reabsorption is in the control of this back-leak process. However, prior to the recent emphasis on the role of back-leak, a multitude of studies directed at elucidating regulatory factors proposed that such factors as tubular geometry, tubular fluid flow rate, and natriuretic hormones regulated proximal tubule reabsorption.

Gertz and his collaborators (88, 89), utilizing the shrinking-drop micropuncture technique, first proposed that tubular reabsorption varied with the cross-sectional area of the proximal tubular lumen. Rector et al (90) and Brunner et al (91), in a series of micropuncture studies on the rat examining the effects of aortic constriction and elevated ureteropelvic pressure, supported Gertz's initial hypothesis that tubular volume was critically related to net reabsorption. However, Brenner et at (92), also utilizing micropuncture in the rat, found no correlation between proximal tubule volume and reabsorption. These authors pointed out and avoided certain technical pitfalls in the earlier studies. Subsequently, Rodicio et al (93) confirmed the findings of Brenner's group and postulated that perhaps hydrostatic and oncotic pressure in peritubular capillaries were responsible for proximal glomerulotubular balance. Finally, Burg & Orloff (94) in an in vitro study failed to find a relationship between luminal volume and reabsorption.

Early in vitro studies showed that the proximal tubule potential difference was flow dependent (59). Subsequently Bartoli, Conger & Earley (95) demonstrated via in vivo microperfusion that perfusion of the rat proximal tubule with ultrafiltrate at low perfusion rates was associated with a decrease in absolute reabsorption. However, Burg & Orloff (94) in an in vitro study and Morgan & Berliner (96) and Morel & Murayama (97) in in vivo studies failed to find a correlation between reabsorption and flow rate. In spite of these differing observations, the results of these studies are not necessarily conflicting. In studies failing to find an effect of perfusion rate (94, 96, 97), rates in excess of 6 to 10 nl/min were used. In studies demonstrating an effect of perfusion rate, the effect was most pronounced at perfusion rates below 8 nl/min. A recent study by Imai, Seldin & Kokko (98), utilizing in vitro microperfusion, demonstrated that net water and unidirectional fluxes of sodium and chloride were flow dependent at perfusion rates less than 11 nl/min. Flow dependence was abolished when glucose and amino acids were removed from the perfusate. These recent observations suggest that slow flow rates, by causing substrate depletion of glucose and amino acids, may play a role in regulating proximal reabsorption, and indeed may contribute to proximal GT balance at low glomerular filtration rates (GFRs). However, glucose and amino acids are normally mostly reabsorbed in the early convolution. One would, therefore, postulate that slow flow rates would affect reabsorption only in the early proximal tubule. Presently, it is safe to say that a component of proximal reabsorption may be flow dependent but the quantitative importance and physiological significance remain to be defined.

One further postulated mechanism for controlling proximal reabsorption was the influence of a natriuretic hormone. deWardener et al (99), studying cross-circulated dogs in which the donor dog was volume expanded while receiving large doses of mineralocorticoid, suggested the presence of a humoral substance causing natriure-

sis. Since this early observation, several studies have both confirmed and refuted the existence of such a substance. A recent review by Levinsky (100) summarizes the evidence against a pivotal role for a natriuretic factor acting in the proximal tubule. In addition, a recent micropuncture study (101) failed to find an effect of plasma dialyzate from volume-expanded animals on sodium and water reabsorption in the proximal tubule of rats. Indeed, recent studies on the existence and physiological significance of a natriuretic hormone have focused attention on a distal site of action (102).

In the aggregate, then, these studies suggested that luminal volume, luminal fluid flow rate, and natriuretic factor do not play a major role in the regulation of proximal reabsorption. Therefore, as mentioned previously, because only a fraction of outwardly transported salt and water actually reaches the peritubular capillary, attention has recently been focused on the role of peritubular capillary uptake as a major regulator of proximal reabsorption.

Evidence for the peritubular control of proximal reabsorption was first advanced by Earley and his associates (103). Infusion of vasodilator drugs into the renal artery of the dog produced natriuresis that was greatly augmented with the superimposition of systemic blood pressure elevation by infusion of vasopressors (104). These authors initially proposed that renal vasodilation and systemic hypertension combine to increase peritubular capillary hydraulic pressure, thus reducing net reabsorption by inhibiting peritubular capillary removal of the outwardly transported salt and water (104). In further clearance studies, Earley and associates (105–107) showed that elevation of plasma oncotic pressure by albumin infusion served to cancel the natriuretic effect of vasodilatation and hypertension. Subsequently, in a group of micropuncture studies, Lewy & Windhager (52) developed the hypothesis further by proposing that net interstitial pressure was the critical factor relating peritubular capillary uptake to net reabsorption. These authors demonstrated a linear relationship between proximal reabsorption and filtration fraction. In addition, during partial renal venous occlusion, proximal fractional reabsorption was shown to remain constant at various levels of glomerular filtration. While these studies served to point out that peritubular factors may regulate proximal reabsorption, they could not determine whether the mechanism was by increased back-leak or decreased outward transport.

Such studies assigned a key role to filtration fraction (FF) in the regulation of proximal reabsorption. Filtration fraction equals glomerular filtration rate/renal plasma flow (GFR/RPF). FF is of critical importance because it influences both Starling forces acting across the postglomerular capillary. For any given afferent arteriolar protein concentration, FF determines the postglomerular oncotic pressure. In addition, since FF reflects the relationship between GFR and postglomerular blood flow, it (FF) varies inversely with postglomerular hydrostatic pressure. Thus, when FF is high postglomerular hydrostatic pressure is low and when FF is low postglomerular pressure is high.

Brenner and his associates are principally responsible for the direct demonstration by micropuncture that peritubular oncotic pressure plays a major role in the regulation of proximal reabsorption. Intra-aortic injection of colloid-free, isoncotic, and

hyperoncotic solution in the rat showed that fractional and absolute reabsorption varied directly with peritubular capillary colloid osmotic pressure (108). Brenner, Troy & Daugharty (109) in an in vivo microperfusion study subsequently showed that selective elevation of peritubular oncotic pressure in volume-expanded rats almost totally reversed the inhibition of proximal reabsorption associated with volume expansion. In addition, Falchuk et al (110), measuring nephron filtration rate, absolute reabsorption, and peritubular hydrostatic pressure, examined renal vein occlusion, aortic constriction, carotid occlusion with vagotomy, and isoncotic as well as hyperoncotic albumin infusion. In all of these maneuvers, proximal reabsorption correlated with changes in peritubular oncotic and hydrostatic pressure, strongly suggesting a regulatory role for these forces. In another micropuncture study Brenner et al (111), utilizing partial aortic constriction in plasma-expanded rats, showed that glomerulotubular balance was blunted when changes in peritubular protein concentration changes were prevented. Similar findings were reported by Spitzer & Windhager (112) who, in an in vivo microperfusion study, showed under both free flow and "split-drop" conditions, that proximal reabsorption correlated with peritubular oncotic pressure as controlled by varying the concentration of dextran in peritubular capillary perfusate. Weinman et al (113), by altering the concentration in postglomerular blood, showed in the split-drop technique, a linear relationship between sodium reabsorption and peritubular capillary protein concentration. Green et al (114), in a series of in vivo microperfusion studies, confirmed the importance of peritubular protein. Although a number of investigators have failed to demonstrate an important role of peritubular oncotic pressure on regulation of proximal reabsorption, these are in the minority (61, 85, 115–120). In addition, Windhager & Giebisch (121) in a recent review, pointed out that several of these studies (61, 116–118) were beset with technical artifacts such as incomplete capillary perfusion.

Several studies have shown that in addition to effective peritubular oncotic pressure, hydraulic pressure may play a role in the regulation of proximal reabsorption. Early studies by Bank et al (122) and Aperia et al (123) on the effects of renal perfusion pressure on proximal reabsorption suggested that elevated peritubular capillary hydrostatic pressure inhibited Na reabsorption. Subsequently, Bank et al (124), in examining the role of peritubular capillary perfusion rate on proximal reabsorption in the rat, postulated that the inhibition of reabsorption observed at high peritubular capillary perfusion rates was secondary to elevated capillary hydrostatic pressure. Less inferential evidence for a direct role of peritubular hydraulic pressure in proximal reabsorption has been obtained in the necturus. Utilizing the necturus, Hayslett (125), measuring the half-time of reabsorption in the split-drop preparation as well as transepithelial potentials, demonstrated that elevated peritubular hydrostatic pressure inhibited proximal reabsorption. In addition, Grandchamp & Boulpaep (126) further strengthened the role of pressure control by demonstrating decreased proximal reabsorption in necturus during volume expansion, quantitating the contributions of changes in peritubular oncotic and hydrostatic pressures.

Finally, several investigators have postulated a role for peritubular capillary flow rate in the regulation of net reabsorption. Lewy & Windhager (52) noted a correla-

tion between absolute proximal reabsorption and renal plasma flow during partial renal venous occlusion in the rat. Daugharty et al (127), studying the dog in which diuretic blockade of distal reabsorption was utilized, found that changes in proximal reabsorption correlated best with changes in plasma flow. Schrier & Humphreys (128), in saline-loaded and water-loaded dogs, found a close correlation between renal plasma flow and proximal reabsorption. Presumably, demonstration of plasma flow dependence in these studies is related to the fact that under a given net hydraulic and oncotic force favoring net reabsorption the slower the peritubular plasma flow rate the greater will be the dilution of peritubular protein by the reabsorbate and the sooner will be the dissipation of the oncotic driving force (129). However, the physiological importance of plasma flow dependence of proximal reabsorption remains to be defined. As pointed out by Deen et al (129), those studies demonstrating a significant role for plasma flow were associated with "reabsorptive pressure equilibrium." In other words, oncotic pressure in the peritubular capillary favoring reabsorption was approached by hydrostatic pressure in the capillary, which inhibited reabsorption. Renal plasma flow will be regulatory in proximal reabsorption when, because of sufficient slowing of flow, the peritubular oncotic pressure is diluted by the reabsorbate to the point that oncotic pressure favoring reabsorption no longer exceeds hydrostatic pressure retarding reabsorption.

A recent study by Myers et al has pointed out the potential importance of peritubular plasma flow rate (130). In this study Wistar rats, a species whose surface glomeruli offer the opportunity to study both glomerular and postglomerular hemodynamics, were studied. Infusion of pressor doses of norepinephrine and angiotensin II produced large increases in filtration fraction and thus postglomerular oncotic pressure. However, the expected increase in absolute proximal reabsorption from the large increase in peritubular oncotic pressure was not seen, because of the opposing effect of a large decrease in efferent arteriolar and thus peritubular capillary flow rate. Therefore, under the conditions of high FF and slow peritubular capillary flow rate as produced by the efferent arteriolar constriction secondary to norepinephrin and angiotensin II, proximal tubular reabsorption was maintained by the slow peritubular plasma flow rate despite Starling forces acting across the peritubular capillary bed that favored greatly increased reabsorption.

The mechanism by which alteration in peritubular physical forces effect proximal reabsorption has been studied extensively. In order to postulate a regulatory role for physical factors, the boundaries through which these forces act require certain properties. Specifically, for oncotic and hydraulic pressure to play a role, the boundary through which they exert their control should ideally be freely permeable to all substances smaller than plasma proteins and have a very high hydraulic permeability. Welling & Grantham (131) in studying the physical properties of isolated perfused tubular basement membranes documented such properties. Peritubular physical forces are thought to regulate proximal reabsorption by determining the fraction of outward transport picked up by the peritubular capillary the remainder returning via a back-leak through the paracellular pathway into the tubule lumen.

The role of peritubular oncotic pressure and the paracellular pathway in the regulation of proximal reabsorption is illustrated in Figure 2. Protein, depicted by black dots, is shown to be present in the peritubular capillary, interstitial space, and

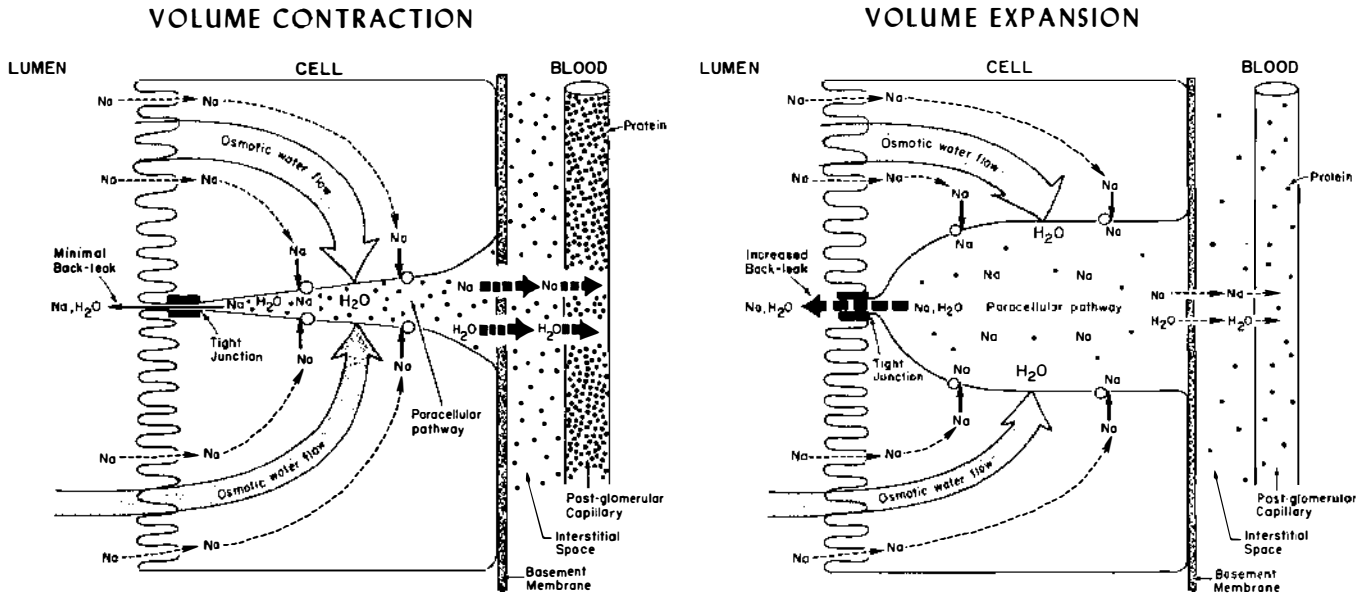

Figure 2 Depicted here is a schematic representation of how protein translates its effect on proximal tubular reabsorption through controlling backleak. On the left is the circumstance of volume contraction and its attendant increase in peritubular protein concentration due to both elevation of systemic arterial protein concentration and increased filtration fraction. Salt and its osmotic equivalent of water is outwardly transported into the paracellular pathway. The relatively high concentration of protein (*black dots*) via its oncotic pressure effect enhances movement of this salt and water from the paracellular pathway and interstitial space into the peritubular capillary. In consequence the paracellular pathway is narrowed, hydrostatic pressure within it is low, and therefore the driving force for back-leak is reduced. As depicted, the protein that enters the interstitial space and paracellular pathway may also exert an oncotic force across the lateral cell membranes (see text). On the right is the circumstance of volume expansion associated with diluted systemic arterial protein concentration and decreased filtration fraction. The less dense arrangement of black dots representing decreased protein concentration depicts the reduced driving force of peritubular (interstitial and paracellular) protein for removal of reabsorbate from the paracellular pathway, thereby causing widening of the paracellular space and increased back-leak.

paracellular pathway. This is in accord with the demonstration of the permeability of the isolated perfused basement membrane to albumin (131) together with the finding of albumin in the paracellular pathway by autoradiography (49). During volume contraction the protein concentration is elevated in the peritubular environment, being highest in the peritubular capillary. This furnishes an oncotic gradient for removal of fluid from paracellular space to peritubular capillary and diminishes the magnitude of the back-leak into tubular lumen. Because fluid is readily taken up by the peritubular capillary, the paracellular space is narrowed. By contrast, during volume expansion the protein concentration in the peritubular environment is reduced, thereby diminishing peritubular capillary uptake of reabsorbate. Therefore, fluid accumulates in the paracellular space, widening it, and thus producing a hydrostatic pressure gradient for back-leak. Hydrostatic pressure in the peritubular environment during volume contraction and expansion changes in a manner parallel to that of oncotic pressure. In volume contraction, a low peritubular capillary hydrostatic pressure promotes fluid removal from the paracellular space, while in volume expansion elevated peritubular hydrostatic pressure serves to retard fluid removal from the paracellular space.

A different set of morphologic findings was illustrated by Tisher & Kokko (49) in electron micrographs of isolated rabbit tubules exposed to a bath containing either high protein (volume contraction) or low protein (volume expansion). Their findings were the opposite of those depicted in Figure 2: widening of the paracellular pathway was observed when bath protein was high; narrowing of the paracellular pathway occurred when bath protein was low. A direct correlation among bath protein concentration, the width of the paracellular pathway, and net reabsorption was demonstrated. They therefore concluded that protein exerts its oncotic effect, not only between paracellular space and peritubular capillary, but also along the lateral walls of the paracellular pathway. Presumably, since the paracellular space is expanded when back-leak is low (volume contraction), it must be assumed that back-leak does not occur principally through the tight junction. It should be noted that the in vitro model involves only variations of oncotic pressure, and therefore differs from the actual in vivo circumstance where oncotic and hydrostatic forces act in concert. What effect the superimposition of changes in hydrostatic pressure would produce on morphologic findings is unknown. Although the width of the paracellular pathway during changes in net reabsorption observed by Tisher & Kokko are the opposite of those depicted in Figure 2, the principle of the peritubular control of back-leak by protein concentration is the same. However, the location of the area of back-leak as well as the channels through which protein exerts its effect differ. In Figure 2, protein exerts its main effect by regulating the movement of fluid between paracellular space and peritubular capillary; back-leak occurs through the tight intercellular junction when the paracellular space is widened and its hydrostatic pressure presumably increased. In the Tisher-Kokko model, protein exerts a major effect, not only on fluid movement between paracellular space and peritubular capillary, but also on fluid movement into the paracellular space across its lateral cell membranes; back-leak occurs when the paracellular space is narrowed; the principal channel of back-leak in this model is therefore not the tight junction.

Finally, a further possible modulator of the role of physical factors and the paracellular pathway on proximal reabsorption has recently been proposed. Gill & Casper (133) demonstrated inhibition of proximal reabsorption during the infusion of cyclic AMP and dibutyryl cyclic AMP into the renal arteries of dogs. Lorentz, Lassiter & Gottschalk (38) demonstrated increased proximal back-leak of extracellular markers when intrarenal pressure was elevated via elevation of ureteral pressure, partial renal venous constriction, and massive saline diuresis. Lorentz (134) subsequently showed that cyclic AMP and dibutyryl cyclic AMP also increased the permeability of the proximal tubule to extracellular markers. Finally, Lorentz (135) has reported in an abstract that parathormone increases proximal tubular permeability. These studies, in conjunction with the demonstration of increased renal cyclic AMP during volume expansion (136) and parathormone administration (137–141), constitute impressive evidence for a role of cyclic nucleotide in altering the permeability characteristics of the tight junction. These findings suggest that the control of proximal reabsorption via a back-leak may be determined by both the physical forces as well as permeability characteristics of the tight junction. It is evident that inter- and intranephron structural heterogeneity must also be considered in evaluating the role of peritubular physical forces in the regulation of proximal reabsorption. Differences in filtration fraction in different nephrons as well as possible differences in tight junction permeability characteristics would result in different degrees of back-leak and thus different net reabsorptive rates. Hamburger et al (22) have already demonstrated a differential effect of cyclic AMP on proximal reabsorption with inhibition found only in the convoluted portion.

Basically, outward transport of salt and water via active and passive processes provides substrate for net reabsorption. This substrate, which is transported to the paracellular pathway, can either be reabsorbed into the peritubular capillary and thus constitute net reabsorption or leak back through the tight junction (or through intracytoplasmic channels) into the tubular lumen. The apportionment of outwardly transported salt and water between these two fates is determined by the net Starling forces operating in the paracellular pathway—the net oncotic pressure and net hydraulic pressure—and perhaps by the permeability characteristics of the tight junction as influenced by cyclic nucleotides. Intranephron and internephron structural heterogeneity can greatly modify the influence of these factors because of intrinsic differences in active and passive permeability properties.

Acknowledgments

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