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Molecular Mechanisms and Regulation of Urinary Acidification

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Abstract

The H^+ concentration in human blood is kept within very narrow limits, ~ 40 nM, despite the fact that dietary metabolism generates acid and base loads that are added to the systemic circulation throughout the life of mammals. One of the primary functions of the kidney is to maintain the constancy of systemic acid-base chemistry. The kidney has evolved the capacity to regulate blood acidity by performing three key functions: 1) reabsorb HCO_3^- that is filtered through the glomeruli to prevent its excretion in the urine; 2) generate a sufficient quantity of new HCO_3^- to compensate for the loss of HCO_3^- resulting from dietary metabolic H^+ loads and loss of HCO_3^- in the urea cycle; and 3) excrete HCO_3^- (or metabolizable organic anions) following a systemic base load. The ability of the kidney to perform these functions requires that various cell types throughout the nephron respond to changes in acid-base chemistry by modulating specific ion transport and/or metabolic processes in a coordinated fashion such that the urine and renal vein chemistry is altered appropriately. The purpose of the article is to provide the interested reader with a broad review of a field that began historically ~ 60 years ago with whole animal studies, and has evolved to where we are currently addressing questions related to kidney acid-base regulation at the single protein structure/function level.

Introduction

Systemic acid-base chemistry is very tightly controlled in normal humans, in spite of the fact that metabolism of typical diets generates a net H^+ load (405). Moreover, there is an inverse association between the blood HCO_3^- concentration and the dietary H^+ load that is greater among middle-aged and elderly persons than younger adults (36). Even small changes in systemic acid-base chemistry may affect bone, skeletal muscle and insulin resistance (1, 213, 469). In postmenopausal women administration of base orally has been shown to improve bone density and decrease renal nitrogen excretion (222, 337, 640).

Diets rich in arginine, lysine, phosphoproteins, and sulfur containing amino acids when metabolized generate net H^+ that are delivered into the venous system (430). The H^+ combine with HCO_3^- (and to some extent other body buffers) extracellularly and intracellularly according to the following reaction: $H^+ + HCO_3^- \rightarrow CO_2 + H_2O$. CO_2 generated in the reaction is excreted by the lungs thereby preventing the systemic CO_2

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concentration from increasing. It is the function of the kidneys to regenerate and delivery to the renal veins the required quantity of HCO_3^- lost in this process (288, 404). This function of the kidney is distinguished from the additional requirement performed predominantly by the proximal tubule (and to a lesser extent the thick ascending limb) to reabsorb HCO_3^- from the glomerular filtrate such that typically less than 0.1% of the filtered HCO_3^- is excreted in the urine (589).

Whole Body Acid-base Balance

The generation of HCO_3^- is an essential function of the kidney ensuring that whole body HCO_3^- content remains relatively constant despite the loss of HCO_3^- due to dietary H^+ loads. The kidney generates new HCO_3^- from metabolizable organic anions including α-ketoglutarate (derived from glutamine), lactate, citrate, and fatty acids (183, 287, 288). These biochemical processes occur predominantly in the proximal tubule and to a lesser extent other nephron segments. In the process of generating α-ketoglutarate that is subsequently converted into 2 HCO_3^- in the Krebs cycle and in gluconeogenesis, 2 NH_4^+ are produced according to the following mitochondrial reactions (256, 622, 795, 796):

1) glutamine + $H_2O \rightarrow$ glutamate + NH_4^+ (catalyzed by phosphate dependent glutaminase)

2) glutamate + H_2O + NAD $\rightarrow$ α-ketoglutarate + NADH +NH_4^+ (catalyzed by glutamate dehydrogenase)

The partitioning of the generated NH_4^+ generated by the kidney between the renal vein and urine is an important factor at the whole organ level that has additional significant effects on systemic acid-base balance. Although new HCO_3^- generated in the proximal tubule is delivered to the renal veins, NH_4^+ produced in the kidney is partitioned between the urine and the renal veins. Of the approximately 75 mEq of NH_4^+ per day produced on an average North American diet, approximately 50% is transferred to the renal veins and an equal amount is excreted (534, 535, 686). Importantly, the NH_4^+ delivered to the renal veins represents a substance that is HCO_3^- consuming, resulting in a decrease the systemic pH. Specifically, NH_4^+ delivered to the circulation upon reaching the liver consumes HCO_3^- in the urea cycle according to the following reaction 2 NH_4^+ + 2 $HCO_3^- \rightarrow$ urea + 3 H_2O + CO_2 (298). This has led to the concept of “effective new HCO_3^- production” defined as HCO_3^- produced by the kidney, which has not been consumed in the urea cycle and thus is available as a buffer for modulating systemic acid-base balance.

The excretion of ~50% of total NH_4^+ production requires the coordinated intertubular transport of NH_3/NH_4^+ from its production site predominantly in proximal tubule cells to the collecting duct lumen. In metabolic acidosis, both the quantity of new HCO_3^- produced in the proximal tubule is increased and the intertubular transport of NH_3/NH_4^+ is altered such that a greater percentage of total NH_4^+ produced is excreted in the urine (less being delivered to the renal veins) thereby significantly increasing the effective new HCO_3^- delivery to the systemic circulation (101, 535, 686, 687). By altering the total new HCO_3^- production rate and renal vein/urine NH_4^+ partitioning, the kidney possesses powerful mechanisms for compensating for the loss of HCO_3^- due to dietary metabolic H^+ generation and in the urea cycle.

A second source of new HCO_3^- generation is derived from tubular luminal protonation of HPO_4^{2-} and subsequent excretion of $H_2PO_4^-$ (titratable acid) (431, 615). Approximately 75% of titratable acid (TA) is derived from $H_2PO_4^-$ excretion whereas the remainder is composed of protonated creatinine and other less defined organic anions. The site of protonation of depends on the luminal pH and the pK of the protonated anion. $H_2PO_4^-$ generation takes place primarily in the proximal tubule as the luminal pH decreases from 7.4 to ~ 6.7 (475), whereas the protonation of other organic anions (average pK ~ 4.4) occurs in the collecting duct (325).

Human urine contains not only NH_4^+, $H_2PO_4^-$, H^+-creatinine, but also ~90 organic anions totaling ~40 mEq per day (147, 172, 432). Approximately 50% of these organic anions have metabolizable carboxyl groups that can be converted into HCO_3^- at the pH of normal blood (123, 354). Normal urine also contains ~10 mEq per day of metabolizable organic cations (172). Under control conditions and following exogenous acid-or alkali loading, the net renal excretion of H^+ or base is traditionally calculated according to the following equation: NAE (meq/time) = volume/time × [NH_4^+ + TA - HCO_3]. The urinary excretion of free H^+ is omitted in the calculation because it's contribution is minimal i.e. at a urine pH of 4.5, the concentration of free H^+ is 32 μmol per liter. A similar calculation can be used to quantitate the magnitude of renal vein acid or base delivery to the systemic circulation. Because of the magnitude of metabolizable organic anion excretion in urine (representing loss of HCO_3^-), several authors have indicated that NAE should be calculated as: NAE (meq/time) = volume/time × [NH_4^+ + TA - metabolizable organic anions - HCO_3^-] (172, 588). The excretion of various metabolizable organic anions is altered predictably during exogenous acid and alkali loading and during normal variations in protein intake (123, 246, 290, 292, 537, 656).

Acid/alkali loading induces changes in NAE associated with alterations in the expression and function of H^+/base transporters throughout the nephron involving complex signaling pathways that will be detailed below. The response of the kidney to exogenous or endogenous acid/alkali loads results in a change in both new effective HCO_3^- generation and HCO_3^- transport (absorption and secretion) that ultimately contributes to achieving a new steady state.

Proximal Tubule

General Properties of Proximal Tubule HCO_3^- Transport

The proximal tubule is the site in the nephron where the majority (~ 75%) of the filtered HCO_3^- load is reabsorbed into the systemic circulation. The glomerular filtrate has a HCO_3^- concentration of ~ 25 meq/l and assuming that the glomerular filtration rate (GFR) is ~ 144 liters/day, the amount of HCO_3^- entering the proximal tubule is ~ 3.6 moles/day. The urinary excretion of HCO_3^- is typically less than 5 mmoles/day. The proximal tubule is divided longitudinally morphologically into a convoluted and straight segment and each portion of the proximal tubule has a different capacity to absorb HCO_3^- (76, 454, 455). HCO_3^- absorption across the apical membrane is indirect and requires that H^+ are secreted from the cells into the lumen thereby decreasing the luminal bicarbonate concentration from 25 to ~ 10 mM, with an associated decrease in luminal pH from 7.4 to ~ 6.8 according to the

following reaction: $H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$. Less HCO_3^- is absorbed quantitatively in the proximal straight tubule. The proximal convoluted tubule is further subdivided into an early S1 segment, and an S2 segment that consists of the end of the convoluted portion followed by a straight segment located in the cortex. The S3 straight segment representing the terminal portion of the proximal tubule is located in the outer stripe of the outer medulla. There are additional differences in the magnitude of HCO_3^- transport depending on whether the segment is from S1, S2, and S3 superficial or juxtamedullary nephrons (3, 58, 387).

The route of HCO_3^- absorption in the proximal tubule is transcellular and active since it occurs against a chemical (HCO_3^-) gradient, and the fact that there is a minimal transepithelial voltage (V_{TE}) of −2 mV (early proximal tubule) and +2 mV (late proximal tubule) to drive transport paracellularly (53, 227). Given that the proximal tubule cell apical membrane voltage is ~ −50 to −70 mV relative to the lumen, with an intracellular pH (pHi) of ~ 7.2, luminal H^+ secretion is active occurring against an electrochemical gradient (78, 610, 813). Luminal acidification could theoretically be mediated by direct luminal H^+ secretion, HCO_3^- absorption, CO_3^{2-} absorption, or CO_2 secretion. To address this question several groups examined whether in the $H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$ reaction, H_2CO_3 and CO_2 are at equilibrium and whether slowing of the interconversion of H_2CO_3 to $CO_2 + H_2O$ with carbonic anhydrase inhibitors resulted in a “disequilibrium pH” (199, 585, 719). In the absence of carbonic anhydrase inhibition, the measured and predicted pH values were found to be essentially equal. However, carbonic anhydrase inhibition generated an acid disequilibrium pH (measured luminal pH lower than predicted) demonstrating that net luminal H^+ secretion occurred. Direct HCO_3^- absorption would have resulted in an alkaline disequilibrium pH. In addition, these experiments showed that the luminal conversion of H_2CO_3 into CO_2 is normally catalyzed by carbonic anhydrase.

Carbonic anhydrase enzymes play a key role in proximal tubule transepithelial HCO_3^- absorption. Each proximal tubule compartment (cell, lumen, peritubular space) has specific CA enzymes that accelerate the interconversion of H_2CO_3 and $CO_2 + H_2O$. In the cytoplasm CAII (29 kDa monomeric protein) is the predominant isoform accounting for most of the carbonic anhydrase activity in the renal cortex (575). Carbonic anhydrase inhibitors affect carbonic anhydrase activity in all three compartments (lumen, cell, and peritubular fluid) and because of their high permeability essentially block all proximal tubule HCO_3^- absorption (171). Several studies have examined the role of the carbonic anhydrase activity in the luminal or basolateral compartments specifically. Luminal perfusion with impermeant CA inhibitors block HCO_3^- absorption almost completely (464). Two CA isoforms have been localized to the brush border of the proximal tubule. CAIV is a glycosylphosphatidylinositol (GPI) anchored membrane bound enzyme with S2 expression > S1⩾ S3 (122, 459, 637). In addition to CAIV, CAXIV has been localized to the brush border membrane of S1 and S2 segments in the mouse proximal tubule (355, 509). The lack of luminal CA activity in S3 proximal tubules was corroborated in the isolated perfused rabbit proximal tubule using a luminal fluorescent pH dye that demonstrated the presence of an acid disequilibrium pH (408). On the basolateral membrane immunofluorescence staining has localized the transmembrane enzyme CA XII to the S1 and S2 proximal tubule segments (411, 541). In addition to CAXII, CAIV is also expressed on the basolateral membrane of

the proximal tubule (122, 459, 637). There appears to be species differences in the relative activity/abundance of these enzymes. In mouse kidney, CA isoforms other than CAIV (e.g. CAXII) account for the bulk of membrane-associated CA activity whereas in rabbit, CAIV accounts for most of the membrane-associated CA activity. The role of basolateral membrane bound carbonic anhydrase activity is highlighted in rabbit isolated perfused proximal tubule experiments where basolateral addition of an impermeant carbonic anhydrase inhibitor blocks ~ 60% of HCO_3^- absorption (698).

Apical Membrane Transporters: H^+-ATPase; NHE3; NHE8; Organic Anion Transporters; CFEX

H^+-ATPase—HCO_3^--stimulated oligomycin-insensitive H^+-ATPase activity and ATP-dependent H^+ translocation in brush border membrane vesicles was first demonstrated by Kinne-Saffrin and Kinne (367-369). Additional experiments in rat proximal tubules also provided evidence for a Na^+-independent apical H^+ transport process. Yoshitomi et al reported that in the rat perfused tubule *in vivo*, following perfusion in Na^+-free solutions, pHi decreased and then recovered (812). Steady state pHi under similar conditions was more alkaline than in the presence of Na^+ suggesting the presence of a Na^+-independent H^+/base transport process (19). In the S3 proximal tubule perfused *in vitro*, following acute intracellular acidification, pHi recovered in the absence of Na^+ (400). The pHi recovery was inhibited by the H^+-ATPase inhibitors *N*,*N*'-dicyclohexylcarbodiimide (DCCD) and N-ethylmaleimide (NEM), and by glycolytic ATP inhibition. In similar studies, Nakhoul et al did not report predictable inhibition by DCCD (521). Additional evidence for an apical H^+-ATPase was derived from experiments by FrÖmter et al using *in vivo* rat proximal tubules perfused in the absence of organics. In the early proximal tubule the V_{TE} was + 1 mV and was 0.2 mV in the late proximal tubule) (225). The positive V_{TE} was insensitive to ouabain and acetazolamide and therefore compatible with electrogenic H^+ secretion (226). These findings were ultimately confirmed by labeling of the proximal tubule with H^+-ATPase specific antibodies demonstrating that the largest expression was at the base of the microvilli (118). Studies by Bank et al used luminal DCCD to block ~ 21% of HCO_3^- absorption but whether complete inhibition occurred is unknown (49) and there are no experiments in mice lacking apical H^+-ATPase activity (congenital or conditional). It is currently believed that the apical H^+-ATPase is responsible for ~ ~35% of transepithelial bicarbonate absorption. An additional role for H^+-ATPase activity in the endosomal pathway was suggested from studies of a4 subunit-deficient mice that have proximal tubule transport abnormalities including proteinuria, phosphaturia, accumulation of material in lysosomes, and abnormal endocytic trafficking (304). Apical H^+-ATPase expression appears to be upregulated in proximal tubule cells by PKA, and AMP-activated protein kinase (AMPK) decreases the PKA-induced increase in H^+-ATPase expression (10). Additional regulatory pathways involved in modulating H^+-ATPase activity are highlighted below in the context of the collecting duct.

Several studies have also reported a role for Cl^- in modulating proximal tubule H^+-ATPase activity. In rabbit S3 proximal tubules perfused in vitro, Na^+-independent pHi recovery following an acid load is dependent on intracellular Cl^- (400) and the shuttling of cytoplasmic H^+-ATPase containing vesicles to the apical membrane is also Cl^--dependent

(477). In rat proximal tubules (superficial S1 and S2 segments), H^+-ATPase activity was shown to be Cl^- -dependent (830) and evidence was provided that CFTR and ClC-5 may play a role (141).

Na^+/H^+ exchangers: NHE3 and NHE8—Electroneutral Na^+/H^+ exchange activity was first demonstrated in rat proximal tubule apical membrane vesicles by Murer et al (513). Additional studies in vesicles demonstrated that external protons compete with Na^+ for a single site with a K_{Na}^+ of ~10 meq/l (pH 7.5) and a K_H^+ of 35 nM (43, 373, 755). Lithium and amiloride were shown to compete with Na^+ at an external binding site by noncompetitive and competitive mechanisms (331, 371, 372). In the *in vitro* perfused salamander proximal tubule Boron and Boulpaep demonstrated a luminal Na^+-dependent pHi recovery process that was amiloride-inhibitable (104). Sasaki et al. reported a similar transport process in the *in vitro* perfused rabbit proximal tubule as did Alpern and Chambers in the *in vivo* perfused rat proximal convoluted tubule (21). Transepithelial HCO_3^- absorption was almost completely inhibited by the removal of Na^+ (lumen, bath), by Na^+-K^+-ATPase inhibition, and by luminal amiloride (21). In total, these data from various preparations and experimental conditions provided convincing functional evidence for an apical membrane electroneutral Na^+/H^+ exchanger that plays a key role in both luminal acidification and transepithelial HCO_3^- transport.

Na^+/H^+ exchangers (NHE proteins) are now known to be encoded by separate 9 separate genes (191). Two Na^+/H^+ exchangers, NHE3 and NHE8, have been localized to the apical membrane of the proximal tubule (96, 99). Several lines of evidence indicate that in the adult, NHE3 is responsible for mediating apical the Na^+/H^+ exchange that was first detected physiologically (28, 30, 32, 62, 65, 87, 133, 134, 532, 533, 555, 566, 624, 691, 692, 751, 798, 817). In general NHEs are ~ 100 kDa proteins with an intracellular N-terminal domain, an ~ 450 aa transmembrane domain composed of 11 or 12 transmembrane regions that mediate Na^+/H^+ exchange, and a C-terminal cytoplasmic tail involved in regulation NHE activity (191). Transmembrane region IV is thought to be involved in ion transport, and transmembrane region IX is involved in amiloride inhibition (12).

The transporter has been localized by immunocytochemistry to the proximal tubule brush border (30, 87, 533, 691). In addition, the inhibitory profile of expressed NHE3 to amiloride, amiloride analogues, and HOE694 is comparable to the native apical membrane Na^+/H^+ exchanger (532, 692, 798). Regulation of expressed NHE3 by acidosis, thyroid hormone and glucocorticoids, angiotensin II, endothelin, parathyroid hormone, and protein kinase A parallels the regulation of native apical membrane Na^+/H^+ exchange by these factors (28, 32, 62, 65, 133, 134, 164, 566, 817) .

The contribution of apical NHE3 mediated H^+ secretion to proximal tubule HCO_3^- absorption has been estimated by several approaches. Howlin et al and Chan and Giebisch found that luminal amiloride inhibited HCO_3^- absorption in the rat proximal convoluted tubule but the completeness of Na^+/H^+ antiporter inhibition remained unclear (152, 317). In separate experiments using high concentrations of luminal amiloride and a more potent analogue, t-butyl amiloride, it was concluded that ~65% of transepithelial HCO_3^- absorption was Na^+/H^+ antiporter dependent (573). In $NHE3^{-/-}$ mice proximal tubule HCO_3^-

absorption was decreased to ~40% of control (624, 751) and the H^+ pump inhibitor bafilomycin decreased HCO_3^- transport by 60% providing evidence for a component of H^+-ATPase mediated transport (751). Disruption of the NHE3 *Slc9a3* gene may lead to compensatory changes in apical membrane H^+-ATPase activity and potentially other NHE isoforms, making it difficult to assess the contribution of NHE3 to transepithelial bicarbonate absorption from these studies (162, 752). Moreover attempts to assess the contribution NHE3 to HCO_3^- absorption in tubules perfused in Na^+-free solutions, or by inhibition of the Na^+-K^+-ATPase are also difficult to interpret because of their potential effect on altering the activity of basolateral NBCe1-A (see below). Until conditional knockout studies of NHE3 are done, the best assessment of the contribution of NHE3 relies on studies using inhibitors.

NHE8 may also contribute to bafilomycin-insensitive HCO_3^- absorption and has been localized to the proximal tubule by immunocytochemistry, Western blotting, and in situ hybridization (269, 270). It is currently thought that in neonates, NHE8 likely accounts for the majority of apical membrane NHE activity since NHE3 is poorly expressed and ethylisopropylamiloride (EIPA) doses that block NHE8 but not NHE3 suppress NHE activity (68, 98, 701). In adults, although NHE8 may be predominantly an intracellular organelle exchanger (98), studies in senile rats suggest that age-related decrease in proximal tubule acidification is due to a decrease in NHE8 expression rather than NHE3 or H^+-ATPase activity (220). The exact mechanism for the age-related switch in apical NHE3 and NHE8 expression is unknown but appears to involve both thyroid hormone and glucocorticoids (63, 98, 234).

Organic Anion Transport—In the *Ambystoma* proximal tubule perfused *in vitro*, Siebens and Boron demonstrated the functional presence of an apical membrane Na^+-lactate cotransporter in parallel with a basolateral membrane H^+-lactate cotransporter (or equivalently an OH^-/lactate exchanger) (652). In the rabbit S3 proximal tubule, Nakhoul and Boron reported apical membrane Na^+-acetate cotransport activity, and both apical and basolateral H^+-acetate cotransport (or equivalently OH^-/acetate exchange) (519, 521). The low intracellular Na^+ concentration would generate a chemical driving force for apical Na^+-acetate uptake and subsequent equivalent H^+ efflux (with acetate) across either the apical and/or basolateral membranes. Geibel examined the importance of this system to transepithelial H^+ secretion and in the presence of physiologic HCO_3^--buffered solutions, concluded it does not play an important role (238).

Cl^-/Base Exchange: CFEX (PAT1)—Lucci and Warnock examined the effect of anion transport inhibitors on the perfused rat proximal tubule and provided the first evidence that apical Na^+/H^+ exchange is coupled to Cl^-/OH^- (or Cl^-/HCO_3^- exchange) (465). Baum et al used luminal stilbene and furosemide inhibitors in the *in vitro* perfused rabbit proximal convoluted tubule to inhibit Cl^- absorption (60). Several labs showed that pH gradients can drive ^{36}Cl transport in voltage clamped apical membrane brush border vesicles and that Cl^- gradients could drive pH changes transport measured with acridine orange (131, 650, 756). Chen et al reported similar results using a Cl^- fluorescent probe (156). In contrast, Seifter et al failed to document pH gradient driven Cl^- transport under voltage clamped conditions

(641) and other groups were also unable to measure Cl^--induced pH changes (142, 329). In the rabbit proximal straight tubule, Ishibashi et al were also unable to detect Na^+-dependent apical Cl^- transport using Cl^- electrodes (326). Similarly, Schwartz was unable in the rabbit proximal tubule to demonstrate an effect of luminal Cl^- on luminal HCO_3^- appearance (631). Several studies have failed to document a significant effect of Cl^- removal on HCO_3^- transport and luminal DIDS (an inhibitor of anion exchange) has even been reported to stimulate HCO_3^- absorption (60, 129, 486, 607). Specifically, following removal of luminal and basolateral Cl^-, the steady state luminal HCO_3^- concentration in rabbit proximal convoluted and straight tubules perfused at slow flow rates was Cl^- independent (129, 486). These findings have been criticized in that apical and basolateral Cl^- was replaced with nitrate that can potentially be transported by anion exchangers (449). Additional studies however in proximal convoluted tubules showed that Cl^- substitution with isethionate also did not alter transepithelial HCO_3^- absorption (607).

Karniski and Aronson advanced the understanding of the underlying transport mechanisms in rabbit brush border vesicles, by first showing the presence of formate-driven Cl^- transport and Cl^--driven formate transport whose activity was significantly greater than Cl^-/OH^- exchange possibly accounting for the previous discrepant results (351). Additional studies also revealed the presence of a Cl^-/oxalate exchange mechanism (350). In the *in vivo* perfused rat proximal tubule, Alpern and subsequently Baum in the rabbit proximal tubule confirmed the presence of apical Cl^-/formate exchange by measuring Cl^--induced pHi changes in the presence of formate (17, 59). Formate stimulated proximal tubule volume absorption in tubules perfused with high Cl^- /low HCO_3^- (low pH) solutions mimicking late proximal tubule composition (617, 618). The finding that there was associated cell volume changes and that basolateral DPC (Cl^- channel blocker) inhibited the formate stimulation of transport provided further evidence that the effect on NaCl transport was trancellular rather than paracellular (616, 745, 747). Wang et al reported additional evidence for such a transport process by showing that formate and oxalate stimulate volume and Cl^- absorption in the rat proximal tubule (745, 747). These studies led to the acceptance of a transport model with parallel apical Cl^-/formate and Na^+/H^+ (NHE3) exchangers and apical formic acid recycling. Saleh et al subsequently identified an apical formate/OH^- exchange process (distinct from the Cl^-/formate exchange) that also could contribute formate recycling (605). As predicted, amiloride blocked Cl^- transport in formate/oxalate-free conditions, and EIPA inhibited the formate-stimulated Cl^- transport (60, 574, 745). Unlike formate, oxalate-stimulated Cl^- transport was not EIPA inhibitable and ultimately modeled to be mediated by sulfate/oxalate exchange coupled to Na^+-sulfate cotransport (40, 41, 745).

An initial difficulty with the formic acid recycling model resulted from the fact that the measured formic acid permeability was too low to account for the observed transport rates (571). Unstirred layer effects resulting in formic acid accumulation above the bulk concentration was raised as a possible explanation, but further analysis suggested that brush border microvilli were too short to result in appreciable differences in the formic acid concentration (389, 390). Furthermore, the activity of apical Cl^-/formate and Cl^-/OH^- exchange was subsequently shown to vary among proximal tubule segments potentially accounting for the discrepancy in earlier vesicle studies. Accordingly, Kurtz et al were

unable to detect apical Cl^-/formate exchange in isolated perfused superficial rabbit proximal straight tubule monitoring Cl^--induced changes in pHi however apical Cl^-/OH^- exchange activity was present (406). Furthermore, Sheu et al. detected apical Cl^-/formate exchange in the superficial proximal convoluted tubule but not in the juxtamedullary segment where Cl^-/OH^- exchange activity was found (648). These findings suggested that apical Cl^-/OH^- exchange may play a more important role in late proximal tubule segments where the generation of a lumen to peritubular Cl^- gradient favors transcellular electroneutral passive Cl^- transport.

Identifying the transporter(s) mediating proximal tubule apical anion exchange subsequently focused on the SLC26 gene family (15). Although initially SLC26A4 (pendrin) was initially thought to be a candidate, immunocytochemistry studies were negative (375) and in pendrin knockout mice brush border Cl^-/formate exchange was unaffected (352). A second protein, CFEX (or PAT1) encoded by SLC26A6 that mediated Cl^-/oxalate, Cl^-/formate, Cl^-/OH^-, and Cl^-/HCO_3^- exchange in expression systems, was shown to be localized to the apical membrane of mouse proximal tubules (160, 375, 799). In $CFEX^{-/-}$ mice, oxalate stimulation of proximal tubule volume absorption was absent however formate stimulation of proximal tubule transport was partially impaired (754). Currently it is thought that CFEX (PAT1) mediates apical membrane Cl^-/oxalate exchange *in vivo*. Interestingly, in $CFEX^{-/-}$ mice, baseline volume (NaCl) reabsorption (in the absence of added formate or oxalate) was normal suggesting that CFEX does not mediate significant Cl^- absorption via Cl^-/OH^- and Cl^-/HCO_3^- exchange. Although intracellular pH studies of $CFEX^{-/-}$ proximal tubules demonstrated that CFEX mediates Cl^-/HCO_3^- exchange (754), under physiologic conditions, the transporter preferentially mediates Cl^- absorption via a Cl^-/oxalate exchange process. The reason other CFEX modes of anion transport are not apparent might result from the concentration and affinity of the various transported substrates *in vivo*. In addition, CFEX may interact with other proteins *in vivo* such as CAII, which can modulate its transport properties, and furthermore, expression studies may not simulate *in vivo* proximal tubule protein-protein interactions (26).

Mathematical models of proximal tubule transport showed that the number of Cl^-/formate exchangers has no significant effect on NaCl transport whereas changing the density of luminal NHE3 does have a significant effect (783). Subsequent studies in NHE3 deficient mice demonstrated that formate unlike oxalate failed to stimulate rat proximal tubule volume absorption (752). Petrovic et al provided evidence that formate may directly stimulate NHE3 in the mouse proximal tubule (560). Currently, it is unclear whether formate can directly interact with NHE3 or an accessory protein to modulate apical Na^+/H^+ exchange. In addition, it is unclear why deletion of *Slc26a6* in mice leads to decreased proximal tubule NHE3 activity.

Basolateral Membrane: NBCe1-A; NHE1; Cl^-/HCO_3^- Exchange (Na^+-Coupled and Na^+-Independent; TASK2; H^+-Coupled Organic Anion Transport (see above)

Electrogenic Na^+-Base Cotransport: NBCe1-A—In the *in vivo* perfused rat proximal convoluted tubule, Burckhardt et al first suggested the presence of a basolateral membrane HCO_3^- conductance that was sensitive to SITS (128). Biagi and Sohtell reported similar

findings in rabbit proximal tubules (80) and Alpern demonstrated barium-sensitive K^+ induced pHi changes that suggested the transport process carried a net negative charge (19). Definitive experiments by Boron and Boulpaep showed that basolateral transport was coupled to Na^+ (103). Studying the *in vitro* perfused salamander proximal tubule, lowering peritubular HCO_3^- led to the depolarization of the basolateral membrane, and decreased pHi and intracellular Na^+. Reduction of peritubular Na^+ also caused a similar basolateral membrane depolarization and decrease in pHi. These changes were Cl^--independent and stilbene inhibitable and were compatible with an electrogenic Na^+-HCO_3^- cotransport process. Biagi and Sohtell (79, 80), Alpern (19, 20), Yoshitomi et al (812), and Sasaki et al (611), subsequently confirmed these findings in mammalian proximal tubules, and Lopes et al reported a similar transport process in *Necturus* proximal tubules (460). The Na^+-HCO_3^-cotransport process was also studied in basolateral membrane vesicles by Akiba et al (6), Grassl and Aronson (271, 272), and Soleimani et al (661, 662). $^{22}Na^+$ flux was found to be stimulated by HCO_3^- gradients, Na^+ gradients could drive HCO_3^-, flux (measured by pH changes with acridine orange), and the transport process was modulated by changes in vesicle potential and was stilbene-inhibitable. Soleimani et al concluded that the ion transport stoichiometry was 1:3 (positive charge: negative charge) and that the species transported were 1 Na^+: 1 HCO_3^-: 1CO_3^{2-} (662). Using BCECF to characterize the quantitate the activity of basolateral electrogenic Na^+-HCO_3^- cotransport in S1-S3 superficial and juxtamedullary proximal tubule segments, Abuladze et al reported significant differences axially along the proximal tubule with the activity in S1 proximal tubules ~ 3-5 fold greater than S2 segments, and the activity in S2 segments ~ 8 times greater than the S3 segment (3).

Electrogenic Na^+-HCO_3^- cotransport is now known to underlie the majority of base efflux in the mammalian proximal tubule. First, depolarizing the basolateral membrane blocks transepithelial HCO_3^- absorption (607). Second, Na^+ removal almost completely blocks transepithelial HCO_3^- absorption whereas Cl^- removal is without effect (129, 152, 155, 486, 607). Third, Cl^- removal has no effect on basolateral membrane H^+/base permeability whereas Na^+ removal has a significant effect (19, 570, 613, 812) Fourth, basolateral stilbene inhibitors block HCO_3^- absorption (151). These studies argue against a significant role for basolateral Na^+-coupled Cl^-/HCO_3^- exchange in modulating net transepithelial HCO_3^- transport (that would be expected to function as a Na^+-base influx and Cl^- efflux process).

The molecular identity of the electrogenic Na^+-HCO_3^- cotransporter was first determined by Romero et al who cloned the protein from *Ambystoma* kidney (595). The transporter (NBCe1-A) has also been identified in mammals (encoded by the *SLC4A4* gene) (4) and is expressed predominantly in S1 and S2 proximal tubules (480, 620). NBCe1-A is a homodimer with each monomer functioning independently (345). Each NBCe1-A monomer has a large N-terminal cytoplasmic region, a transmembrane region with 14 transmembrane regions, and a short C-terminal cytoplasmic tail (827, 828). Three NBCe1 variants (encoded by the *SLC4A4* gene) have been identified at the protein level in mammals (NBCe1-A,-B,-C) and two variants at the transcript level in mice (NBCe1-D and -E) that are expressed in various tissues (2, 4, 456, 482). These NBCe1 variants differ in their N-terminal regions and/or C-terminal tails, but share the same predicted topological structure and

transmembrane (transporting) region as NBCe1-A. Mutations in these NBCe1 variants might account for some the extrarenal manifestations of patients with autosomal recessive proximal RTA (pRTA) due to mutations in the transporter (see below).

The direction of ion flux mediated by NBCe1-A in the proximal tubule is determined by the electrochemical driving force (μ) through the transporter, which is a function of the basolateral membrane potential, the substrate ion activities, and the NBCe1-A charge transport stoichiometry (407, 829). It has been implicitly assumed (in lieu of *in vivo* measurements of the native human transporter) that the NBCe1-A has charge transport stoichiometry of 1:3 (Na^+-CO_3^{2-}-HCO_3^- cotransport mode) in the human proximal tubule largely based on *in vivo* measurements in other species (512, 564, 812). When expressed in a mammalian expression system (829) or oocytes (425), human NBCe1-A has a charge transport stoichiometry of 1:2. Various factors including phosphorylation state, (276), cell-type (275) and cell Ca^{2+} (511) have been reported to modulate its value and yet the relevance of these findings to the proximal tubule *in vivo* is unclear.

Recent electrophysiologic data using NO_3^- as a surrogate for CO_3^{2-} transport indicated that human NBCe1-A functioning with a charge transport stoichiometry of 1:2 mediates Na^+-CO_3^{2-} cotransport (829). Preliminary data in the *Xenopus* oocyte expression system using surface pH electrodes has also suggested that rat NBCe1-A transports Na^+-CO_3^{2-} (424) recent analysis using published rat proximal tubule data showed that NBCe1-A functioning as a Na^+-CO_3^{2-} cotransporter (1:2 charge transport stoichiometry) would also be capable of mediating cell to peritubular base flux while being more sensitive than in the 1:3 mode of changes in in the electrochemical gradient across the transporter (829).

Na^+/H^+ Exchange: NHE1—Boron and Boulpaep first reported apical and basolateral Na^+/H^+ exchange processes in the salamander proximal tubule (104). In renal cortical basolateral membrane fractions, initial studies could not detect Na^+/H^+ exchange activity (330, 602), whereas Grassl and Aronson subsequently reported pH gradient driven Na^+ uptake that was not amiloride inhibitable (271). Experiments in rat and rabbit proximal convoluted tubules, showed that peritubular Na^+ changes altered pHi but the effect was not amiloride sensitive (19, 392). In the rabbit S3 proximal straight tubule, Kurtz provided evidence for an amiloride sensitive basolateral membrane Na^+/H^+ exchanger (401) and Giebel et al found a similar process in juxtamedullary S1 and S2 proximal tubules (237). In the rabbit, immunocytochemistry studies have detected basolateral NHE1 in all proximal tubule segments whereas rat proximal tubules are unstained (88). Cytoplasmic CAII can interact with NHE1 and the association between these proteins increases through an ERK-dependent pathway (446). Holthouser et al reported that in human kidney proximal tubule cell lines, ouabain-mediated regulation of Na^+-K-ATPase activity is dependent on its interaction with NHE1 (310)

Na^+-Coupled and Na^+-Independent Cl^-/HCO_3^- Exchange—The presence of baslateral Cl^-/HCO_3^- exchange was first detected in *Necturus* proximal tubules (202). The Na^+-dependence of the transport process was subsequently shown by Guggino (280). These and other studies concluded the transporter was a Na^+-coupled Cl^-/HCO_3^- exchange process (279, 649) whereas Alpern and Chambers reported the presence of both Na^+-

coupled and Na^+-independent Cl^-/HCO_3^- exchange (20). Because the data could also have been mediated by electrogenic Na^+-base transport in parallel with a basolateral Cl^- conductive pathway, additional studies were done which concluded that in the rat proximal tubule greater than 25% of basolateral H^+/base flux is mediated by a Na^+-coupled Cl^-/HCO_3^- exchange process (570) and similar findings were obtained in the rabbit proximal straight tubule (613). The rabbit S3 proximal tubule was reported to have a Na^+-independent Cl^-/HCO_3^- exchange process only, in addition to electrogenic Na^+-base transport (401, 520). Grassl et al studying rabbit basolateral membrane vesicles provided evidence for electroneutral Cl^-/HCO_3^- exchange that was not Na^+-coupled whereas in rat vesicles, Na^+-dependence could be demonstrated (272). Similarly Chen and Verkman in rabbit basolateral membrane vesicles found evidence for a Na^+-coupled Cl^-/HCO_3^- exchange process (157). In summary, it appears that the basolateral membrane of the proximal tubule mediates Cl^-/HCO_3^- exchange however its Na^+-dependence still remains controversial. Moreover, there is currently no data that sheds light on the molecular nature of the specific protein(s) involved.

TASK2—TASK2 pH-sensitive K^+ channels are expressed on the basolateral membrane of proximal tubule cells and TASK2$^{-/-}$ mice have metabolic acidosis and elevated urine pH (757). During HCO_3^- administration, the fractional excretion of Na^+ and Cl^- is increased. The acid-base abnormalities in these mice are thought to be potentially due to a depolarization of the basolateral membrane potential with impaired NBCe1-A base efflux leading to a pRTA phenotype. Thus far, mutations in TASK2 have not been reported in humans.

$H^+/OH^-/HCO_3^-$ Permeability—Net luminal H^+ secretion in the proximal tubule is potentially modulated by its $H^+/OH^-/HCO_3^-$ permeability properties. The apical H^+/OH^- permeability using different preparations is ~ 0.5 cm/sec when corrected for surface area (328, 586). Passive H^+/OH^- flux is predicted to be quantitatively unimportant in the early proximal tubule where the luminal pH is initially 7.4 and cell pH is ~ 7.3 (571) whereas in the later portion of proximal tubule, where the luminal pH decreases to ~ 6.8, it is estimated that ~ 30% of secreted H^+ would diffuse back into the cells. The basolateral membrane H^+/OH^- permeability of 0.67 cm/s approximates the apical membrane permeability and plays a very minor role in basolateral base efflux. The estimated transepithelial H^+/OH^- permeability (0.3 cm/sec) is identical with the transcellular H^+/OH^- permeability (calculated from the apical and basolateral values measured separately) suggesting that paracellular H^+/OH^- flux is insignificant (291, 571, 632). Estimates of the transepithelial HCO_3^- permeability of 1.7 −3.5 × 10^{-5} cm/sec in rat proximal convoluted tubule and 2.0 × 10^{-5} cm/sec in rabbit proximal convoluted tubules, also indicate that passive HCO_3^- flux in the early proximal tubule is insignificant (22, 153, 309). However, because of a lower luminal pH (and HCO_3^- concentration) in the late proximal tubule the calculated peritubular to luminal HCO_3^- backleak becomes more quantitatively significant (22).

Regulation of Proximal Tubule H^+/Base Transporters and Whole Tubule Transport

NHE3

In the current topological model of NHE3, the cytoplasmic C-terminus functions as a regulatory domain that dynamically interacts with accessory proteins that modulate NHE3 function and membrane expression. Several NHE3 binding partners and regulatory proteins have been reported including megalin, PDZK1, DPPIV, and Shank2, however their functional role in most instances is unknown (86, 242-245, 295). Of the known regulatory factors, one of the most important is inhibition by cAMP-dependent phosphorylation via PKA (342, 503, 775). In experiments designed to stimulate cAMP acutely, early studies showed that the appearance of luminal cAMP as an index of cytosolic cAMP in S1 tubules correlated inversely with the proximal tubular HCO_3^- transport rate (452). NHE3 is also phosphorylated via PKC (349, 492, 774, 789), and regulated through G-proteins (11), and tyrosine kinase (244). Rapid regulation of NHE3 is mediated by changes in brush border insertion/retrieval NHE3 (94, 212, 305, 821). Early micropuncture and tubule perfusion studies had shown that PTH inhibits proximal tubule HCO_3^- absorption due to inhibition of transcellular H^+ secretion (48, 322, 490, 491, 577). Luminal Na^+/H^+ exchange activity was decreased in response to PTH in perfused tubules (184, 289), which mirrored the effect of cAMP in tubule suspensions (190) and brush border vesicles (342). PTH decreased the sensitivity of NHE3 to changes in intracellular pH (342, 499, 566) and Na^+/H^+ exchange activity increased in parathyroidectimed animals (174). Vesicles studies showed that the effect of PTH on Na^+/H^+ exchange activity and NHE3 phosphorylation occured within minutes (212). The scaffolding protein NHERF-1, which contains a C-terminal PDZ domain was shown to play a key role in cAMP mediated inhibition of NHE3 (778, 781, 831). Specifically, NHE3 and NHERF-1 are linked to the actin cytoskeleton with the PKA anchoring protein/actin binding protein ezrin (an ERM family actin binding protein) and the interactions between these proteins is required for PKA-mediated inhibition of NHE3 (181, 723, 776, 777, 779, 780, 782, 819, 831).

The signaling pathways involved in NHE3 modulation have been for the most part performed in the OKP cell line that expresses NHERF-1, and has Na^+-H^+ activity kinetics similar to NHE3 (32, 416). These cells were used as a model system for analyzing the interaction between NHERF-1 and NHE3, and NHERF-1 and ezrin (773, 777). Ezrin, NHERF-1 and NHE3 have been immunolocalized to the brush border of the rat proximal tubule where they form a protein complex (724). In mice lacking NHERF-1, NHE3 inhibition by cAMP is absent and the function of NHE3 in proximal tubule cells cultured from these mice is not regulated by PTH (182, 647, 779). cAMP inhibition of NHE3 also involves EPAC (exchange protein directly activated by cAMP) (311). Both EPAC and PKA each contribute ~50% of the cAMP inhibitory effect on NHE3 (514). NHERF-1 is required for cAMP inhibition of NHE3, and occurs via both PKA- and EPAC-dependent mechanisms (514). Finally PP1, a calyculin A sensitive phosphatase stimulates NHE3 by dephosphorylating the transporter (201).

The NHE3 residue(s) that are phosphorylated via PKA/cAMP of NHE3 remains controversial (503, 822). Kurashima reported the phosphorylation of NHE3-Ser^{634} and that Ser^{605} is also required for the effect but remains unphosphorylated (398). Zhao reported that PKA induces the phosphorylation of NHE3-Ser^{552} and Ser^{605} (822). Further studies by Kocinsky showed that in normal rats, NHE3-Ser^{552} is significantly more phosphorylated than Ser^{605} and is localized to the coated pit region of the brush border that has inactive NHE3 (378, 379). In addition, phosphorylation at both sites does not alter NHE3 function.

PTH may also modulate NHE3 activity via PKC through phospholipase C activation (318, 492, 774). Although the data is somewhat conflicting, acute PKC activation appears to increase transcellular HCO_3^- absorption whereas chronic PKC activation decreases transport (64, 744). Changes in cytosolic Ca^{2+} do not affect the intrinsic function of NHE3 unlike NHE1, which has a cytosolic calmodulin binding domain (residues 636-656) (729, 731).

Casein kinase 2 stimulates the basal activity of NHE3 by interacting with the C-terminal tail and phosphorylating Ser^{719}, which increases plasma membrane delivery of newly synthesized NHE3 (606). PTH decreases the membrane expression of the transporter over a period of hours (212). This effect has been observed in brush border vesicles and OKP cells (175). Disruption of the actin cytoskeleton leads to an increase in NHE3 expression (148). The exact role of actin in the retrieval/insertion of NHE3 in the brush border is unclear however its role in PKA mediated NHE3 phosphorylation has been shown (397, 681). NHE3 appears to transfer to the base of the microvilli following mediated PKA phosphorylation (806). Retrieval of NHE3 with megalin to a vesicle compartment is also involved (85, 86). PTH has also been shown to decrease NHE3 expression due to altered NHE3 mRNA stability with an associated inhibitory effect on the *SLC9A3* promoter (77).

Indirect binding of ezrin to NHE3 via NHERF-1 (NHE3 amino acids 585 to 689) also regulates the transporter signaling through cAMP (776, 818, 819), cGMP (144), Ca^{2+} (363, 427), and lysophosphatidic acid (161, 426). Ezrin can also bind directly to NHE3 (amino acids 475 to 589) affecting NHE3 trafficking (delivery from the synthetic pathway, basal exocytosis) and NHE3 movement within the brush border that may alter NHE3 endocytosis (145). Ca^{2+} induced NHE3 inhibition requires PKCα, which binds to E3KARP decreasing surface NHE3 expression likely by inducing endocytosis (427). CHP1 (calcineurin homologous protein) increases NHE3 membrane abundance and ezrin phosphorylation (Thr-567) (187). NHE3 basal activity is currently thought to be regulated by sequential effects of Akt and GSK3 acting on the same NHE3 C-terminal ezrin binding domain (658).

NBCe1-A

NBCe1-A has a unique N-terminal autostimulatory domain (ASD) that enhances the function of the transporter via an unknown mechanism (482). Mg^{2+} causes NBCe1-A rundown in *Xenopus* oocytes, that may involve a Mg^{2+}-dependent phosphatase (5′-lipid phosphatase) which dephosphorylates PIP_2 (797). PIP_2 *per se* activates NBCe1-A, however the mechanism has not been determined (797). Various systemic and hormonal factors alter the expression and/or function of NBCe1-A. Angiotensin II has a biphasic effect on NBCe1 mediated transport (176, 177, 313, 558, 823) and NBCe1-A inhibition via the AT_{1B} receptor

leads to decreased NBCe1-A surface expression mediated by Ca^{2+}-insensitive PKCε (558, 559). Endocytosis of NBCe1-A is modulated by PKCs (PKCαβγ) and a novel PKCδ (54, 557, 815). ATP increases the NBCe1-A function via an unidentified protein kinase (511).

The function and/or expression of NBCe1-A is also modulated by PTH, norepinephrine, dopamine, and changes in blood pressure. PTH decreases the function NBCe1-A in the rat (possibly via a cAMP) whereas in the rabbit, PTH is without effect (609). Infusion of norepinephrine in rats increases the expression of the transporter (663) whereas dopamine decreases the activity of NBCe1-A (396). NBCe1-A expression in the SHR rat was increased ~2 fold above control rats via an unknown mechanism (664).

NBCe1-A expression is altered in various models of renal tubular acidosis (RTA). The transporter is upregulated in lithium induced distal RTA (dRTA) (364), however in hyperkalemic dRTA induced by ureteral obstruction its expression in the proximal tubule is decreased (741). In humans, hypothyroidism is associated with incomplete dRTA, and NBCe1-A expression is decreased in a rat hypothyroid model (505). Concomitant NH_4Cl loading increases the expression of NBCe1 (505). The calcineurin inhibitor FK506 which has been reported to cause both pRTA and hyperkalemic distal RTA, induces a decrease in NBCe1-A expression (506)

Carbonic anhydrase II (CAII) binds to NBCe1-A at a C-terminal $D^{986}NDD^{989}$ motif and Gross et al proposed that CAII and NBCe1 form an intermolecular transport metabolon (277). Pushkin et al. and Becker et al. provided further evidence for functional interaction between NBCe1 and CAII (69, 578). CAIV and CAIX were subsequently shown to bind extracellular loop 4 in NBCe1-B (and presumably NBCe1-A) (25, 531). Not all groups however have been able to demonstrate functional interaction with CAII (461, 563, 803). Interestingly, the loss of CAII function results in a moremild phenotype compared to patients with NBCe1 mutations (444, 659). Moreover, mutations in CAIV cause retinitis pigmentosa (RP17) without a pRTA phenotype having been reported (584). In *Xenopus* oocytes, CAI, CAII and CAIII stimulated NBCe1-A transport is due to carbonic anhydrase enzymatic activity rather than intramolecular proton shuttling (623).

Proximal Tubule HCO_3^- Transport

Acute and Chronic Changes in Acid-Base Chemistry and K^+—The first studies by Malnic and Mello Aires addressing the dependence of luminal HCO_3^- concentration on HCO_3^- absorption using the split droplet technique showed that the kinetics were first order hence the rate of luminal H^+ secretion was proportional to the luminal HCO_3^- concentration (476). These findings were confirmed by other studies using a similar preparation, and in separate tubule perfusion experiments (22, 703). *In vivo* microperfusion studies that accounted for passive HCO_3^- flux demonstrated that there is a dependent on H^+ secretion below a luminal HCO_3^- concentration of ~ 45 meq/l (22). Since HCO_3^- cannot be transported by NHE3, these findings were likely dependent the effect of changes in the luminal HCO_3^- concentration on luminal pH and/or cell pH, since both factors can potentially alter the function of NHE3 and NBCe1-A independently.

Transepithelial HCO_3^- absorption varies inversely with the peritubular HCO_3^- concentration because of its effect on transcellular H^+ secretion with minimal effect on paracellular HCO_3^- diffusion (23, 151, 239, 493, 608, 703, 826). The effect had been attributed to a change in peritubular pH (with secondary changes in cell pH) modulating the function of basolateral Na^+-base cotransport (NBCe1-A). An elevation of peritubular pCO_2 increases proximal tubule HCO_3^- absorption while a decrease has the opposite effect (169, 333, 438, 493, 608, 826). The exact mechanism is complex to address because of the rapid diffusion of CO_2 across all proximal tubular compartments with accompanying changes in pH and HCO_3^-. Moreover, apical and basolateral membrane H^+/base transport processes have different sensitivities to changes in H^+ activity in each compartment. For example, apical NHE3 is allosterically regulated by an acidic cytoplasmic pH thereby increasing its Na^+-H^+ exchange function greater than would be predicted from the concentration of the transported ions (42). A potential explanation for these findings is derived from studies of NHE1 that have identified residues 567-635 in the cytoplasmic C-terminus as playing an important role in cytoplasmic pH “sensing” (730).

NHE3 stimulation by a decrease in pH requires the activation of c-Src that complexes with Pyk2 (445). A second pathway involves ERK1,2/c-fos and both pathways converge to activate the endothelin ET_B receptor ultimately increasing NHE3 membrane expression (568). In both rat and rabbit proximal tubules, ET-1 stimulates apical Na^+/H^+ exchange (203, 282). In OKP cells transfected with the ET_B receptor, ET-1 stimulates NHE3 activity and is associated with phosphorylation of the transporter and increased plasma membrane expression (164, 554, 555). Metabolic acidosis is associated with increased endothelin-1 (ET-1) mRNA expression (415, 448). Increased ET-1 expression appears to involve the AP-1 transcription factor (312). The metabolic acidosis stimulation of NHE3 activity is blocked in mice with targeted disruption of the ET_B receptor (415, 448). Tyrosine kinase, CaM kinase, and an increase in cell Ca^{2+} are involved (164, 165). Cortisol levels increase in metabolic acidosis and adrenalectomized rats fail to manifest a metabolic acidosis induced stimulation of Na^+/H^+ activity (370, 481). Glucocorticoids act concomitantly with metabolic acidosis to increase NHE3 trafficking and plasma membrane expression whereas aldosterone has no effect (29).

Using “out of equilibrium” solutions, Boron et al was able to analyze the effect of pH, HCO_3^-, and CO_2 individually and found that pH per se was not a factor in modulating proximal tubule HCO_3^- transport (825, 826). The authors proposed that the basolateral membrane possesses HCO_3^- and CO_2 sensors that modulate transepithelial HCO_3^- transport. Genistein (tyrosine kinase inhibitor) eliminated the CO_2 sensitivity of HCO_3^- transport (825). Basolateral CO_2 sensing signaled through the apical membrane AT2 receptor via secreted angiotensin II peptide (824).

Chronic changes in systemic acid-base balance appear to have profound effect on proximal tubule H^+/base transport processes and transepithelial HCO_3^- transport. These studies are complicated by the concomitant changes in renal hemodynamics and hormonal milieu that can independently modulate HCO_3^- transport. Kunau et al showed that chronic metabolic acidosis stimulates proximal tubule HCO_3^- absorption to a greater extent than more severe acute metabolic acidosis (394). Cogan showed that chronic hypercapnia is more potent than

acute hypercapnia (168). Cohn et al demonstrated in apical vesicles that the effect of chronic metabolic acidosis on Na^+/H^+ exchange activity was retained *in vitro* at pH 7.4 (memory effect) suggesting a change in membrane expression or structure (174). Further studies showed that the effect was indeed due to an increase in Vmax (370, 690). Chronic metabolic acidosis also stimulated basolateral electrogenic Na^+-base transport (NBCe1-A) that was retained *in vitro* at pH 7.4 (7, 570) whereas chronic metabolic alkalosis had the converse effect. NaCl and $NaHCO_3$ administration could modulate proximal tubule HCO_3^- absorption by decreasing the expression of NBCe1-A thereby contributing to the recovery from metabolic alkalosis and/or volume overload (33). Unlike the effect of metabolic acid-base disorders, mixed results have been reported in chronic respiratory acidosis (7).

Acid-base disorders are often accompanied by changes in K^+ balance. K^+ depletion increases bicarbonate absorption by ~ 25% increase whereas a lowering peritubular K^+ has no effect (151). These results differ from studies in OKP cells bathed in media with low K^+ where Na^+/H^+ exchange activity was stimulated that has been attributed to a decrease in pHi (31). In K^+ depletion, the expression of NBCe1-A is increased providing a potential mechanism for enhancing proximal tubule HCO_3^- transport during hypokalemic metabolic alkalosis (34).

Luminal Flow Rate, Extracellular Volume, Renin-Angiotensin System, Aldosterone and Catecholamines—The phenomenon of glomerulotubular balance where increased GFR leads to enhanced proximal tubule HCO_3^- absorption prevents significant renal excretion of HCO_3^-. Experiments in the perfused proximal tubule both *in vivo* and *in vitro* have shown that tubular HCO_3^- absorption is flow-dependent (24, 151, 196). Possible mechanisms include: 1) an alteration in the axial HCO_3^- concentration profile; 2) an effect on paracellular permeability; 3) effect on an unstirred layer in the bush border; 4) flow is transduced into a torque by its effect on brush border microvilli. Each of these potential factors has been studied. Chan et al (151) and Alpern et al (24) showed that changes in the axial HCO_3^- concentration profile can only account for a small portion of the effect. Du et al (196) and Chan et al (153) also showed that changes in paracellular permeability are not involved. Preisig et al showed that increased flow results in an increase in pHi due to enhanced apical Na^+/H^+ exchange (569). Involvement of apical Na^+/H^+ exchange was further shown in mice with targeted disruption of NHE3 where glomerulotubular balance is impaired (135). Du et al demonstrated flow-dependence in the mouse proximal tubule and concluded that the apical H^+-ATPase activity was also involved (196). Other studies have documented an increase NHE3 or NBCe1-A activity in models of chronically increased luminal flow that are also associated with renal hypertrophy (uninephrectomy, increased protein intake) (173, 297, 524, 572).

A brush border acidic unstirred layer would be predicted to impede H^+ secretion wherein as luminal flow increases, the effect of the unstirred layer would diminish thereby enhancing luminal H^+ secretion. However, experiments in the rat proximal tubule indicated that there is not a significant brush border diffusion barrier (24, 569). An alternate mechanism was proposed whereby luminal flow varies linearly with the torque on the brush border microvilli (195, 196, 742). The flow-dependence of both volume and HCO_3^- absorption in the mouse proximal tubule was modeled where the magnitude of the torque was the “sensor”

that signaled enhanced H^+ secretion and HCO_3^- absorption. Over a 5-fold increase in luminal flow, microvillus torque increased 2-fold, and correlated with HCO_3^- transport changes. The actin cytoskeleton played an important role in affecting both NHE3 and H^+-ATPase function. Du et al re-analyzed the rabbit tubule perfusion data of Burg and Orloff and found that the reported changes in flow would increase microvillus torque by ~43% that could account for the observed increase in volume absorption (130, 195). To account for these species differences, it was suggested that the rabbit tubule is more distendable so that the changes in luminal diameter prevent significant changes in mivrovillus torque that occur in the mouse.

Proximal tubule HCO_3^- absorption is also modulated by the extracellular volume status and pressure independent of altered luminal flow rate. Volume expansion has been shown decrease HCO_3^- absorption in the rat proximal tubule although the magnitude of the effect differs among studies (84, 170). The underlying mechanism involves several factor including an increase in paracellular backleak (due changes in paracellular HCO_3^- permeability), and modulation of net transcellular H^+ secretion resulting possibly from alteration in peritubular pH and/or HCO_3^- (18, 23) Interestingly, parathyroidecomized rats have a significantly decreased response without the underlying the mechanism(s) having been defined (496). A decrease in dietary Na^+ was also shown to induce an increase in brush border Na^+/H^+ exchange *in vitro* due to an increase in Vmax (504). Conversely, chronic dietary Na^+ loading induced the phosphorylation of NHE3-Ser^{552}, and redistribution of NHE3 to the base of the microvilli driven by myosin VI, and redistribution of the NHE3 regulator DPPIV (807).

Because the proximal tubule synthesizes and secretes angiotensinogen, the luminal concentration of angiotensin II is 1 – 10 nM while the systemic concentration is significantly less (0.01-0.1 nM) (108, 565, 642). In the *in vivo* perfused rat proximal tubule, angiotensin II was shown to enhance HCO_3^- absorption (452, 453). In the *in vitro* perfused rabbit proximal tubule, the mechanism of the stimulation involved both apical Na^+/H^+ exchange and basolateral Na^+-base transport (236). Angiotensin II increased the Vmax of apical Na^+/H^+ exchange and at higher concentrations also increased H^+-ATPase activity in a proximal tubule OKP cell line by enhancing plasma membrane expression involving signaling through tyrosine kinase, PI3K, and P38 (140, 603). Angiotensin II has also been reported to increase apical H^+-ATPase membrane vesicle insertion in rat proximal tubule fragments (727). Peritubular angiotensin II has a biphasic effect on transepithelial Na^+ transport in rat and rabbit proximal tubules where lower concentrations are stimulatory and higher concentrations that are likely unphysiologic are inhibitory; a similar phenomenon was shown in OKP cells examining NHE3 activity (134, 316, 629). The inhibitory effect was reported to involve angiotensin III interacting with AT2 receptor (284, 538, 539). Studies in rat tubules and cortical homogenates have concluded that angiotensin II signals through a decrease in adenyl cyclase activity, however in OKP cells, NHE3 activity was stimulated by angiotensin II in the absence of changes in cAMP (134, 452, 794). In both OKP cells and rats treated chronically with angiotensin II, NHE3 activity was increased likely due to increased functional protein content (189, 802). Other investigators found no effect on NHE3 content but detected increased NBCe1-A protein that was blocked using an AT1

receptor blocker (700). An additional effect involves angiotensin II mediated translocation of NHE3, NHERF-1, ezrin and the H^+-ATPase from the tip to the base of the brush border microvilli (433, 593). Others have shown that PKC, CaM kinase, c-Src, and PLA2 are involved in angiotensin II signaling and that a functional intracellular angiotensin system is active in the proximal tubule (205) Acid-base disturbances such as metabolic acidosis can also increase AT1 receptor expression and thereby modulate angiotensin II signaling (518).

Unlike angiotensin II, the plasma peptide ANG-(1–7) concentration increases following extracellular volume expansion (341, 551, 552). In vivo stationary microperfusion studies in rat proximal tubules have shown that luminal ANG-(1–7) has a biphasic dose-dependent effect on HCO_3^- reabsorption mediated by the Mas receptor via NHE3 (143). Unlike angiotensin II high concentrations of ANG-(1–7) stimulate HCO_3^- reabsorption whereas low concentrations inhibit transport. In the rat proximal straight tubule, basolateral ANG-(1–7) has a biphasic mediated by AT_1 receptors such that at physiologic levels, it increases HCO_3^- reabsorption, whereas at high concentrations, it decreases transport (231).

Basolateral membrane transporters are also affected by renin-angiotensin signaling. Specifically, angiotensin II (see above) increases NBCe1-A activity in part via PKC and by increasing transporter density (594, 599). Additional effects include a stimulation of the basolateral Na^+-K^+-ATPase via phosphorylation (810), and an increase basolateral membrane K^+ conductance (176). Apical Na^+ uptake pathways appear to predominate since angiotensin II increases intracellular Na^+ (587).

Aldosterone in rats increased proximal tubule NHE3 brush border protein content and stimulates transepithelial water reabsorption (393). In microperfusion studies of rat S2 proximal tubules, Pergher found that aldosterone (luminal or peritubular) stimulated HCO_3^- absorption via glucocorticoid receptors through a nongenomic mechanism (556). In cultured human proximal tubule cells, aldosterone signaling was reported to be mediated through the EGF receptor (194). Basolateral NHE1 is regulated by aldosterone through genomic (aldosterone receptor) and nongenomic mechanisms. At lower concentrations, aldosterone increases intracellular Ca^{2+} and stimulates basolateral NHE1, whereas higher concentrations (10^{-6} M) decrease intracellular Ca^{2+} and inhibit the transporter (428). The glucocorticoid receptor appears to be involved in the rapid nongenomic effects of aldosterone on NHE1 activity that may play a role during changes in volume status.

Proximal tubule transport is reduced ~40% following renal denervation (72). Conversely, an increase in renal nerve activity can stimulate transport by ~ 30% (70). In the rabbit perfused proximal tubule, norepinephrine increased both HCO_3^- and Cl^- transport (67). In rabbit proximal tubule suspensions and rat proximal tubules perfused *in vivo*, catecholamines stimulated Na^+/H^+ exchange activity (150, 525). NHE3 stimulation is mediated by α_2 receptor binding associated with decreased adenyl cyclase signaling through $G\alpha_i$, and α_1 receptor binding signaling through MAPK (451). β_2 receptor stimulation increases the association of NHERF-1 with the receptor resulting in increased Na^+/H^+ exchange by preventing cAMP driven downregulation of NHE3 (285). Sympathetic nerve activity may also stimulate NBCe1-A through PKC (598). Renal nerves also modulate local angiotensin synthesis and potentially AT1 receptor density (386, 580, 581). Proximal tubule Na^+

transport is modulated by NO that is generated from renal nerve activity or interstitial endothelial cells or (447). NO release in pericapillary perfusion experiments increased apical Na^+/H^+ exchange (37). Mice lacking neuronal NOS have decreased proximal tubule HCO_3^- transport (749). Wang et al shed light on these findings by showing that tubule perfusion with sodium nitroprusside was dose-dependent where a low dose increased transport, a high does decreased transport, and NOS inhibition decreased HCO_3^- absorption (743). NO signaling appears to be mediated through cGMP (338). NO stimulates cultured human proximal tubule cells expressing soluble guanylate cyclase to secrete cGMP resulting in inhibition of apical NHE3 through Src (612).

Dopamine, Glucorticoids, Insulin, and Uroguanylin—Dopamine receptors are present on the luminal and basolateral membranes of the proximal tubule (527). In the proximal straight tubule, and tubule suspensions, dopamine inhibits Na^+ transport (73, 417). Other studies suggest that prior exposure to norepinephrine is required for the dopamine inhibitory effect (66). The inhibitory effect of dopamine is mediated through NHE3 (cAMP/PKA) and the Na^+-K^+-ATPase (PKC) (241). In the rat *in vivo*, dopamine mediated phosphorylated NHE3 shifts from the brush border to a subapical region (379). Dopamine also decreases the activity of basolateral NBCe1-A (396).

Glucocorticoids stimulate NHE3 activity through several mechanisms. Acutely, dexamethasone administration increases NHE3 trafficking to the apical membrane following phosphorylation of NHE3-Ser^{663} via glucocorticoid-dependent kinase 1 (SGK1) (97, 739). ClC-5 appears to play a key role in basal and dexamethasone-stimulated exocytosis of NHE3 (450). As discussed in the context of metabolic acidosis, glucocorticoids synergistically increase NHE3 trafficking to the plasma membrane (29). Systemic administration of glucocorticoids or *in vitro* exposure of proximal tubule cell cultures or OKP cells stimulate NHE3 activity via the glucocorticoid receptor by modulating NHE3 mRNA abundance (62, 65, 740).

Insulin stimulates fluid absorption in the proximal tubule perfused *in vitro* (61) and alters NHE3 activity both acutely and chronically via separate mechanisms. Although the mechanism of acute activation is unknown, several potential pathways have been ruled out including phosphatidylinositol 3-kinase-serum- and glucocorticoid-dependent kinase 1 (PI3K-SGK1), cbl/CAP/TC10, NHE3-megalin interaction, NHE3 phosphorylation, and increased apical membrane trafficking (228). Chronically, insulin stimulates NHE3 activity via PI3K-SGK1(228). Glucocorticoids also augment the effect of insulin on NHE3 potentially via the induction of SGK1 (374).

Uroguanyln is a member of the guanylin family of peptides that are involved in pH and volume regulation (434). Renoguanylin was first isolated from eels and is expressed in kidney and intestine (816). In microperfused rat proximal tubules renoguanylin decreased HCO_3^- absorption via an inhibition of apical Na^+/H^+ exchange and H^+-ATPase via a protein kinase dependent pathway (434). In additional studies in rat proximal tubules and LLC-PK cells, NHE3 inhibition involved the activation of both cGMP/PKG and cAMP/PKA, NHE3 phosphorylation, and decreased NHE3 surface expression (435).

Isolated Familial Proximal Renal Tubular Acidosis: Mutations in NBCe1—Of the proteins responsible for H^+/base transport in the proximal tubule, only mutations in NBCe1 cause a severe form of isolated pRTA as no mutations in NHE3 have been described and CAII mutations often cause a mild form of combined proximal and distal RTA. pRTA is the end result of both acquired and genetic abnormalities in multiple pathways that mediate proximal tubular HCO_3^- absorption (reviewed in detail (296)). Defective proximal tubule HCO_3^- absorption can occur in isolation or accompanied by other proximal tubule transport defects (Fanconi's syndrome). Mutations in NBCe1 are the only known cause of isolated familial pRTA (321). While other proximal tubular transport functions are normal, patients have extrarenal abnormalities including short stature, neurological findings (mental retardation, basal ganglia calcifications, migraine headaches), ocular abnormalities (cataracts, band keratopathy, glaucoma), tooth (enamel) defects, and elevated amylase and lipase (402). The extrarenal manifestations are likely due to local abnormalities in H^+/base transport due to defective NBCe1 variant function. The additional role that systemic acidemia may play remains to be determined.

2 nonsense mutations (Q29X, W516X), 2 frameshift deletions (2311 delA, and a C-terminal tail 65bp-del), and 8 missense mutations (R298S, S427L, T485S, G486R, R510H, L522P, A799V, and R881C), have been reported. All cases reported thus far are inherited in an autosomal recessive fashion. Whether individuals heterozygous for NBCe1 mutations have subtle defects in proximal tubule bicarbonate transport and/or mild ocular, brain, growth, and pancreatic enzyme abnormalities is unknown. Mice with targeted disruption of NBCe1 have a shortened lifespan and neurologic and ocular manifestations do not occur suggesting that these abnormalities require a longer time period to develop (235, 413). Headaches have been reported in patients with R510H, L522P, R881C, 2311 delA, and 65bp-del mutations, and also in heterozygous family members of a patient with a 65 base-pair C-terminal deletion and the L522P mutation (680). It has been hypothesized that headaches are due to ER retained misfolded NBCe1-B in brain astrocytes associated with abnormal NMDA-mediated neuronal hyperactivity (804).

Autosomal dominant isolated pRTA has also been reported in patients with decreased bone density and short stature (109, 353, 429). Various proximal tubule proteins involved in H^+/base transport including CA II, IV, and XIV; NBCe1; NHE3; NHE8; NHERF-1 and -2, and PAT1 (CFEX) were not found to have mutations in their coding regions. It remains to be determined whether any of these genes are mutated in their intron and promoter regions.

Loop of Henle

Approximately 10-20% of the filtered HCO_3^- load entering the nephron is absorbed in the loop of Henle (139) and the major site of active HCO_3^- absorption is thought to be the thick ascending limb (TAL; (126, 198, 255, 267). The initial segment of the loop of Henle, the thin descending limb, has apical and basolateral Na^+/H^+ exchangers that likely function to regulate pHi (399); with little else known about it's H^+/base transport properties. Passive processes are potentially involved that promote HCO_3^- absorption in the thin descending limb. Osmotic equilibration due to water absorption in the thin descending limb (384, 385) would be predicted result in an increase in the concentration of HCO_3^- and an elevation of

the luminal pCO_2. The subsequent flux of CO_2 down its concentration (depending on the CO_2 permeability of the thin descending limb) would increase the luminal pH resulting in the back-titration of HCO_3^- from other luminal buffers (NH_4^+ and $H_2PO_4^-$). This process would effectively mediate the efflux of HCO_3^- in the form of CO_2. The elevated luminal pH also plays an important role in the transport of ammonia from the thin limbs to the collecting ducts (257). Unlike the descending limb of Henle, the ascending limb is water impermeable with a high Na^+ and Cl^- permeability (323, 324). Na^+ transport is mediated by passive diffusion whereas Cl^- transport occurs via passive diffusion and an undefined carrier-mediated process. Whether HCO_3^- transport occurs in this segment is unknown.

The main site of HCO_3^- absorption is the medullary and cortical TAL (mTAL and cTAL respectively) (255, 267). In the TAL, in addition to apical NHE3 which plays the same role as in the proximal tubule, NHE2 and the vacuolar H^+-ATPase have also been localized to the apical membrane however their role in HCO_3^- absorption is unclear (30, 89, 118, 414, 601, 678, 748, 766). As in the proximal tubule, luminal HCO_3^- is absorbed across the apical membrane indirectly via H^+ secretion mediated by NHE3 that combines with luminal HCO_3^- generating CO_2 and H_2O that are transferred across the apical membrane (414, 748). In addition, an apical K^+-dependent HCO_3^- transport process that opposes transepithelial HCO_3^- absorption has also been described (763). K^+-dependent ATP-ase activity has also been reported (814). TAL cells express cytoplasmic CAII and XV, apical and basolateral CAIV, basolateral CAXII, and apical CAXIV however species differences exist (411, 575, 600, 633). Loop diuretics such as furosemide that block cellular Na^+ uptake via NKCC2 stimulate HCO_3^- transport potentially via enhanced NHE3 activity or changes in membrane potential (255).

A basolateral stilbene-sensitive Na^+-base transport process was initially described in the rat and mouse TAL however its molecular identity is unknown (357, 391). Both electrogenic Na^+-base transport and the AE2 anion exchanger (16, 204, 224, 436, 583) that is also expressed on the basolateral membrane may potentially contribute to cell HCO_3^- efflux and transepithelial HCO_3^- absorption. HCO_3^- uptake across the basolateral membrane of the mTAL is currently thought to be mediated in part by NBCn1, an electroneutral stilbene-insensitive sodium bicarbonate cotransporter that could also play a role in cellular $NH_3 + H^+$ efflux and transepithelial tubular ammonia absorption (106, 410, 721). A basolateral K^+-dependent HCO_3^- transport process has been reported in the rat mTAL (93). These transporters could play important roles in transepithelial HCO_3^- absorption, intracellular pH regulation, cell volume regulation, and NH_3/NH_4^+ transport although their exact roles in each of these processes is currently unresolved.

Basolateral membrane ClC-K1 and ClC-K2 chloride channels (or their human orthologs ClC-Ka and ClC-Kb, respectively), play an important role in transcellular Cl^- absorption (209, 211, 377, 706). Bartter's syndrome (a cause of Cl^--resistant metabolic alkalosis) types 3 and 4 is caused by mutations in genes coding for ClC-Kb and the regulatory subunit, Barttin (90, 388, 655). Barttin promotes ClC-K insertion into the plasma membrane (209, 412, 732). Rarely Bartter's syndrome can be caused by compound mutations in ClC-Kb and ClC-Ka (619). The membrane expression and physiologic role differ among species and in

that ClC-K2$^{-/-}$ mice die at a young age and ClC-K1$^{-/-}$ mice have nephrogenic diabetes insipidus (478).

The TAL is also an important sight for transporting NH_3/NH_4^+ from the lumen to the peritubular interstitium for subsequent transport into the collecting duct (233, 248, 267, 358, 359, 764, 771). NH_4^+ is transported across the apical membrane via NKCC2 and potentially via the ROMK potassium channel. The very low apical membrane NH_3 permeability prevents the backflux of NH3 from cell to lumen following apical NH_4^+ uptake (358). The basolateral Na^+/H^+ exchanger NHE4 mediates the cell peritubular efflux of NH_4^+ (NH_3 may also exit the TAL passively) (107, 315). In metabolic acidosis, NHE4 mediated NH_4^+ efflux is stimulated (107).

Regulation of Thick Ascending Limb Bicarbonate Transport

Acute and Chronic Changes in Acid-base Chemistry

As in the proximal tubule changes in acid-base status alter HCO_3^- transport in the TAL. Acute and chronic metabolic acidosis stimulate HCO_3^- transport in both rat microperfusion and isolated perfused mTAL studies (138, 249). Chronic metabolic acidosis also stimulates mTAL ammonia absorption (249). These effects are associated with the upregulation of NHE3 and AE2 (HCO_3^- transport); and NBCn1 (ammonia transport) (360, 410, 414, 583). In the cortex, sodium bicarbonate loading had no effect on AE2 expression unlike potassium bicarbonate loading that decreased AE2 expression, whereas in the outer medulla, sodium bicarbonate loading increased AE2 expression (583).

Basolateral Na^+/H^+ exchange mediated by NHE1 and NHE4 play an important role in modulating the function of apical NHE3, NH_3/NH_4^+ transport, and cell volume regulation (107, 268). Changes in NHE1 mediated transport are coupled to apical NHE3 via the actin cytoskeleton (759). In NHE1$^{-/-}$ mice, HCO_3^- transport in mTALs is significantly reduced (268). Furthermore, the inhibition of HCO_3^- transport by NGF is mediated through mPI3K-mTOR and ERK signaling pathways that result in NHE1 inhibition (253, 263, 765). NHE1 is also involved in the inhibition of mTAL HCO_3^- absorption by LPS (760) (see below).

Aldosterone, Glucocorticoids, Peptide Hormones, PGE2, and Sepsis

Although less studied than the proximal tubule, various hormones and peptides modulate HCO_3^- transport in the loop of Henle and TAL (139). *In vivo* microperfusion studies in rats showed that infusion of angiotensin II stimulates loop segment HCO_3^- absorption thought to involve the TAL although the exact tubule segment involved cannot be discerned from these studies (138). In similar microperfusion studies, the *in vivo* administration of high dose aldosterone and glucocorticoids restored HCO_3^- absorption to basal levels in adrenalectomized rats (704). Aldosterone inhibits TAL HCO_3^- transport via a nongenomic ERK-dependent inhibition of apical NHE3 (261, 264, 758) and angiotensin II inhibits HCO_3^- absorption through a cytochrome P-450 dependent pathway (260). Furthermore, glucagon and arginine vasopressin (AVP) inhibit transport via a cAMP dependent process (82, 252, 495). In the mTAL nerve growth factor inhibits HCO_3^- transport but stimulates absorption in the presence of AVP through distinct signaling pathways (253, 765). The effect of AVP on transport is distinct from the effect of osmolality (250, 251). Specifically,

an increase in osmolality inhibits luminal NHE3 and transport via tyrosine kinase signaling whereas a decrease in osmolality increases HCO_3^- transport through PI-3 kinase signaling (250, 251, 258, 766). The effect of AVP but not hyperosmolality can be reversed by PGE_2 through PKC and G protein (pertussis toxin-sensitive) pathways (254, 259). The stimulatory effect of hyposmolality on HCO_3^- absorption is blocked by AVP and cAMP (258). PTH directly inhibits transport in the isolated perfused rat mTAL (252). *In vivo* PTH stimulates HCO_3^- transport however this effect is complicated by potential changes in the luminal HCO_3^- concentration profile (83).

HCO_3^- absorption in the mTAL is inhibited by gram-negative lipopolysaccharide (LPS) by activation of TLR4 (toll-like receptor 4) and by gram-positive lipoteichoic acid and peptidoglycan through TLR2 (toll-like receptor 2) activation (262, 265, 266). Basolateral LPS inhibits blocks HCO_3^- absorption via through ERK-dependent inhibition of NHE3 (262, 761). Apical LPS inhibits HCO_3^- absorption via TLR4/MyD88-dependent activation of the PI3K-Akt-mTOR pathway coupled to inhibition of NHE1 (760, 762).

Distal Convoluted Tubule/Connecting Tubule

The distal convoluted tubule (DCT) is the next segment of the nephron that is capable of HCO_3^- transport. HCO_3^- absorption has been documented in micropuncture studies and in microperfusion experiments although the magnitude varies among studies (136, 137, 154, 395, 439, 440, 463). In the early DCT, apical H^+ secretion is mediated by Na^+/H^+ exchange (NHE2) and H^+-ATPase activity (46, 149, 750). In the latter portion of the DCT, luminal H^+ secretion is mediated by H^+-ATPase and H^+-K^+-ATPase transport (216, 717, 750, 785). It is difficult from micropuncture and *in vivo* microperfusion studies to clearly determine whether the next portion of the nephron, the connecting tubule (CT), and even the early cortical collecting duct (CCD) is accounting for the reported experimental results. The colonic form of the H^+-K^+-ATPase has been localized to the connecting and early cortical collecting duct (216, 717). In addition to HCO_3^- absorption, studies by Levine have also provided evidence for luminal HCO_3^- secretion (443, 750). This transport process is likely mediated by luminal pendrin, which will be discussed below.

Collecting Duct: Cortical, Outer Medullary and Inner Medullary Collecting Ducts

The collecting duct is subdivided anatomically into the CCD, and outer medullary (OMCD) and inner medullary collecting ducts (IMCD), with each tubule segment having unique H^+/base transport properties. The CCD has a heterogenous cell population with ~ 60% of the cells being principal cells (PCs) that are responsible for Na^+ absorption, K^+ secretion, and water absorption in response to AVP (528). PCs also possess H^+/base transport pathways that are involved in pH_i regulation rather than transcellular H^+/base transport (146, 753, 768). Approximately 40% of the cells in this tubule segment are intercalated cells (ICs) that are further subdivided into Type A and Type B subtypes (sometimes referred to as alpha and beta IC cells respectively). Morphologically Type A ICs have apical microplicae and microvilli and intramembranous rod-shaped particles whereas Type B ICs have few apical microvilli and have basolateral rod-shaped particles (473, 714, 715). Type A ICs mediate

HCO_3^- absorption whereas Type B ICs secrete HCO_3^-. Type A cells have an apical H^+-ATPase and basolateral anion exchange mediated predominantly by AE1, whereas Type B ICs have apical Cl^-/HCO_3^- exchange mediated by pendrin (SLC26A4) and basolateral or diffuse H^+-ATPase expression (14, 117, 118, 365, 500, 501, 712). These properties are best distinguished and characterized in the rat.

Among mammalian species, heterogeneity exists in the expression of these transporters and the overall HCO_3^- transport properties of ICs. For example, at the whole tubule level, rabbit CCDs secrete HCO_3^- whereas rat CCDs absorb HCO_3^- (44, 240, 457, 485, 626, 628, 669). Intramembranous rod-shaped particles that are thought to be associated with the H^+-ATPase are present in the apical membrane of rat Type A ICs and absent in rat Type B ICs (714). In the majority of rabbit ICs, these particles are present apically and basolaterally to varying degrees (592). In addition, rat Type B ICs have basolateral H^+-ATPase staining whereas in the rabbit staining is typically diffuse (628). Moreover, the majority of ICs in the rabbit unlike the rat have H^+-ATPase restricted to cytoplasmic vesicles (713). In the mouse CCD, Type B ICs are less common then in rat or rabbit and lack a dark cytoplasm with numerous mitochondria typical of other species (685). In addition, in mouse Type B ICs, small vesicles without studs are localized beneath the apical gray zone (685). AE1 in the rat is localized to the basolateral membrane of Type A ICs (711, 712) whereas in the rabbit, it is primarily located in multivesicular bodies and cytoplasmic vesicles and occasionally on a portion of the basolateral membrane (471). Differences in IC CA isoform expression among various species also exists (see below).

Cells that don't fit the classic model of Type A or Type B ICs have also been described. Intercalated cells in the rabbit CCD termed γ or G cells have been identified functionally as having apical and basolateral Na^+-independent Cl^-/HCO_3^- exchange, however the percentage of ICs with this property is controversial (207, 772). While the apical transporter is thought to be pendrin, the transporter responsible for basolateral Cl^-/HCO_3^- exchange is not known. Based on their specific ultrastructural properties, Kim et al (362) and Madsen et al (474) reported ICs in the CNT that that differed from classic Type A and Type B ICs that are called non-A non-B ICs. Subsequent studies in mice and rats showed that these cells express apical H^+-ATPase and pendrin, but not basolateral AE1 (362, 365, 685). Breton and Brown have suggested that they are a modified Type B IC (115). The categorization of ICs into various subtypes becomes more complex given that the expression of the H^+/base transporters (pendrin, H^+-ATPase, AE1) in these cells may be modulated by systemic acid-base status and other factors (55, 639).

In addition to the aforementioned transport proteins, Type A and Type B ICs possess other key transporters whose molecular identity is unclear. In Type A ICs, basolateral Cl^- channels have been demonstrated in the CCD and in other collecting duct segments (380-382, 516). In Type B ICs, a basolateral Cl^- conductive pathway contributes to transcellular Cl^- transport that is stimulated by cAMP, modulated by the intracellular HCO_3^- concentration, and is inhibited by DPC and anthracene-carboxylate (479, 625, 682, 683). ClC-3 mRNA is expressed in Type B ICs (530) however it has not been localized in these cells at the protein level. Type A and B cells also possess an unidentified basolateral

Na^+/H^+ exchange process likely plays a role in pH_i regulation rather than transcellular transport (500, 768).

Unlike the CCD, which can secrete or absorb HCO_3^-, the OMCD only absorbs HCO_3^- (44, 457, 487). In the outer stripe portion ($OMCD_{os}$) approximately 2/3 of the cells are PCs and 1/3 are Type A ICs (715). Type A ICs are distinguished from PCs in that they have a basolateral Cl^- conductive pathway, a lower basolateral membrane voltage, and essential no apical conductive pathways (381). In the OMCD Type A ICs generate the lumen positive transepithelial voltage due to electrogenic apical H^+ secretion; with basolateral HCO_3^- efflux mediated by the AE1 Cl^-/HCO_3^- exchanger coupled to Cl^- recycling across the basolateral membrane (628). Given the lack of Cl^- chloride channels on the apical membrane, Cl^- is thought to enter the lumen paracellularly driven by the positive luminal transtubular potential. Type A ICs in the OMCD also express the basolateral SLC26A7 anion exchanger and endosomes containing the transporter are targeted to the basolateral membrane during hypertonicity and K^+ depletion (51, 561, 801). These cells also have intracellular H^+-K^+-ATPase activity (see below) (790).

In the rat and rabbit in the $OMCD_{os}$ and inner stripe portion of the OMCD ($OMCD_{is}$), ~33% of the cells are Type A ICs (715). In the rabbit $OMCD_{is}$, the outer portion of the $OMCD_{is}$ has Type A ICs, however the inner portion has cells which cannot be classified as PCs or ICs morphologically and have been termed inner stripe cells (592). Furthermore in the $OMCD_{is}$ there is cell-cell heterogeneity with regards to both H^+-ATPase and AE1 expression (118, 627, 628). The cells on electron microscopy (in the rabbit) have apical intramembranous particles that are thought to represent H^+-ATPase transporters (592) and there is functional evidence for both apical Na^+-independent H^+ transport and basolateral Cl^-/HCO_3^- exchange (112, 301, 302). An unidentified basolateral Na^+/H^+ exchange process is also present (112, 301). HCO_3^- absorption appears to mediated in part by an apical H^+-K^+-ATPase and a Na^+-dependent process that has not been characterized (38, 39, 697, 811). Finally unlike the CCD, there is physiologic evidence for apical membrane carbonic anhydrase activity (670). The basolateral membrane of ICs in the $OMCD_{is}$ is predominantly Cl^--conductive (380, 516) that can potentially be modulated by HCO_3^- (302).

The IMCD is divided anatomically into either the initial ($IMCD_i$) and terminal segment ($IMCD_t$), or categorized into thirds ($IMCD_1$, $IMCD_2$, and $IMCD_3$) (167, 470). As in the OMCD, species differences are apparent. In the rabbit, the $IMCD_1$ cells are of a single type and resemble inner stripe cells with respect to their staining positive for carbonic anhydrase and Na^+-K^+-ATPase (592), whereas in the rat ~ 10% of the cells are Type A ICs (167, 470). Like the $OMCD_{is}$, in the $IMCD_i$ there is functional evidence for apical carbonic anhydrase activity (lack of an acid luminal disequilibrium pH) (734). Unlike Type A ICs, IMCD cells lack staining for the H^+-ATPase, AE1, and H^+-K^+-ATPase. In the rat $IMCD_i$ and $IMCD_t$ segments, there is evidence for H^+ secretion and HCO_3^- absorption via a Na^+-independent mechanism (736, 737). Although there is conflicting evidence for an H^+-ATPase, the data in rat $IMCD_t$ suggests there is H^+-K^+-ATPase activity (737). In the rabbit, no evidence for luminal H^+ secretion has been found (327). Basolateral base transport is mediated by a Cl^-/HCO_3^- exchanger that is possibly AE2 (16, 217, 668, 676). In the basolateral membrane

there is functional evidence for a Na^+/H^+ exchange process (307) and a HCO_3^- conductance whose molecular identities are unknown (667).

H^+-ATPase (V-ATPase), Pendrin, OXGR1, NDCBE, AE4, KCC4, H^+-K^+-ATPase, Carbonic Anhydrase

H^+-ATPase—The H^+-ATPase is assembled into two domains: A V_o transmembrane domain and a V_1 cytplasmic domain (ATP6V1) (111, 166, 221, 725). The V_1 domain is composed of eight separate subunits with a specific stoichiometry whereas the V_o domain is composed of four subunits. ATP hydrolysis in the V_1 domain occurs at the B/A subunit interface. H^+ in the V_o domain are translocated between the a- and c-ring. In addition to transcellular and organelle H^+ transport, additional functions include the regulation of GTPase activity (314), modulation of Wnt (180), and notch signaling (805).

Transcellular H^+ flux in the CCD depends on the cell membrane voltage, which is influenced by Cl^- (possibly directly) and by other electrogenic processes such as Na^+ transport in PCs. Although the ClC-5 Cl^- channel colocalizes with the apical H^+-ATPase in Type A ICs, Cl^- channel activity has not been demonstrated in the native tubule (380, 381, 604). The ClC-5 chloride channel that co-localizes with the apical H^+-ATPase in Type A ICs may play a role in endocytosis rather than transepithelial transport (604). Regulation of H^+ secretion in Type A ICs is also mediated by several factors including recycling of subapical H^+-ATPase containing vesicles, modulation of the interaction between the two H^+-ATPase domains which has been studied in lower organisms (188, 343, 344, 510, 722), and potentially changes in the coupling efficiency between the enzymatic and H^+ translocating machinery.

Recycling of vesicles represents an important mechanism for modifying the number of H^+-ATPase molecules expressed on the cell surface (120, 472). The actin cytoskeleton plays an import role where subunits B1, B2, and C bind to actin (158, 308, 720). Inhibition of RhoA depolymerizes actin and increases H^+-ATPase membrane expression (651). Changes in systemic acid-base status also modulate the recycling machinery. An increase in the pCO_2 stimulates exocytosis of vesicles that is inhibited by colchicine (634). During exocytosis the H^+-ATPase interacts with the SNARE complex (47). Although the exact mechanism is unclear, vesicles coated on their surface with H^+-ATPase enzyme direct the recycling process (116) or help to recruit coat proteins to endosomes (498).

Alterations in pH are potentially sensed by soluble adenylate cyclase (sAC), which is expressed in ICs and has been found to co-immunopreciptate with the H^+-ATPase (545). It is hypothesized the an increase in cytoplasmic HCO_3^- concentration increases cAMP leading to PKA activation and increased plasma membrane H^+-ATPase expression (542, 543, 545). The PDZ motif in C-terminal tail of the electroneutral sodium bicarbonate cotransporter NBCn1 also interacts with H^+-ATPase B1 subunit in keeping with the presence of a HCO_3^--sensing signaling pathway (579). The specific H^+-ATPase subunit that is phosphorylated is unclear but has been shown to involve the A subunit (27, 286). pH sensing may signal through GPR4 as a mechanism for increasing cAMP (247, 546). Studies in other cell types suggest that purinergic receptor and Ca^{2+} signaling may also be involved (71, 159).

In Type A ICs, angiotensin II increases H^+ secretion likely via stimulation of translocation from a cytoplasmic pool to the apical membrane (550, 596, 728) PKC signaling is involved following binding of angiotensin II to the AT1 receptor (596). Aldosterone stimulates proton secretion in the collecting duct acutely via a nongenomic effect mediated by Gαq, PKC, and the ERK1/2 MAPK kinase pathway (792, 793). Chronic exposure to aldosterone increases translocation to the plasma membrane (792). Loss of aldosterone signaling leads to hyperkalemic dRTA partially due to loss of aldosterone-dependent signaling of H^+-ATPase mediated Type A IC apical H^+ secretion (409).

Patients with mutations in the B1 subunit have autosomal recessive hypokalemc dRTA (347). Since $B1^{-/-}$ mice don't have a hyperchloremic metabolic acidosis and it has been suggested that B1 subunit mutations in humans prevents the adaptive formation and expression of B2 subunit containing H^+-ATPase transporters. (219, 547). Patients with mutations in the a4 subunit have autosomal recessive hypokalemc dRTA (660). Studies in $a4^{-/-}$ mice have led to the suggestion that patients with ATP6V0A4 gene mutations have both proximal and distal acidification defects accounting for their severe metabolic acidosis (304, 526). Loss of the a4 subunit also leads to downregulation of other H^+-ATPase subunits and may affect the assembly of the transporter. The transcription factor Fox1 directly regulates the expression of the a4 subunit and $Fox1^{-/-}$ mice have loss of the a4 subunit in addition to pendrin and AE1 (95, 718).

Pendrin—Pendrin, the apical Cl^-/HCO_3^- exchanger in Type B ICs and non-A, non B ICs (365, 597) was first shown to be an iodine transporter that was mutated in Pendred syndrome (goiter and deafness) (192, 210). Whether patients with Pendred syndrome have a defect in Type B IC HCO_3^- secretion is unknown. Mice with targeted disruption of pendrin either lack CCD HCO_3^- secretion (597) or have reduced apical Cl^-/HCO_3^- exchange and CCD HCO_3^- secretion (35) suggesting that at least in mouse, additional apical Cl^-/HCO_3^- exchange process(es) may be present. Loss of pendrin in mice also modulates the expression of several Na^+, Ca^{2+}, H^+/base and NH_3 transporting proteins (52, 366, 549). Pendrin overexpression in mice results in Cl-sensitive hypertension (335). The transporter in CCD Type B cells has the following halide affinity, $Cl^- \sim Br^- > I^- > F^-$ (206), with an apparent affinity for luminal Cl^- of ~ 10 mM in the rabbit (625). Pendrin mediated transport is modulated by changes in luminal Cl^- concentration and likely plays an important role in the recovery phase of Cl^--sensitive metabolic alkalosis following administration of Cl^--containing salts (232, 443, 669). Pendrin mediated HCO_3^- secretion via Type B ICs is acetazolamide inhibitable (696) and stimulated by cAMP (625, 626). cAMP/PKA signaling appears to mediate the isoproterenol (β-adrenergic agonist) induced increase in pendrin membrane expression/activity (45). Changes in whole body Cl^- balance, and water balance also modulate pendrin expression (507, 582, 710, 735). Pendrin expression is also affected by acid and base loading, and mineralocorticoids (223, 507, 562, 709, 726) but is not involved in Type B IC pHi regulation (767).

Recent studies have shown that luminal α-ketoglutarate (α-KG) via the OXGR1 α-KG receptor that is localized to the apical membrane of Type B and non-A, non-B ICs in the CNT and CCD modulates pendrin and Type B IC function (688). In isolated perfused CCDs, α-KG stimulates apical Cl^-/HCO_3^- exchange, and transtubular Na^+ and Cl^- transport that is

thiazide inhibitable. Base loading significantly increased urinary α-KG levels providing a luminal signal to enhance CCD Type B IC cell HCO_3^- secretion. OXGR1$^{-/-}$ mice do not respond to luminal α-KG with enhanced Cl^-/HCO_3^- exchange and have reduced ability to excrete a base load.

ENaC, NDCBE, Pendrin and Type B IC Na^+ Transport—There is recent evidence suggesting that the function of Type B ICs modulates Na^+ transport in PCs, and that type B ICs per se transport Na^+. Pendrin$^{-/-}$ mice have decreased expression of ENaC in PCs and changes in luminal HCO_3^-/pH (pendrin function) can alter ENaC Na^+ transport (549, 738). Secondly, studies in mice suggest that Type B ICs in addition to apical pendrin, have a thiazide sensitive Na^+-coupled Cl^-/HCO_3^- exchange process that is thought to be mediated by NDCBE (*Slc4a8*) providing an additional mechanism for coupling the transport of Na^+ and Cl^- (278, 437). The coupling of pendrin ($2Cl^-/2HCO_3^-$ exchange) and NDCBE (Na^+-coupled $Cl^-/2HCO_3^-$) transport would be predicted to mediate the net cell influx of NaCl. Thirdly, Type B ICs B1$^{-/-}$ mice have renal loss of Na^+, Cl^-, K^+, polyuria, decreased ENaC expression in PCs, and decreased pendrin expression in Type B ICs (278). The expression of ENaC, the large conductance calcium-activated potassium channel, and aquaporin 2 were normalized when Type B IC ATP-triggered PGE2 paracrine signaling was blocked.

In addition to purported NDCBE, another member of the SLC4 base transporting family AE4 has been localized to CCD IC cells. AE4 was initially thought to mediate Cl^-/HCO_3^- exchange (693) however its amino acid sequence more closely resembles members of the family that mediate Na^+-coupled base transport (403). The expression pattern varies among studies and between species. AE4 has been immunolocalized to the apical and lateral membranes of rabbit CCD Type A ICs (376). A separate study in rabbit showed apical co-localization with peanut lectin (a Type B IC marker) (800). In the rat, AE4 is expressed on the basal and lateral membrane of CCD Type A and B ICs (376). In the mouse AE4 is localized to the basolateral membrane of CCD Type B ICs (95, 306). Mice with targeted disruption of AE4 do not have an overt phenotype however CCD Type B IC function was not reported (657).

KCC4—Mice with loss of the KCl cotransporter KCC4 develop dRTA and deafness suggesting a role for the transporter in basolateral Cl^- efflux in Type A ICs (100). In the rabbit, KCC4 has been immmunolocalized to the basolateral membrane of cells in the DCT, CNT, that dissipates gradually with the transition to the CCT (708).

H^+-K^+-ATPase—H^+-K^+-ATPases are ATPases (E1, E2 or P-type) secrete H^+ in exchange for K^+ electroneutrally (179, 274, 281). The transporter consists of an α and β subunit, and 4 α subunit isoforms and 2 β subunit variants have been characterized. The known variants differ in their inhibitory profiles (127). The gastric or HKα1 variant is inhibited by SCH28080 and omeprazole and not ouabain. The colonic form, HKα2, is inhibited by ouabain but not SCH 28080. The HKα4 form found in skin is sensitive to ouabain and SCH 28080. There is evidence that HKα1 and HKα2 mediate the functional activity in the mouse collecting duct (132, 186, 274, 281). The inhibitory profile in the CCD and OMCD of K^+-replete rats is the same as the gastric isoform (type I profile) whereas in K^+-depleted animals activity was partially SCH 28080- and ouabain-sensitive and K^+ could be replaced by Na^+

(type III profile) (127). Type I activity was not detectable in mice with disruption of HKα1 (*Atp4a* gene) and the type III activity was preserved, whereas in mice with loss of HKα2 (*Atp12a*), type I activity was present and type III activity was lost (186). These findings and subsequent studies by Shao et al (646) suggest that either the kidney also expresses an HKα2 different from the colonic variant, or technical experimental reasons account for the findings. Mice with loss of both HKα1 and HKα2 have normal acid-base parameters possibly due to upregulation of compensatory mechanisms (494, 666). Lynch et al examined acid secretion in ICs of CCDs from $HK\alpha1^{-/-}$ and $HK\alpha2^{-/-}$ or combined $HK\alpha1^{-/-}/HK\alpha2^{-/-}$ mice and demonstrated a decrease in H^+ transport in both Type A and Type B ICs (467, 468). Interestingly, 35-70% of HCO_3^- transport in the $OMCD_{is}$ is thought to be H^+-K^+-ATPase dependent (283, 697). In the CCD, acute respiratory acidosis appears to stimulate H^+-K^+-ATPase transport (654). Calcitonin and isoproterenol also activate H^+-K^+-ATPase activity via ERK and cAMP (218, 418). $HK\alpha2^{-/-}$ mice have reduced colonic ENaC activity, which is of interest since Na^+-transporting PCs in the rabbit collecting duct (in addition to IC and OMCD cells) express HKα2c (717). Whether the collecting duct H^+-K^+-ATPase plays a role in mediating Na^+ transport *per se* is unclear, however a low Na^+ diet has been reported to stimulate its activity (178, 653).

Carbonic Anhydrase—In general, HCO_3^- transport in the collecting duct is sensitive to carbonic anhydrase inhibition (457, 483, 484, 487, 591, 702). ICs in the collecting duct in all species stain for cytoplasmic CAII (119, 121, 458, 665) however differences exist among various species in the expression of membrane anchored CAIV (122, 459, 694). The expression of both CAII and CAIV is increased by metabolic acidosis (694, 791). In addition to playing a role in H^+/base transport, studies in mice suggest that CAII may be important for the development of IC cells and for the expression of other transporters. In $CAII^{-/-}$ mice there is a loss of Type A and Type B ICs (110), and pendrin expression is significantly decreased (679). Cells in the CCD lack luminal carbonic anhydrase and because of this, a spontaneous luminal disequilibrium pH is present due to net luminal H^+ secretion. In addition to the CCD, the superficial DCT, $OMCD_{os}$, and IMCD lack luminal carbonic anhydrase. The basolateral membrane of PCs stains for CAXII whose significance in unclear but may play a role in pHi regulation (411, 638).

NH_3-NH_4^+ Transport: Rhesus Proteins RhBG and RhCG and Sulfatides—The acidification of the collecting duct lumen is associated with the secretion of NH_3 from the interstitium and its protonation in the lumen to NH_4^+ (770, 771). NH_3 permeates the collecting duct plasma membrane via specific rhesus (Rh) membrane proteins. RhBG and RhCG are expressed in murine and human collecting ducts in essentially the same pattern except that in humans, PCs don't express either protein. RhBG is expressed basolaterally in the CNT, Type A ICs, and non-A, non-B cells (294, 716), whereas RhCG is expressed on both the apical and basolateral cell membranes of the DCT, CNT, Type A ICs, and non-A, non-B cells (293, 361). Chronic metabolic acidosis increases RhCG expression in both OMCD and IMCD ICs (643) and in the $OMCD_{is}$ increases apical RhCG expression in ICs and PCs (644). In mice lacking IC RhBG basal urinary NH_4^+ excretion is essentially normal, however following acid-loading or K^+-depletion, NH_4^+ excretion is significantly decreased (91, 92). Mice with targeted loss of RhCG in the collecting duct or specifically in ICs have

normal acid–base parameters with only mildly reduced urinary NH_4^+ excretion, however following acid-loading, a more severe metabolic acidosis develops with decreased urinary NH_4^+ excretion (421, 422). In mice with deletion of RhCG in the collecting duct with intact RhCG in the CNT, a less severe phenotype exists suggesting that the CNT and possibly the late DCT contribute to RhCG mediated NH_3 permeation (422). Complete loss of RhCG leads to an 80% decrease in CCD NH_3 permeability (105). Mice with RhCG haploinsufficiency have a 40% decrease in CCD NH_3 permeability and following chronic acid loading have a blood HCO_3^- that is less than controls (105). Combined collecting duct $RhBG^{-/-}/RhCG^{-/-}$ mice have normal acid-base base parameters but following acid-loading have a more severe metabolic acidosis than controls (423). These studies in mice establish the role of Rhbg and Rhcg in the renal response to extrarenal metabolic acidosis. Interestingly, Rh gas channels also mediate CO_2 permeation however the relevance to collecting duct H^+/base transport is currently unknown (515). Recently, highly charged anionic glycoshingolipids (sulfatides) have been reported to play an important role in maintaining the high concentration of NH_4^+ in the papillary interstitium required for collecting duct NH_3 secretion (673).

Regulation of Collecting Duct Acidification

Acid-Base and Electrolyte (Na^+, Cl^-, K^+, and Ca^{2+}) Chemistry

In the CCD and OMCD, an acute decrease in basolateral pH and HCO_3^- stimulates bicarbonate absorption in perfused tubules *in vitro* (113, 327, 334). Raising the basolateral pCO_2 in the CCD has led to conflicting results that may be due to differences unidirectional HCO_3^- absorption versus secretion at baseline (113, 489). In the OMCD, raising the basolateral pCO_2 increases HCO_3^- absorption (489). Although not yet determined, the stimulation of transport could result changes in pHi and or the intracellular HCO_3^- concentration that kinetically alter the rate of apical H^+-ATPase and basolateral Cl^-/HCO_3^- exchange in Type A ICs. In addition, in the CCD, Type B and non-A, non-B IC HCO_3^-secretion could decrease. As discussed above other mechanisms including H^+-ATPase pH sensing and recycling of H^+-ATPase containing vesicles into the plasma membrane likely play an important role in modulating collecting duct acidification in response to acute acidosis (metabolic and respiratory). The insulin receptor-related receptor (InsR-RR) is expressed on the basolateral membrane of Type B ICs and non-A and non-B ICs that may act as an alkaline pH sensor signaling through ERK1/2, the actin cytoskeleton, and modulation of pendrin expression (56, 185, 536)

Chronic changes in systemic acid-base balance induce changes in collecting duct transport that can be demonstrated *in vitro* in dissected tubules (memory effect). This is best illustrated by studies showing the direction of net HCO_3^- transport (absorption and secretion) can be predictably altered in CCDs dissected from animals with metabolic acidosis or alkalosis (44, 484, 485, 671). Similar effects have been described in rat DCTs perfused *in vivo* (320, 442). HCO_3^- transport by the IMCD is also regulated in metabolic acidosis and alkalosis (74, 75, 702, 736). In contrast the OMCD does not appear to be regulated by systemic acid-base balance (420, 457, 487).

In the CCD, early studies suggested that Type A and Type B ICs interconvert in response to *in vivo* acid-base changes (636). Subsequent studies reported modulation of transport and anion exchanger expression in CCDs exposed to acidic peritubular fluid *in vitro* (576, 614, 639, 695). Al-Awqati and colleagues reported that the changes in the transport properties of ICs are due to hensin/DMBT1 that interacts with galectin-3 and cypA (9, 630, 635, 639, 684, 705) and cyclophilins are also reportedly involved (8, 230, 553). Other studies have suggested that there is remodeling of individual Type A and Type B cells and intermediary hybrid cells rather than a strict change in polarity (55, 117, 628, 714). A reversal of polarity is now considered unlikely given that IC expression of apical AE1 and basolateral pendrin have never been detected.

In the mouse, Type A ICs proliferate in response to metabolic acidosis that involves signaling through GDF-15 (200). More recent studies in rat have shown that chronic metabolic acidosis leads to Type A IC proliferation in the CCD and OMCD (784). PCs also proliferate but Type B ICs under the same conditions do not. Because acetazolamide induced the same response as NH4Cl loading, systemic rather than urinary pH likely mediated the proliferative response (784).

Unlike peritubular pH, luminal pH changes are unlikely to alter intracellular pH in the DCT, CCD, and $OMCD_{is}$ because of the low H^+/HCO_3^- apical permeability (113, 154, 302, 668, 767). The lack of change in pHi also suggests that the H^+-ATPase in Type A and IMCD cells is rather insensitive to changes in luminal pH. In the DCT, luminal flow rate and the axial profile of the luminal HCO_3^- concentration modulate HCO_3^- absorption as in the proximal tubule (136, 154, 320). In Type B ICs that secrete HCO_3^- via pendrin, changes in the luminal HCO_3^- concentration also alter the rate of apical Cl^-/HCO_3^- exchange (767).

Increasing the Na^+ concentration in the lumen of the CCD increases PC Na^+ transport and in the absence of transportable anions (particularly in the presence of aldosterone), leads to an increased transepithelial voltage (383, 419). In this setting although Type A ICs don't absorb Na^+, it would be predicted that their apical membrane would depolarize due to circular intraepithelial current loops leading to enhanced H^+ secretion. Accordingly, diseases such as Liddle's syndrome where PC ENaC mediated Na^+ transport is increased (567) secondarily enhances Type A IC H^+ secretion. Conversely blocking ENaC in PCs with amiloride would in the CCD be predicted to hyperpolarize the apical membrane of ICs as has been shown in the $OMCD_{os}$ (382) leading to decreased electrogenic H^+ secretion and HCO_3^- absorption (529).

The luminal Cl^- concentration is a factor determining the rate of Type B cell apical Cl^-/HCO_3^- exchange, and the magnitude paracellular Cl^- transport (232, 443, 625, 669). In Cl^--sensitive metabolic alkalosis, increasing the Cl^- concentration in the lumen of the CCD likely enhances pendrin (Km for luminal Cl^- ~ 5-10 mM) mediated HCO_3^- secretion associated with an increase in basolateral H^+-ATPase transport (711) contributing to the correction of the acid-base disorder. The apparent Km of basolateral Cl^-/HCO_3^- exchange for basolateral Cl^- in the $OMCD_{is}$ is ~ 115 mM (302) however whether clinical variations in the peritubular Cl^- concentration are physiologically relevant remains to be determined.

Determining the direct role of K^+ on collecting duct H^+/base transport is complex given that its effect(s) *in vivo* are potentially mediated by changes in extracellular and/or intracellular K^+. Moreover, in clinical disorders affecting K^+ balance, there often are accompanying changes in mineralocorticoid levels and systemic acid-base balance that can independently modulate tubule transport. In the DCT, hypokalemia enhances HCO_3^- absorption (136, 137). CCDs dissected from K^+ depleted animals (with hypoaldosteronism and metabolic acidosis) have increased HCO_3^- absorption *in vitro* whereas OMCD HCO_3^- absorption is decreased (488). K^+ depletion is also associated with increased collecting duct H^+-K^+-ATPase activity as discussed (193), and increased expression of apical H^+-ATPase, basolateral AE1, and basolateral *Slc26a7* (50, 672).

Ca^{2+} (5.0 mM) and the CaSR agonist neomycin significantly enhance H^+-ATPase activity in the OMCD (590). In TRPV5$^{-/-}$ mice, activation of apical CaSR (Ca^{2+}-sensing receptor) increased luminal Ca^{2+} concentration in the DCT and collecting duct could potentially increase H^+-ATPase activity lowering urinary pH and downregulate AQP2 (aquaporin 2) thereby preventing stone formation (590). In addition, disruption of the *Atpv1b1* gene in TRPV5$^{-/-}$ mice results in normalization of urinary pH and tubular precipitation of Ca^{2+}-phosphate in the medullary collecting duct. These observations indicate that increased H^+-ATPase–mediated urinary acidification in TRPV5$^{-/-}$ mice protects against renal Ca^{2+}-phosphate stone formation.

Peptide Hormones, Renin-Angiotensin System, Mineralocortocoids, and Prostaglandins

In the rat DCT and CCD, ADH converts HCO_3^- secretion to net HCO_3^- absorption however the mechanism is unknown (82, 441, 689). Glucagon stimulates HCO_3^- secretion and/or decreases HCO_3^- absorption in the DCT and collecting duct potentially via signaling increase through cAMP (208, 495).

Isoproterenol or VIP increases HCO_3^- absorption in the rat DCT, (441). In the CCD, isoproteronol increases cAMP and stimulates HCO_3^- secretion likely via an increase in apical pendrin activity and the basolateral Cl^- conductance (299, 625, 626, 682). H^+-ATPase expression is modulated by cAMP/PKA and sAC as discussed whereas signaling through PKC doesn't appear to play a role (247, 303, 542, 543, 545).

PTH increases adenylate cyclase in the DCT and CNT (508, 540). In metabolic acidosis PTH is increased and the increase in collecting duct acidification induced by PTH may be due to enhanced phosphate delivery where phosphate acts as a buffer or a non-reabsorbable anion (81, 497). Metabolic acidosis may also downregulate the PTH receptor (340).

In the DCT, ET-1 administration *in vivo* increases acidification by stimulating H^+ secretion and by decreasing and decreasing HCO_3^- secretion (following HCO_3^- loading) (787). Metabolic acidosis stimulates endothelial ET-1 secretion (788). In the DCT, inhibition of the ET_B receptor following protein loading (mild metabolic acidosis) *in vivo* blocks the aldosterone induced stimulation of H^+ secretion (356). In the CCD, binding of endothelin to the ET_B receptor decreases HCO_3^- secretion signaling through NO-guanylate cyclase (699).

Prorenin binds to the (pro)renin receptor ((P)RR) inducing renin-angiotensin system activity. The signal transduction pathway is independent of angiotensin II generation (522, 523). (P)RR has been identified as an accessory protein of the H^+-ATPase (466) and colocalizes with the H^+-ATPase in the collecting duct (5). Evidence in Madin-Darby canine kidney (MDCK) cells suggests that (P)RR and H^+-ATPase activity is required for prorenin-induced activation of ERK1/2 (5). Activation of the H^+-ATPase by aldosterone and angiotensin II is also dependent on ERK1/2 (596). Knockdown of (P)RR expression in MDK cells blocked prorenin and AVP-induced H^+-ATPase activation perhaps via changes in membrane insertion, suggesting that (P)RR is needed for prorenin-dependent and -independent activation of the H^+-ATPase (462). The importance of the prorenin induced stimulation *in vivo* is unclear given the unphysiologic concentration of prorenin required.

The effect of angiotensin II on collecting duct H^+/base transport is complex. Angiotensin II has been reported to increase luminal HCO_3^- secretion in the rabbit CCD (769) and Type B IC H^+-ATPase activity in the mouse CNT and CCD (728); whereas in rat, HCO_3^- absorption is increased (746). In the mouse, Pech et al (548, 550) have shown that angiotensin II directly stimulates the Type A IC H^+-ATPase with increased plasma membrane expression and that Type B IC HCO_3^- secretion is secondarily increased potentially via a lowering of the luminal HCO_3^- concentration (increased driving force) and generation of luminal CO_2 (501). In the mouse although angiotensin II increases Type B IC H^+-ATPase membrane expression, pendrin expression is unchanged (728) HCO_3^- absorption is decreased in the OMCD in response to angiotensin II (733).

The are several mechanisms by which mineralocorticoids stimulate luminal H^+ secretion in the collecting duct. In the CCD, mineralocorticoids stimulate PC ENaC mediated Na^+ transport that indirectly depolarizes the apical membrane of Type A ICs resulting in an increase in H^+ secretion (544). Furthermore there is a direct effect on Type IC H^+-ATPase transport in both the CCD and $OMCD_{is}$ (383, 674). H^+ secretion in the rat IMCD is also stimulated by mineralocorticoids (197). A nongenomic mechanism causes rapid translocation of H^+-ATPase to the apical membrane signaling through G(αq) protein-coupled receptors, and intracellular Ca^{2+} signaling, PKC, and ERK1/2 are involved (792). In addition, cAMP/PKA has a modulatory role. In mice lacking the V1a receptor that develop type 4 RTA fludrocortisone ameliorated the acidosis by restoring excretion of urinary ammonium via increased expression of H^+-K^+-ATPase and RhCG and decreased H^+-ATPase expression (332). The activity and expression of the H^+-K^+-ATPase regulated by mineralocorticoids involves increased α2 subunit mRNA (273). HCO_3^- secretion by the Type B IC is stimulated by mineralocorticoids (383, 674). This effect is blocked by ameliorating the accompanying metabolic alkalosis with acid-loading (232).

As discussed in Type B ICs, proton pump inactivation induces release of PGE2 via calcium-coupled purinergic receptor activation (278). In the $OMCD_{is}$ PGE_2 inhibits HCO_3^- absorption (300). Base loading increases the urinary excretion of PGI_2 associated with increased HCO_3^- secretion in the rat DCT via changes in cAMP signaling (786).

Isolated Familial Distal RTA: Mutations in CAII, AE1, H^+-ATPase Subunits

Patients with mutations (23 mutations reported thus far) in CAII have autosomal recessive combined pRTA and dRTA because of the presence of CAII in proximal tubule cells, Type A intercalated cells, and medullary collecting duct cells. (57). CAII deficiency tends to have a higher incidence in the Arabian Peninsula possibly due to consanguinity with more than 70% of the cases described from this region (214, 319). A splice site mutation at the junction of exon 2–intron 2 (c.232+1 G > A) is commonly detected in these patients (215). Extrarenal manifestations include osteopetrosis, intracerebral calcification and developmental delay (645). Mild hearing loss due to a conductive defect has also been reported (517).

AE1 is a 12-14 transmembrane spanning protein whose topologic structure has been recently modeled after prokaryotic ClC channels (102). Two variants, kAE1 (kidney AE1) and eAE1 (erythrocyte AE1) are transcribed by the *SLC4A1* gene that differ in their N-terminal sequence; kAE1 is shortened by 65 residues in its N-terminus because of alternative promoter usage. eAE1 is expressed in the erythrocyte and kAE1 is localized to the basolateral membrane of Type A ICs (114, 621, 820). AE1 mutations causing dRTA were first reported by Bruce et al and subsequently by Karet *et al* (124, 348). Mutations in AE1 also cause hereditary spherocytosis (HS) without dRTA (336). Only in very rare instances do patients have both dRTA and red cell hemolysis (125). Thus far, 16 separate mutations in AE1 have been reported to cause dRTA with associated hypokalemia, nephrocalcinosis, hypercalciuria, and nephrolithiasis; both autosomal recessive and dominant inheritance has been described. Interestingly, the mutated proteins have been found to function essentially normally *in vitro* suggesting other mechanisms such as misfolding and ER or Golgi retention, or mistargeting to the plasma membrane play an important role. Importantly, there are no patient biopsy results that have addressed this issue; rather, interferences are made on mutated AE1 ER/golgi retention, or mistargeting using *in vitro* cell model systems. Loss of polarized expression has been reported in the context of the C-terminal R901X truncation mutant, AE1-G609R, and M909T, whereas intracellular retention in polarized cells characterizes the C479W, R589H, S613F, and G701D mutants (summarized in (13, 57)). AE1 is a dimer and it has been shown that in the context of autosomal dominant mutations, mixed mutant/wild-type dimers are retained intracellularly and cannot be rescued by the wild-type monomer (809). In contrast, mutations inherited autosomal recessively can be expressed on the plasma membrane normally as mutant/wild-type dimers (809). Recent experiments have shown that trafficking of kAE1 mutants can be partially restored *in vitro* by various treatments (163).

Karet et al described patients with autosomal recessive dRTA and sensorineural hearing loss that have mutations in the *ATP6V1B1* gene encoding the H^+-ATPase B1 subunit (347). The hearing loss is progressive however occasionally a conductive component is present and bilaterally enlarged vestibular aqueducts have been reported (339). In addition, the patients are hypokalemic with nephrocalcinosis, and can have hypercalciuria and rickets. Karet et al also reported mutations in the *ATP6V0A1* gene encoding the a4 subunit in patients with dRTA and normal hearing (346). The patients also had hypokalemia with nephrocalcinosis, and several had hypercalciuria. Auditory brain stem response tests were normal. Subsequent studies of patients with mutations in the a4 subunit did have hearing loss, such that hearing

loss *per se* can no longer be considered diagnostic for a specific H^+-ATPase subunit abnormality (502, 675, 707). Underlying mechanisms include abnormal pump assembly, impaired function, abnormal targeting, and loss of interaction with phosphofructokinase-1(PFK-1) (229, 677, 808).

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