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Proximal Nephron

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Abstract

The kidney plays a fundamental role in maintaining body salt and fluid balance and blood pressure homeostasis through the actions of its proximal and distal tubular segments of nephrons. However, proximal tubules are well recognized to exert a more prominent role than distal counterparts. Proximal tubules are responsible for reabsorbing approximately 65% of filtered load and most, if not all, of filtered amino acids, glucose, solutes, and low molecular weight proteins. Proximal tubules also play a key role in regulating acid-base balance by reabsorbing approximately 80% of filtered bicarbonate. The purpose of this review article is to provide a comprehensive overview of new insights and perspectives into current understanding of proximal tubules of nephrons, with an emphasis on the ultrastructure, molecular biology, cellular and integrative physiology, and the underlying signaling transduction mechanisms. The review is divided into three closely related sections. The first section focuses on the classification of nephrons and recent perspectives on the potential role of nephron numbers in human health and diseases. The second section reviews recent research on the structural and biochemical basis of proximal tubular function. The final section provides a comprehensive overview of new insights and perspectives in the physiological regulation of proximal tubular transport by vasoactive hormones. In the latter section, attention is particularly paid to new insights and perspectives learnt from recent cloning of transporters, development of transgenic animals with knockout or knockin of a particular gene of interest, and mapping of signaling pathways using microarrays and/or physiological proteomic approaches.

INTRODUCTION

A homeostasis of body extracellular electrolyte composition and fluid volume is essential for all animals and humans to survive. Either excess or deficit of key extracellular electrolytes or overall fluid volume may lead to disturbance of the circulation, including cardiac output and blood pressure, and the abnormalities of cellular functions, including cell volume and intracellular pH (46; 178; 187; 295; 358; 396). Although the digestive system (small and large intestines), the skin, and the lungs may also be involved in body electrolyte and fluid excretion, there is no doubt that the kidneys play the most important role in the regulation of body electrolyte and fluid balance (79; 81; 101; 178; 179; 187; 291; 336; 375). Indeed, the importance of the kidney is best supported by the simple statistics that the kidneys of a normal adult human filter approximately 180 liters of blood daily, and 99% of filtered electrolytes, solutes and fluid are reabsorbed and returned to the circulation. Only 1% of the filtered load is eventually excreted in urine. With a healthy kidney, animals and humans may survive in extreme conditions such as being trapped in a collapsed mine or the

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rubbles of earthquakes for days without ingestion of any water and food. Conversely, rapid ingestion of large quantity of fluid and electrolytes in a short period of time leads to marked diuresis and natriuresis, with little retention of excessive salt and fluid at least in the short term. Thus, the kidney has the unique capacity to precisely adjust the urinary excretion of electrolytes and fluid in order to match spontaneous variations in their intake to maintain body electrolyte and fluid homeostasis, acid-base balance, and normal blood pressure (79; 81; 101; 178; 179; 187; 291; 336; 375).

The kidney plays a fundamental role in maintaining precise body and/or extracellular electrolyte and fluid balance and blood pressure homeostasis primarily through its proximal and distal tubular segments of nephrons. However, it is well recognized that proximal tubular segments exert a more prominent role. Proximal tubules are responsible for reabsorbing approximately 65% of filtered load and most, if not all, of filtered amino acids, solutes, and low molecular weight proteins (358; 413; 422; 537; 547). Proximal tubules also play an important role in the maintenance of body acid-base balance by reabsorbing 80% of the filtered bicarbonates (1; 5; 6; 46; 59; 60; 154; 401), and glucose metabolism by reabsorbing all filtered glucose and regulating gluconeogenesis (24; 301; 339; 468; 516; 552; 553). The purpose of this review is to provide a comprehensive overview of new insights and perspectives in our understanding of proximal tubules, with an emphasis on the ultrastructure, molecular biology, cellular and integrative physiology, and the underlying signaling mechanisms. Since the historical perspectives and the classic physiology of proximal tubules are described in other legacy articles, this review will focus more on the new insights and perspectives learnt from recent studies on newly cloned transporters, transgenic or mutant animals with knockout or knockin of a particular gene, and newly identified signaling transduction pathways using microarrays and physiological proteomic approaches.

CLASSIFICATION OF NEPHRONS

Definition of nephrons

Historically, the term of nephron was derived primarily from a Greek term, nephros, which generally means the kidney (Wikipedia, the free encyclopedia). The definition of the nephron has not changed during the last several decades. Nephron is defined as the essential structural and functional unit of the kidney. In the structural context, each nephron consists of a renal corpuscle including the glomeular tuft, which contains a network of capillaries and Bowman’s capsule (291; 336), and a tubule unit including proximal tubule, loop of Henle, distal tubule, connecting tubule, and perhaps the collecting duct (see reviews on Nephron heterogeneity; Proximal tubule, loop of Henle, distal tubule and connecting tubule, collecting duct for details). All major structural components of the nephron are believed to embryologically originate from the metanephric blastema (291; 336). However, some renal anatomists have argued that the entire cortical and medullary collecting ducts should not be considered to be parts of the nephron, because they are embryologically derived from the ureteric bud rather than the metanephric blastema (291; 336). In the physiological context, a nephron represents a functional unit that filters blood, reabsorbs the filtered electrolytes, solutes and fluid, and excretes wastes and excessive electrolytes and water (184; 291; 336; 343; 401; 497; 537; 546). The glomerulus is exclusively responsible for filtering blood up to 25% of a normal cardiac output (see reviews on GFR and Glomerular filtration for details). The tubules of the nephron are responsible for reabsorbing 99% of glomerularly filtered electrolytes and water and returning them to the circulation (184; 291; 336; 343; 401; 497; 537; 546).

Classification of nephrons and their intrarenal distribution

Nephrons are broadly classified depending on the location and the structural characteristics of the nephrons. For instance, nephrons are often classified into superficial cortical and juxtamedullary nephrons, based on the localization of its associated glomerular tuft (291; 294; 336). Superficial cortical nephrons have their glomerular tufts located in the superficial cortex, whereas juxtamedullary nephrons have their glomerular tufts situated in the juxtamedullary region, also called deep nephrons (Fig. 1) (291; 336). The localization and structural heterogeneity of superficial and juxtamedullary nephrons have been extensively investigated since the 1960s (68; 68; 84; 115; 182; 221; 248; 249; 335; 350; 411; 431; 439). Studies using light and high resolution electron microscopes have demonstrated that nephrons in rodents and humans differ not only in their glomerular localization, but also in their structural characteristics. The glomeruli are usually larger in juxtamedullary nephrons than in superficial nephrons in rats (22), dogs (83), and rabbits (26). The genetic and molecular mechanisms underlying the nephron structural heterogeneity in animals and humans are not well understood. One theory is that the glomeruli develop from the tips of the branching ureteric buds in a centrifugal manner, and thus those glomeruli located in the juxtamedullary region are expected to develop first and become larger at birth and postnatally (439; 481). This explanation remains unsatisfactorily at least in humans. For instance, human studies using the maceration or the dissector/Cavalieri technique showed no differences in mean glomerular diameters between the superficial and juxtamedullary nephrons across different ages (135; 385; 439). However, there is evidence that genetics may play a role, for example American Blacks do have larger glomerular volume or size than American Whites in juxtamedullary nephrons independent of age, body surface area and glomerular number (439). The differences in gestational lengths between animals and humans may partly explain the presence of nephron structural heterogeneity in animals but not in humans.

For several decades, nephrons are also classified into short-loop and long-loop nephrons, based on the length of their respective loop of Henle (291; 336). Most superficial and midcortical nephrons are referred to as short-loop nephrons, because these nephrons have short loops of Henle in the inner stripe of the outer medulla (291; 336). By contrast, most juxtamedullary nephrons have long loops of Henle with long thin descending and ascending limbs entering the inner medulla (291; 336). Rodent and human kidneys appear to have more short-loop than long-loop nephrons. Alternatively, many renal physiologists often simply divide nephrons into proximal and distal nephrons, and the practice still continues today. Proximal nephrons are generally referred to proximal convoluted tubules and proximal straight tubules from S1 to S3 segments (Fig. 2) (291; 336). Distal nephrons generally include the loop of Henle, distal convoluted and connecting tubules, and perhaps collecting ducts (see the overviews on Nephron heterogeneity; Proximal tubule, loop of Henle, distal tubule and connecting tubule, collecting duct for details). Some renal physiologists may simply define the proximal nephron as the segment between the glomerulus and the macula densa, since the latter provides a clear feedback point to define proximal versus distal nephron function. However, the classification of proximal and distal nephrons remains an issue of continuous debates, because the definition of proximal or distal nephron has not been established (see the definition of nephron in Wikipedia and medical dictionaries). In this article, the scope of the overview will accordingly focus on the structural and functional characteristics of proximal tubular segments of the nephron, proximal convoluted tubule (pars convoluta) and proximal straight tubule (pars recta).

Nephron numbers in health and diseases

The exact number of the nephrons in animal and human kidney remains an issue of continuous debates. For more than a century, renal histologists, pathologists and

nephrologists have attempted to estimate the number of nephrons in animal and human kidneys using different techniques (38; 45; 212; 224; 230; 415; 593). Although the technique used may vary from laboratory to laboratory, the number of nephrons in a given kidney is often determined by estimating the number of its glomeruli (38; 45; 212; 224; 230; 415; 593). Since it is laborious and time-consuming to accurately count every glomerulus in a kidney, the current understanding of the nephron numbers in animal and human kidneys is primarily derived from indirect estimations (38; 44; 45; 212; 224; 230; 415; 593).

The number of nephrons in the human kidney was first estimated by Eysenhardt as early as in 1818 (131; 212). The nephron number was later reported in the rat kidney by Kittelson almost one century later (273). The number of nephrons and their intracortical distribution in the dog kidney were not reported until early 1970s (136; 219). A number of quantitative techniques have been developed to estimate the number of nephrons in the kidneys of different species. The so-called “dissector” unbiased stereological method as described by Sterio in 1984 (485) and magnetic resonance imaging (MRI) of the kidney by Basgen in 1994 (34) are widely used today. Although there is still disagreement on which technique is more accurate for estimating the nephron numbers in animals and humans, the unbiased stereological technique is generally considered to be the gold-standard approach to estimate the number of nephron or glomeruli in the kidney (226; 231; 415; 450; 593).

As estimated by the non-biased stereological technique or the noninvasive MRI technique, the number of nephrons varies widely from animals to humans (Table 1). Mice and rats have the lowest number of nephrons, ranging from approximately 20,000 per kidney in the former (360) to 35,000 per kidney in the latter species (38; 45; 212; 348; 452; 488). However, there are no marked differences in the number of nephrons among different strains of rats from Lewis, Sprague-Dawley, to Spontaneously Hypertensive rats (Table 1) (38; 45; 212; 452; 488). Rabbits have about 170,000 nephrons (337; 493), while dogs have 350,000 to 550,000 nephrons per kidney (34; 219). In humans, each kidney consists of between 800,000 and 1 million nephrons (178). In a recent report on the nephron numbers of 5 ethnic groups from 3 continents (225), the number of nephron can vary widely from ~460,000 to 1.3 million among healthy American Caucasians and African subjects (224; 230–232; 593). In the European Spanish population, the number of nephrons may reach 730,000 per kidney (144). Finally, the numbers of nephrons ranges from 364,262 to 1.1 million in Australian aborigines and from 380,517 to 1.5 million in Australian non-aborigines (226). Thus even in healthy human subjects, there can be nearly 5-fold differences in the number of nephrons per kidney.

The nephron number may be physiologically relevant and important. There is evidence that low nephron numbers may be associated with the development of hypertension and kidney diseases. Brenner et al. first hypothesized an association between low nephron numbers in the kidney and the risk in the development and progression of hypertension, glomerular injury and chronic renal diseases, and renal allograft survival (63). According to the hypothesis, any reduction in the filtration surface area, whether acquired in renal disease or after surgical renal ablation, can lead to systemic hypertension and progressive renal insufficiency. For example, hypertension and progressive renal diseases are commonly found in individuals born with a solitary kidney, oligomeganephronia, or in certain inbred rat strains in which the filtration surface area is congenitally decreased (63). Brenner further postulated that a reduced number of nephrons may also contribute to the increased susceptibility of certain Type I and Type II diabetes to develop overt glomerulopathy (63). Brenner’s hypothesis has led to intensive investigations on the associations between the deficit of nephron number and the risk of hypertension and chronic renal diseases in animal models and different ethnic human populations (34; 45; 144; 226; 231; 328; 337; 348; 415; 450; 452; 488; 493; 593). However, the conclusive evidence supporting this association

remains to be established (360; 450; 452). While a low nephron number in the kidney has been linked to a high risk for the development and progression of hypertensive and chronic kidney diseases in African Americans and Australian aborigines (226; 231; 415; 450; 593), the reduction of the nephron number by 50% by surgically removing one kidney from healthy rodents or by donating one kidney for transplantation in humans may not lead to the development of glomerulosclerosis and renal failure. This suggests that the nephron number may not necessarily be the most important factor in maintaining a normal kidney function and blood pressure (407).

ULTRASTRUCRAL HETEROGENEITY OF PROXIMAL TUBULE

Superficial vs. juxtamedullary nephrons

The ultrastructure of proximal tubular segments in rodents and humans has been extensively studied and characterized (291; 336). Proximal tubules of the nephron in animals and humans include proximal convoluted tubules, which are situated in the cortical labyrinth and connected directly to the glomerulus, via the Bowman's space, and proximal straight tubules in the inner cortex and outer stripe of the outer medulla (Figs. 1–3) (291; 336). Only those proximal convoluted tubules of superficial nephrons usually traverse the cortical surface of the kidney, which are accessible to in vivo micropuncture or microperfusion investigations. By contrast, proximal convoluted tubules in juxtamedullary nephrons run deep into the medullary rays and are not accessible to micropuncture and microperfusion in vivo. Proximal convoluted tubules are approximately 25% longer in juxtamedullar nephrons than superficial nephrons (551). In vitro juxtamedullary preparation has been extensively used to study hemodynamic and vascular responses in juxtamedullar nephrons (84; 203; 204; 237; 238; 240; 241; 370), but whether the preparation can be adapted for micropuncture or microperfusion of proximal tubules of juxtamedullary nephrons still remains uncertain. Accordingly, the current understanding of proximal tubular function, which is largely based on in vivo micropuncture studies, may only apply to the proximal convoluted tubules of superficial nephrons.

Ultrastructures of segmental proximal tubules of the nephron

At the high resolution light microscopic level, each proximal tubule consists of three inter-connecting segments, namely: a) the S_1 segment which comprises the beginning and middle portion of the proximal convoluted tubule, b) the S_2 segment which includes the late portion of the proximal convoluted tubule and the beginning portion of the proximal straight tubule, and c) the S_3 segment which is the remaining portion of the proximal straight tubule (Figs. 2 & 3) (291; 336). Thus, the proximal convoluted tubule of both superficial and juxtamedullary nephrons contain S_1 and S_2 segments, the proximal straight tubule of superficial nephrons consists of S_2 and S_3 segments, whereas only S_3 segment can be found in the proximal straight tubule of juxtamedullary nephrons (246; 291; 551). However, the subdivision of three proximal tubular segments is generally not clear-cut. At the high resolution electron microscopic level, basic ultrastructural characteristics can be further differentiated between three segments of proximal tubules. As summarized in Table 2 and Figs 2 & 3, the S_1 segment has much wider brush border membranes with greater number of microvilli, endocytic compartments, and a well-developed vacuolar-lysosomal system per unit length and therefore greater luminal surface area for transport and endocytic function. Furthermore, the S_1 segment also has more extensive lateral interdigitations or invaginations on the basolateral membranes, a larger network of mitochondria and well-developed Golgi apparatuses in the cytoplasm, compared with the S_2 and S_3 segments of proximal straight tubules (291; 336). Thus, it is not surprising that the S_1 segment possesses the highest capacity for sodium, solute, amino acid, and fluid transport among all renal tubular segments. By comparison, the brush border appears to be shorter, invaginations on the

basolateral membranes are fewer, mitochondria are smaller, and endocytic compartments are less prominent in the S_3 segment. Nevertheless, most of tubular transport functional studies often use the classification of proximal convoluted and straight tubules instead of the S_1 to S_3 segment description.

FUNCTIONAL HETEROGENEITY OF PROXIMAL TUBULE

Functional heterogeneity of proximal tubules of the nephron has been widely investigated and documented since 1960s (Table 3) (246; 248; 249; 291; 551). It was reported that glomerular filtration rate is relatively higher in juxtamedullary nephrons compared with that of superficial nephrons (221; 246; 248). As expected, absolute proximal tubular reabsorption of sodium, bicarbonate, and fluid in juxtamedullary nephrons exceeds that of superficial nephrons, so that fractional proximal tubular reabsorption would be similar between superficial and juxtamedullary nephrons (244; 245). The heterogeneity in transport activity between superficial and juxtamedullary nephrons have been described and compared previously by Lameire et al. (294). Early biochemical studies showed that the sodium to chloride permeability ratio also differs along the length of superficial pars convoluta, with sodium more permselective in early and chloride more permselective in late proximal convoluted tubules, suggesting that the rate of sodium transport is higher in the early than the late segment of superficial proximal tubules (333). By contrast, proximal convoluted tubules do not exhibit this heterogeneity in relative sodium and chloride permeability in juxtamedullary nephrons (246). With respect to the bicarbonate to chloride permselectivity ratio, it is greater in juxtamedullary proximal tubules than in superficial proximal tubules (10). Finally, a lumen-negative electrical potential difference persists in juxtamedullary but not in superficial proximal convoluted tubules. Thus depletion of organic solute and bicarbonate, or abolition of a transepithelial chloride concentration gradient alters the rate of fluid reabsorption in superficial but not in juxtamedullary proximal convoluted tubules (244). The mechanisms underlying this functional heterogeneity of proximal tubular segments are not fully understood. However, the heterogeneity in the expression and distribution of biological enzymes, aminopeptidases, sodium and hydrogen exchangers or antiporters, such as the sodium and hydrogen exchanger 3 (NHE3), Na^+-K^+-ATPase, Na^+/HCO_3^-, organic solutes and glucose, different G protein-coupled receptors (GPCRs) and signaling mechanisms is clearly implicated (291; 401; 433; 435; 460; 468; 469; 521; 537).

PHYSIOLOGICAL REGULATION OF PROXIMAL TUBULE FUNCTIONS

Role of basolateral membrane Na^+-K^+-ATPase in active sodium transport

It was well established in the 1960s to 1970s that in proximal tubules, sodium is primarily reabsorbed via an active transport process mediated by an energy-dependent mechanism (14; 42; 43; 159; 160; 283; 284; 422; 537; 537; 540; 542) (also see reviews on Na^+ transport mechanisms, principles of electrolyte transport across plasma membranes of renal tubular cells for details). Wesson and Anslow appeared to first suggest that sodium might be actively transported across the proximal tubular epithelium against a sodium concentration gradient, but had no direct evidence to support the hypothesis at the time (540; 542). Kokko et al. subsequently showed that the sodium concentration gradient was developed apparently due to fluid retention within the tubular lumen by the nonelectrolytes, while sodium transport continuously proceeded (283; 284). In addition to the sodium concentration gradient, sodium transport appears to occur against a transtubular electrical potential gradient as well, with the proximal tubular lumen being about 20 mv negative vs. the interstitial and peritubular fluid (73; 158; 296; 544). However, later studies found that the transtubular electrical gradient across proximal convoluted tubules was probably smaller than previously reported, which only ranged from −6 to +2 mv (143; 510). Nevertheless, it is

still possible that even such smaller transepithelial electrical gradient may play an important role in the regulation of proximal tubular sodium transport.

Molecular characteristics of Na^+-K^+-ATPase—The molecular nature of Na^+ and K^+ concentration gradient across the plasma membranes was not known until Skou isolated an enzyme from the cell membranes of nerves that may be activated by Mg^{2+}, Na^+ and K^+, and involved in the active transport of Na^+ and K^+ across the cell membrane (470). Skou was awarded the Nobel Prize in Physiology and Medicine in 1997 for discovering of Na^+-K^+-ATPase (97). It is now well recognized that Na^+-K^+-ATPase plays an indispensable role in driving active sodium transport across proximal tubules (132). Na^+-K^+-ATPase was isolated and purified in the early 1970s (251; 252), and molecularly cloned in the 1980s (266; 267; 459; 464–467). Molecular characterization of Na^+-K^+-ATPase confirmed that Na^+-K^+-ATPase belongs to the P-type family of ATPase and has two major subunits namely the catalytic α and glycosylated β subunits (119; 132; 260; 334; 444). The α subunit consists of four isoforms, α_1 to α_4, and its protein contains about 1000 amino acids with a molecular wt. of 110 kDa (119; 132). It has a total of 10 transmembrane domains (M_1 to M_{10}) with both binding sites for Na^+ and ATP and phosphorylation site at the cytoplasmic domain and binding sites for ouabain and K^+ at the extracellular domain (119; 132). The β subunit, which is smaller with about 300 amino acids, has three isoforms, β_1 to β_3, a single transmembrane domain, and a large extracellular domain with glycosylation sites (119; 132; 260). The α subunit is responsible for the enzymatic or transport activity of Na^+-K^+-ATPase, whereas the β subunit may provide a supporting role. In addition to α and β subunits, a γ subunit with 53 amino acids has been cloned, but its role in the regulation of Na^+-K^+-ATPase activity is not well understood (39; 132; 349). Beguin et al. reported that the γ subunit does not influence the formation and cell surface expression of functional Na^+-K^+-ATPase α-β subunit complexes, but it may interact with assembled, transport-competent α-β subunit complexes and modulate the K^+ activation of Na^+-K^+-ATPase (39). For a comprehensive update on molecular identities of all isoforms and subunits of Na^+-K^+-ATPase, please consult with http://www.genenames.org.

Expression and localization of Na^+-K^+-ATPase in proximal tubules of the nephron—In the kidney tubules, Na^+-K^+-ATPase is expressed (96; 444) and localized primarily on the basolateral plasma membranes (Fig. 4) (20; 353), where it is more active in proximal convoluted tubules than in proximal straight tubules (129; 132; 263; 264; 434; 489). Na^+-K^+-ATPase is also expressed in basolateral membranes of other nephron segments including the loop of Henle, distal tubules and collecting ducts. Although it has been suggested that the $\alpha_1\beta_1$ heterodimer is the exclusive Na^+-K^+-ATPase in proximal tubules of the kidney (132), up to eight different Na^+-K^+-ATPase isoforms may be expressed in the kidney (96; 444).

Effects of Na^+-K^+-ATPase on sodium transport in proximal tubules—The role of Na^+-K^+-ATPase in active sodium transport has been studied extensively since the 1970s. Na^+-K^+-ATPase is very sensitive to the inhibition by ouabain, a natural inhibitor and thus ouabain has been widely used to inhibit Na^+-K^+-ATPase in epithelial transport studies (132). Using in vivo micropuncture, Gyory and Kinne showed, as early as in the 1970s, that inhibition of Na^+-K^+-ATPase by ouabain effectively abolished sodium and fluid reabsorption in proximal tubules (181). The effect of ouabain on sodium and fluid reabsorption by blocking Na^+-K^+-ATPase was later confirmed in the in vitro microperfusion studies in proximal tubules (149; 166). It is now understood that sodium transport across the proximal tubular epithelia is mediated by a two-step mechanism. First, Na^+-K^+-ATPase provides necessary energy to drive active sodium extrusion from basolateral plasma membranes, which facilitates passive entry of sodium into proximal tubular cells via various

sodium antiporter or cotransporters expressed or localized on apical membranes (132). However, the role of Na^+-K^+-ATPase or its α or β subunits in the regulation of active sodium transport has not been studied in transgenic mice with either global or tissue-specific deletion of Na^+-K^+-ATPase in proximal tubules. The reasons may be due to the fact that mice with genetic deletion of the α_1 subunit gene die during embryogenesis, and mice with deletion of the α_2 subunit gene also die immediately after birth (28; 119; 236; 247; 357). Accordingly, nephron segment- or cell-specific deletion or overexpression of α or β subunits of Na^+-K^+-ATPase may provide new insights and perspectives in this field.

Na^+-K^+-ATPase as a signal transducer in proximal tubules—There is evidence that Na^+-K^+-ATPase not only regulates active sodium transport, but also acts as a signal transducer via intracellular calcium (3). Many humoral factors, high salt intake, or hormones regulate proximal tubular sodium transport at least in part by altering the expression and activity of Na^+-K^+-ATPase or by inducing the endocytosis of Na^+-K^+-ATPase into proximal tubule cells (95; 132; 324). For example, Yingst et al. demonstrated that the vasoactive peptide angiotensin II (ANG II) directly stimulates the activity and alters the phosphorylation of Na^+-K^+-ATPase in rat proximal tubules with a rapid time course (561; 562). Similar effects of ANG II on Na^+-K^+-ATPase activity were reported in proximal tubule cells or proximal straight tubules in vitro (126; 152). Most of ANG II-stimulated effects on Na^+-K^+-ATPase activity are mediated by AT_1 receptors (47; 132; 185; 185). Periyasamy et al. fed Sprague-Dawley rats a high (4% NaCl) or normal diet for one week, and found that high salt diet significantly decreased proximal tubular Na^+-K^+-ATPase α_1 subunit proteins and activity in the plasmalemmal fraction containing basolateral membranes (406). These responses were correlated with the increased natriuretic responses in rats (80). Liu et al. demonstrated that ouabain stimulated the clathrin-dependent endocytic pathway, which translocates Na^+-K^+-ATPase into intracellular endosomal compartments (322). Likewise, caveolin-1, dopamine, or α adducin have also been shown to modulate the internalization of Na^+-K^+-ATPase in proximal tubular cells (133; 161; 323; 499). Finally, pressure natriuresis may also involve suppression of Na^+-K^+-ATPase activity during hypertension (344).

Role of apical membrane Na^+-H^+-antiporters or Na^+-H^+ exchangers (NHEs)

Molecular characteristics of NHEs in proximal tubules—While Na^+-K^+-ATPase on the basolateral plasma membranes provides the driving force for extrusion of intracellular sodium into the peritubular interstitial fluid compartment and thus into the circulation, luminal Na^+ entry into proximal tubular cells from apical membranes is mediated by various antiporters or exchangers, and cotransporters. One of these important antiporters is the sodium and hydrogen antiporter or exchanger 3 (NHE3) (118; 567). The early evidence for the presence of a sodium and hydrogen exchanger or antiporter in the proximal tubular epithelium was provided by Murer et al. more than three decades ago in renal brush border membrane vesicles (361). The findings of Murer et al. led to extensive studies on this antiporter and subsequent recognition that the apical membrane of proximal tubules in mammals has the unique ability to acidify the tubular fluid by secreting hydrogen ions in exchange for luminal sodium (6; 14; 16; 60; 423). A gene encoding a Na^+/H^+ exchanger was cloned in 1989 by Sardet et al. (440), which was followed by subsequent cloning of additional members of the NHE gene family in renal and intestinal epithelial cells (389; 500–503; 532). It is now understood that NHE3 belongs to one of nine isoforms of the mammalian Na^+/H^+ exchanger (NHE) gene family (118; 567). Characterization of the NHE gene family showed that the isoforms of NHE1–5 are localized primarily in plasma membranes of epithelial cells, where the isoforms of NHE3 and NHE5 may traffic from the plasma membranes to intracellular organelles, primarily of recycling endosomes, under physiological conditions (19; 23; 48; 50; 118; 389; 500). Unlike NHE3 and NHE5, the

isoforms of NHE 1, 2 and 4 mainly stay on plasma membranes and appear not to traffic from plasma membranes into recycling endosomes (118). Thus trafficking of NHE3 between the plasma membranes and recycling endosomes plays an important physiological role in regulating sodium reabsorption in proximal tubules (Fig. 5) (103). The remaining four isoforms of NHEs, NHE6, 7, 8, and 9 are localized mainly intracellularly, where they are present in the membranes of organelles and play an important role in the regulation of intraorganellar pH (169; 170; 351; 366; 555).

Expression and localization of NHEs in proximal tubules—Although there are nine members of the NHE gene family, only the NHE3 isoform is most relevant to the proximal tubules due to its unique expression and localization. Indeed, NHE1 has not been localized in the apical membrane of proximal tubules cells, such as opossum kidney cells and S1 and S2 proximal tubular segments of the rat renal cortex (289). Interestingly, immunohistochemical staining of NHE1 proteins was localized in basolateral rather than apical membranes of rabbit proximal tubules, distal convoluted tubules, thick ascending limbs of the loops of Henle, and the collecting ducts (49). Likewise, NHE2 and NHE4 mRNAs may be expressed in the kidney, but their expression is localized mainly in the medulla, perhaps on basolateral membranes of inner medullary collecting ducts, where they may be involved in volume or osmolality regulation (57; 475). Both NHE1 and NHE2 are sensitive to the inhibition of amiloride and its analogue ethylisopropyl amiloride (EIPA) (100; 388), whereas NHE4 is not responsive to the inhibition by amiloride (57). Yun et al. has suggested that NHE1 may play a “housekeeper” role (567). By contrast, molecular, biochemical, immunohistochemical, and transgenic mouse studies all point to the important roles of NHE3 in the regulation of proximal tubule sodium reabsorption and blood pressure homeostasis. In the kidney, most of NHE3 mRNA is expressed in the cortex of rabbit (500), rat (389), and humans (389). Immunohistochemical studies localize NHE3 protein primarily in the apical, or brush border, membranes of proximal tubules (48). The proximal portion of the descending thin limb and the thick ascending limb of the loop of Henle may also express small amount of NHE3 proteins, but the level of NHE3 expression in the loop of Henle pales in comparison with that in the apical membranes of proximal tubules (118).

Regulation of NHE3 activity in proximal tubules

The NHE3 activity in proximal tubules of the kidney is regulated by a complex of humoral factors and signaling mechanisms (210; 254; 313; 343; 352; 535). The Na^+-H^+ exchanger regulatory factor-1, NHERF-1, is one of these factors (534; 535). NHERF-1 is expressed and localized in apical membranes of proximal tubules (520), binds to NHE3 and the sodium-dependent phosphate transporter 2a (Npt2a), and plays an important role in cAMP-mediated phosphorylation and inhibition of NHE3 activity (215; 534; 535). Studies in NHERF1(-/-) mice suggest that both the exchanger protein directly activated by cAMP (EPAC)-dependent and protein kinase A (PKA)-dependent mechanisms are involved in the NHERF-1-mediated regulation of NHE3 activity in proximal tubules (363; 461). The vasoactive peptide ANG II is another major factor that may actively regulate NHE3 activity in proximal tubules (25; 54; 123; 210; 223; 302; 313; 425; 530). The effects of ANG II on NHE3 activity in proximal tubules are likely mediated by protein kinase C (PKC) (87; 122; 223; 255; 261; 262; 313; 320), inositol 1,4,5-triphosphate (IP_3) receptor binding protein released with IP_3 (IRBIT) and Ca^{2+}/calmodulin-dependent protein kinase II (210), or oxidative stress (25). In vivo, the effects of ANG II on NHE3 activity in proximal tubules may be blood pressure-dependent (302; 313; 343; 428). For example, we have recently demonstrated that infusion of a pressor or nonpressor dose of ANG II for 2 weeks induced differential NHE-3 responses and distribution in proximal tubules of the rat kidney, with increased membrane phospho-NHE3 proteins during infusion of the nonpressor dose of ANG II, and vice versa during infusion of the pressor does of ANG II (Fig. 6 & Fig. 7)

(313). Finally, dopamine (21; 55; 124; 227; 531), glucocorticoid (400; 526), insulin (145), glucagon (7) have been shown to alter NHE3 activity in proximal tubule cells in vitro or proximal tubules in vivo.

New insights and perspectives into the roles of NHE3 in the regulation of proximal tubule sodium transport and blood pressure, as revealed from studies on NHE3 transgenic mice—Most of previous studies on the roles of NHE3 were primarily performed in isolated proximal tubules or cultured proximal tubule cells using isoform-specific or non-specific inhibitors of NHEs. It is difficult to deduce whether NHE3 plays a critical role in mediating sodium reabsorption in proximal tubules of the entire kidney and whether NHE3 plays an important role in the physiological regulation of blood pressure. Global and proximal tubule-specific deletion of the NHE3 gene may provide new insights and perspectives on the role of NHE3 proteins in the physiological regulation of sodium reabsorption in the kidney. Gary Shull's group first generated mice lacking the NHE3 gene (*Slc9a3−/− or Nhe3−/−*) with or without the NHE3 gene rescue in small intestines, and demonstrated for the first time that.NHE3 indeed plays an important role in the regulation of proximal tubule sodium reabsorption in the kidney, body sodium and fluid balance, and blood pressure homeostasis (8; 50; 536). These elegant studies confirmed that approximately 50% to 60% of filtered NaCl and 70% to 80% of filtered HCO_3^- reabsorption in proximal tubules are mediated by NHE3 proteins (5; 14; 352; 451). Furthermore, virtually all of the measured Na^+/H^+ exchanger activity in renal apical membrane vesicles are dependent on NHE3 (530; 554). Knockout of the NHE3 gene in mice (*Nhe3−/−*) leads to 60% to 70% decreases in fluid, Na^+ and HCO_3^- absorption in proximal convoluted tubules, causes renal salt wasting, and significantly decreases basal blood pressure (Fig. 8) (300; 380; 451; 550). These phenotypes are accompanied by absorptive defects in the intestines resulting in mild diarrhea due to intestinal NHE3 deletion. Although *Nhe3*$^{-/-}$ mice with rescue of the NHE3 transgene in small intestines (tg*Nhe3*$^{-/-}$) tolerate sodium depletion or loading better than the nontransgenic *Nhe3*$^{-/-}$ mice, basal blood pressure was similar to *Nhe3*$^{-/-}$ (550). Renin expression in the kidney and circulating aldosterone level are increased in *Nhe3*$^{-/-}$ mice by ~ 5-fold, suggesting that ANG II is markedly activated in these mice as a result of salt wasting and volume depletion (451). When fed a normal salt diet, blockade of AT_1 receptors with losartan markedly decreased basal blood pressure further in both *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice (380). However, when fed a high salt intake, blood pressure-reducing effect of losartan was blunted to the wild-type levels in tg*Nhe3*$^{-/-}$ but not in *Nhe3*$^{-/-}$ mice (380). These results may be interpreted in three ways. First, NHE3 indeed plays a critical role in the physiological regulation of proximal tubular sodium transport and blood pressure by ANG II, because deletion of the NHE-3 gene decreases proximal tubular sodium and fluid reabsorption by >60%, increases fractional sodium excretion by 4-fold, and decreases basal blood pressure in the presence of marked activation of the renin-angiotensin system (RAS) (300; 451). Second, further blood pressure-reducing responses to losartan below their basal levels in both *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice may be due to blockade of the vascular effect of ANG II (380). Third, since basal blood pressure is similar in *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice and the RAS is activated under normal salt intake (380; 451; 550), intestinal NHE3 may not play a significant physiological role in blood pressure regulation. Whether blood pressure responses to long-term administration of ANG II would be different in *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice with or without intestinal NHE3 transgene is not known. Thus *Nhe3*$^{-/-}$ and tg*Nhe3*$^{-/-}$ mice may be excellent models to further determine the interactions between ANG II and NHE3 in proximal tubules of the kidney.

Sodium and glucose cotransporters and the role of apical membrane SGLT2

Expression and localization of *SGLT2* in proximal tubules—It is now understood that the sodium and glucose cotransporter gene family includes six members, namely SGLT1 to SGLT6, but not all of these SGLTs are expressed in proximal tubules (24; 552; 553). SGLT1 is a low-capacity, high affinity sodium and glucose cotransporter and is expressed and functions mainly in the small intestines of the digestive system (552; 553). By contrast, SGLT2 is a high-capacity, low affinity sodium and glucose cotransporter, and is localized almost exclusively in the apical membranes of proximal convoluted tubules (Fig. 9) (24; 155; 301; 552; 553). Unlike SGLT1, which mediates sodium and glucose cotransport in a 2:1 ratio, SGLT2 mediates sodium and glucose cotransport in a 1:1 ratio (211; 552; 553; 564). The remaining members of the SGLT gene family, SGLT1 to SGL6, are expressed widely in the kidney or other tissues, but their physiological roles in the sodium and glucose cotransport remain incompletely understood (552; 553).

Effects of *SGLT1* on glucose transport in proximal tubules—The important role of the kidney, proximal tubules in particular, in the regulation of body glucose metabolism and homeostasis has long been overlooked by endocrinologists and diabetic researchers. A widely-held dogma is that insulin alone, controls glucose metabolism, and its deficiency contributes most, if not exclusively, to the development of type 1 and type 2 diabetes. However, recent studies on the role of SGLT2 in the regulation of glucose transport and metabolism in proximal tubules and the potential of its inhibitors in treating type 2 diabetes may challenge this century-old dogma (24; 155; 339; 365; 552; 553). The kidneys of a normal adult human filter approximately 180 L of plasma a day. Given a normal blood glucose concentration of 100 mg/dL, this means that 180 g glucose will be filtered by the glomeruli daily. However, 99.9% of the filtered glucose is taken up by proximal convoluted and straight tubules (552; 553). As a result, virtually no glomerularly filtered glucose will appear in urine. In addition to being responsible for glucose uptake by proximal tubules, SGLT2 also plays an important role in sodium and glucose cotransport through apical membranes.

Effects of *SGLT2* on sodium transport in proximal nephrons—The presence of sodium and glucose cotransporters in the intestinal epithelium was proposed more than 50 years ago (553), and in proximal tubules in 1980s (17; 213). There was early evidence that luminal Na^+ not only enters proximal tubular cells from apical membranes through the actions of NHE3, but also does so through a number of Na^+ and glucose cotransporters (see the review on Glucose transport in the renal proximal tubule and Genetic models of diabetes insipidus for a comprehensive review) (17; 213). In isolated brush border membrane vesicle preparations, D-glucose was found to be cotransported with sodium into and diffuse out of proximal tubule cells down an electrochemical gradient (29; 30; 36; 37; 354; 506). These cotransport processes are highly sodium-dependent (213; 511). If sodium is replaced by other cations such as lithium, the co-transport process ceases (71). For instance, Burg et al. perfused proximal convoluted tubules with artificial solutions containing glucose, lactate, alanine, and citrate. The effect of these solutes on sodium transport was examined by selective removal or replacement of the solutes individually or in combination from the perfusate (70; 71). It was found that complete removal of these solutes from the luminal perfusate decreased the rate of sodium reabsorption by 45–75%; whereas adding glucose or alanine individually induced a small, but significant, increase in sodium reabsorption (70). Alternatively, phlorizin, a glucose transport inhibitor, decreased the transepithelial voltage and the rate of sodium and fluid reabsorption in proximal tubules of the kidney. These early studies indicate that the sodium and glucose cotransport system indeed plays an important role in isosmotic fluid reabsorption by proximal tubules of the kidney.

New insights and perspectives into the roles of *SGLT2* in proximal tubules from studies on *SGLT2*$^{-/-}$ mice—Recently, the important role of SGLT2 in the regulation of glucose reabsorption in the kidney was determined in SGLT2-deficient mice (SGLT2$^{-/-}$) (329; 515; 516). The complete knockout of the SGLT2 gene was verified by the complete absence of SGLT2 immunostaining in the brush border membranes of the early proximal tubules (516). SGLT2$^{-/-}$ mice developed glucosuria and polyuria with significantly lower fractional glucose reabsorption, as showed in whole-kidney clearance and free-flow micropuncture studies (Fig. 10) (516). No significant differences in GFR and fractional excretion of sodium, potassium and chloride were observed between wild-type and SGLT2$^{-/-}$ mice, probably due to substantial increases in food and fluid intake in SGLT2$^{-/-}$ mice (516). However, since absolute and fractional sodium reabsorption has not been determined by free-flow micropuncture, it remains unknown whether deletion of the SGLT2 gene would impair sodium reabsorption in these mice. Nevertheless, SGLT2 inhibitors have been recently used to inhibit glucose reabsorption by the proximal tubules and therefore to lower blood glucose for treating type 2 diabetes in animals and humans (24; 155; 339; 365; 552; 553). These mutant mice may also be used as a novel tool to further study interactions between SGLT2 and Na^+ transport in proximal tubules in addition to SGLT2 inhbitors.

Role of basolateral membrane Na^+/Ca^{2+} exchanger in sodium transport

Molecular characteristics of Na^+/Ca^{2+} exchanger—The molecular and protein structures and physiological implications of the sodium and calcium exchanger (Na^+/Ca^{2+} exchanger) in the kidney and other physiological systems have been reviewed elsewhere (53; 140; 243; 330; 409). This section only reviews the role of basolateral membrane Na^+/Ca^{2+} exchanger in sodium transport in proximal tubules. The Na^+/Ca^{2+} exchanger gene was first cloned from the dog and human cardiac muscle (286; 378). The super family of the Na^+/Ca^{2+} exchangers (the NCX family) consists of three gene members, NCX1, NCX2 and NCX3 (286; 378). The NCX gene family is widely expressed in different mammalian tissues (286; 378). While the localization and functional significance of the Na^+/Ca^{2+} exchanger have been extensively studied in cardiac tissues and vascular smooth muscle cells (286; 378), its role in the regulation of sodium transport in proximal tubules remains poorly understood. In the kidney, localization of the Na^+/Ca^{2+} exchanger in the basolateral membranes of proximal tubules remains an issue of debate (116; 117; 426; 427).

Effects of Na^+/Ca^{2+} exchanger on sodium transport in proximal tubules—Most of our current understanding of the Na^+/Ca^{2+} exchanger in the regulation of sodium and fluid reabsorption in proximal tubules of the kidney is still largely based on earlier studies in the 1960s to 1990s. It has been suggested that the changes in intracellular calcium concentrations ($[Ca^{2+}]_i$) play an important role in the regulation of sodium transport in absorptive epithelia (142; 492). Gmaj et al. appeared to first demonstrate that two pathways of Ca^{2+} transport might exist in the basolateral membranes of proximal tubule cells, one via the Ca^{2+}-ATPase and the other involving a Na^+/Ca^{2+} exchanger (164). Studies on the properties of the Na^+/Ca^{2+} exchanger revealed that this system operates in an electrogenic manner and is very sensitive to the changes in intracellular and peritubular Na^+ concentrations (326; 492). Unlike the Ca^{2+}-ATPase, the Na^+/Ca^{2+} counter-transport is not directly coupled to ATP hydrolysis, but rather is dependent on the electrochemical potential gradient of sodium generated from Na^+-K^+-ATPase (52; 164; 359). It was further suggested that Na^+ entry into proximal tubular cells across the apical membranes and Na^+ uptake from the basolateral membranes into peritubular capillaries are tightly linked to the Na^+/Ca^{2+} exchanger via the changes in $[Ca^{2+}]_I$ concentrations (492).

Mechanisms underlying Na^+/Ca^{2+} exchanger-regulated sodium transport in proximal tubules—The mechanisms whereby the changes in $[Ca^{2+}]_i$ concentrations mediate transepithelial Na^+ transport remain incompletely understood. The widely held view is that increases in cytosolic free Ca^{2+} inhibit sodium and fluid reabsorption in proximal tubules whereas decreases in cytosolic free Ca^{2+} would have opposite effects (142; 192; 359; 492). Friedman et al. perfused isolated rabbit proximal tubules with quinidine and A23187, compounds known to selectively increase intracellular free Ca^{2+} concentrations in other epithelia, and demonstrated that these compounds inhibited proximal tubular sodium reabsorption (140; 141). In other studies, increases in $[Ca^{2+}]_i$ concentrations were also found to inhibit Na^+-K^+-ATPase in vitro (563), or to alter apical membrane permeability to Na^+ via the Na^+/Ca^{2+} exchanger (492). Furthermore, $[Ca^{2+}]_i$ may also act as a second messenger in the regulation of proximal tubular sodium transport in response to certain neurotransmitter or peptide hormones. For instance, acethylcholine is known to elevate intracellular calcium and inhibit proximal tubular sodium reabsorption in vivo (484). The effects of the vasoactive peptide hormone ANG II on proximal tubular sodium transport are well documented to involve the changes in $[Ca^{2+}]_i$ (Fig. 11) (99; 120; 193; 590; 591). However, whether the Na^+/Ca^{2+} exchanger plays an important role in the regulation of proximal tubular sodium and fluid reabsorption in the kidney has not been studied in transgenic animals with global or cell-specific deletion or expression of the Na^+/Ca^{2+} exchangers (53; 573; 574). Generation of transgenic mice with deficiency or overexpression of the Na^+/Ca^{2+} exchangers, NCX1, NCX2 or NCX3, selectively in proximal tubules of the kidney may be necessary to further determine the role of these Na^+/Ca^{2+} exchangers in proximal tubules.

Role of basolateral membrane eletrogenic Na^+/HCO_3^- co-transporters

Expression of carbonic anhydrases in proximal tubules—Carbonic anhydrases (CA) are a family of enzymes that catalyze the rapid interconversion of carbon dioxide (CO_2) and H_2O to proton (H^+) and bicarbonate (HCO_3^-) or vice versa (Wikipedia). The CA family includes at least five distinct sub-families (α, β, γ, δ and ε). The α-CA enzymes, expressed primarily in mammals, are divided broadly into membrane CAs (CAIV, CAIX, CAXII, CAXIV and CAXV), cytosolic CAs (CAI, CAII, CAIII, CAVII and CAXIII), mitochondrial CAs (CAVA and CAVB), and secreted CAs (CAVI) (for details, please refer to http://www.genenames.org) (417). In the kidney, CAII, a 29 kDa protein, and CAIV, a ~35 kDa protein, are predominantly expressed in humans and rabbits, while CAXII and CAXIV are also expressed in rodents (67; 356; 416; 417; 455; 504). CAII is localized in the cytoplasm of most nephron segments including proximal convoluted tubules, proximal straight tubules, the thick ascending limbs, distal tubules and collecting ducts (417). In proximal tubules, CAIV is localized in both apical and basolateral membranes of the S1 and S2 segments (67; 417), where CAXII is expressed primarily in basolateral membranes (417). Approximately 95% of total CA activity in the kidney is mediated by the cytosolic CAII, while the remaining 5% of the CA activity in the kidney is mediated by the membrane-associated CAIV and CAXII (416; 417).

Role of *CAII* and Na^+/HCO_3^- co-transporters in proximal tubule sodium and fluid reabsorption—The kidney plays a critical role in the maintenance of intracellular pH by regulating acid-base transport in proximal tubules (59; 401). Proximal tubules are responsible for reabsorbing ~ 80% of the filtered HCO_3^- load from the kidney. Although the acid-base transport process is primarily associated with the regulation of intracellular and blood pH, it also indirectly regulates sodium transport by proximal tubules through apical membrane NHE3 (59). HCO_3^- transport in proximal tubules involves three major steps (Fig. 12) (59). First, CO_2 and H_2O are converted by the cytosolic enzyme CAII into H_2CO_3, which subsequently dissociates to H^+ and HCO_3^- within proximal tubule cells (265; 472).

Second, proximal tubule cells exchange luminal Na^+ for cytosolic H^+ through the action of NHE3 (15; 522). Third, the electrogenic Na^+/HCO_3^- co-transporter NBCe1-A, expressed on basolateral membranes, transports Na^+/HCO_3^- into the interstitial fluid compartment and blood (59; 217; 433). Thus, the factors that stimulate the expression and activity of basolateral membrane NBCe1-A are expected to indirectly promote sodium and fluid reabsorption in proximal tubules (15; 59; 554). Alternatively, the factors that regulate CAII expression and activity are expected to alter NHEs and NBCe1-A expression and proximal tubule sodium and fluid reabsorption. Indeed, humans with genetic CAII enzyme defect or mice with CAII deficiency develop metabolic renal tubular acidosis with markedly impaired Na^+/HCO_3^- reabsorption (61; 303; 471; 473). However, the precise roles of CAII or other CAs and Na^+/HCO_3^--cotransporters in proximal tubule sodium and fluid reabsorption should be further studied in mutant mice with deficiency of a specific CA enzyme selectively in proximal tubules.

Isotonic fluid absorption in proximal tubules

Historical considerations—The classic dogma of isosmotic fluid reabsorption in mammalian proximal tubules remains well recognized by epithelial transport physiologists. The early evidence for isosmotic fluid reabsorption in proximal tubules of the kidney was first obtained from the pioneering micropuncture studies of Walker and colleagues (523; 524). These early investigators used the micropuncture technique to collect proximal tubular fluid in rats and guinea pigs, and demonstrated that the osmolalities of proximal tubular fluid and plasma were virtually identical. These findings led them to conclude that *"…This fluid reabsorption is an isosmotic process, accomplished without producing any increase in osmotic pressure of the fluid remaining within the tubule*; …". Using a microcryoscopic technique, Gottschalk & Mylle measured the osmolality of tubular fluid samples collected from the proximal convoluted tubules by micropuncture under the conditions of hydropenia, hypertonic mannitol infusion, urea and sodium diuresis, and confirmed that proximal tubular fluid was essentially isosmotic to plasma with or without superimposed osmotic diuresis (168). Similar conclusions were reached by Kokko and colleagues (283; 284), who found that during fluid reabsorption, the cryoscopic luminal fluid osmolality remained unchanged in superficial proximal convoluted tubules. Schafer and associates further demonstrated that fluid reabsorption from proximal straight tubules of the rabbit kidney was also an isosmotic process (443). However, it should be pointed out that there were disagreements on the concept of isosmotic fluid reabsorption in proximal tubules in 1980s (31; 172; 173; 442).

The mechanisms underlying isosmotic fluid reabsorption may involve several hypotheses. As in other leaky epithelia such as small intestines and gall bladder, it was widely thought early that fluid transport by proximal tubular epithelium is a passive process as a result of active sodium and solute reabsorption. This is because active sodium and solute transport across proximal tubular epithelium creates an effective transepithelial osmotic gradient that drives water down an osmotic gradient. However, this explanation may be too simplistic, given the complexity of sodium and fluid reabsorption in proximal tubules of the kidney especially in vivo. Over the last 50 years, several hypotheses have been put forwarded to explain isosmotic fluid reabsorption in proximal tubules of the kidney, as discussed below.

Role of lateral intercellular space hypertonicity—The so-called lateral intercellular space is defined as that at the luminal side, apical membranes of proximal tubular cells are joined together via tight junctions, whereas at the peritubular side, basolateral membranes of two adjacent proximal tubular cells are closely opposed to each other, forming an intercellular space between tight junctions and basolateral membranes of two adjacent cells (291; 336). According to the lateral intercellular hypertonicity hypothesis, the active Na^+ transport process is powered by the activity of Na^+-K^+-ATPase at the basolateral

membranes and transport of Na^+ into the lateral intercellular space, which creates a hypertonic intercellular compartment (102; 113). A hypertonic fluid compartment in the lateral intercellular space serves as a driving force promoting water transport from the tubular lumen into the peritubular capillaries, and therefore may be an important factor in the regulation of proximal tubular fluid reabsorption by the so-called peritubular physical factors.

To test the lateral intercellular hypertonicity hypothesis in the regulation of isosmotic fluid transport in leaky epithelia, Curran & McIntosh designed a model system for water transport, which consisted of three compartments separated by two membranes with different reflection coefficients (102). These investigators established an osmotic pressure gradient and a hydrostatic pressure gradient across the membranes and were able to demonstrate isosmotic water transport in this model system, which provided a possible mechanism or explanation for water transport in small intestine and proximal tubules of the kidney (102). Diamond and Bossert extended Curran & McIntosh's work further by proposing a standing-gradient osmotic flow hypothesis, which retained the basic concept of Curran & McIntosh, but with some modifications based on the presence of Na^+-K^+-ATPase on the lateral basolateral membranes (113). The hypothesis of Diamond and Bossert was based on several assumptions, namely: a) sodium and solutes are continuously transported into the lateral intercellular compartment, b) the lateral basolateral membranes are not permeable to solutes, so back-diffusion of solutes across lateral basolateral membranes into proximal tubular cells would not occur, and c) water permeability across apical, lateral basolateral and basement membranes remain high. Thus, a standing osmotic gradient or hypertonicity would be established within the lateral intercellular compartment as a result of active sodium transport into this compartment, which would provide an osmotic driving force for isosmotic water movement from the lumen into the lateral intercellular space either through tubular cells or tight junctions. According to Diamond and Bossert, the accumulation of solute and water within the lateral intercellular compartment will generate a sufficient hydrostatic pressure gradient to move water out of the space across the high water-permeable basolateral and basement membranes into peritubular capillaries (113).

While the lateral intercellular hypertonicity hypothesis remains debatable since the 1960s, there is some evidence suggesting that the lateral intercellular hypertonicity may indeed play an important role in water transport in proximal tubules. For instance, Maunsbach and Boulpaep observed that in Necturus and rabbit proximal tubules, the dilatation or collapse of the lateral intercellular space was closely associated with the presence or cessation of water reabsorptive volume flux (342). It has also been long recognized that the changes in peritubular physical forces resulting from aortic constriction (64; 424), volume expansion (33; 62), or increased renal venous pressure (304) may directly or indirectly alter the osmolality and hydrostatic pressure within the lateral intercellular compartment, thereby altering fluid reabsorption by proximal tubules.

Role of Na^+ recirculation—The role of the Na^+ recirculation hypothesis in the regulation of solute-coupled fluid reabsorption in proximal tubules has been recently reviewed by Larsen and Moberg, and Larsen et al., respectively (297; 298). The hypothesis appears to be an expansion of the standing-gradient osmotic flow hypothesis proposed by Diamond & Bossert (113). To help explain isosmotic fluid transport in adsorptive epithelia, Ussing & Eskesen proposed the alternative so-called Na^+-recirculation hypothesis (512; 513). The latter theory suggests that the recirculation of Na^+ ions, or the "surplus of solutes" may be returned to the lateral space via the action of the lateral membrane Na^+-K^+-ATPase, and may regulate the osmolality of the absorbate and promote fluid absorption in absorptive epithelia, such as small intestines and proximal tubules of the kidney. Although this hypothesis may predict isosmotic or hyposmotic transport, solvent drag, or the remaining

hydraulic permeability in proximal tubules of AQP1$^{-/-}$ mice, they appear to be inadequate to explain the markedly decreased water reabsorption in AQP1$^{-/-}$ mice (297; 298).

Role of intraluminal hypotonicity—An alternative hypothesis in explaining isosmotic fluid reabsorption in proximal tubules was proposed in the late 1970s and through the 1980s (31; 172; 173; 184; 321; 441; 442). This hypothesis argues that the lateral intercellular compartment lacks sufficient restraint for solutes and water diffusion, because it is physically very narrow and has remarkably low diffusion resistance, and therefore, it is unlikely can provide enough diffusion resistance to maintain a significant hypertonicity in the compartment for water transport (441). Instead, water reabsorption in proximal tubules may be driven by a relatively small but effective osmotic pressure difference, i.e., luminal hypotonicity, between the tubular lumen and the peritubular capillaries (10; 172; 441). To test the role of intraluminal hypotonicity in driving water reabsorption, Green and Giebisch simultaneously perfused proximal convoluted tubules and peritubular capillaries with isotonic NaCl. These authors demonstrated that intraluminal hypotonicity developed proportionally to the perfusion rate and the rate of volume reabsorption (172). Barfuss and Schafer (31) perfused isolated rabbit proximal convoluted and straight tubules with an ultrafiltrate of rabbit serum or a similar artificial solution, and found that the osmolality of the absorbate was significantly higher than that of the luminal perfusate and a positive correlation between fluid reabsorption and the osmolality differences between the absorbate and luminal perfusate. These studies provided support to the hypothesis of intraluminal hypotonicity, or a small transepithelial osmotic gradient, in driving fluid reabsorption in proximal tubules of the kidney. Further evidence in favoring luminal hypotonicity as a driving force for isosmotic fluid reabsorption in proximal tubules was obtained in in vivo micropuncture studies in rats (172; 184; 321). It was estimated that approximately 50% of water is reabsorbed transcellularly due to luminal hypotonicity (41). Nevertheless, due to the difficulty in measuring such a small luminal hypotonicity in proximal tubular fluid (<5 mosmol/kg H_2O), which is close to the limitation of the methodology for detection, the luminal hypotonicity is also unlikely the sole driving force for isosmotic fluid reabsorption in proximal tubules.

Role of axial anion asymmetry—As both lateral intercellular hypertonicity and intraluminal hypotonicity are insufficient to drive transepithelial fluid reabsorption in proximal tubules, it has also been proposed that preferential reabsorption of organic solutes or anions and bicarbonate in the early proximal convoluted tubules, i.e., axial anion asymmetry, may create an effective osmotic gradient and therefore a driving force for water transport across proximal tubular epithelium (172; 173; 321; 333; 377; 441; 443). The axial anion asymmetry hypothesis suggests that the luminal bicarbonate concentrations would fall due to preferential reabsorption of bicarbonate in early proximal convoluted tubules, while chloride concentrations would rise along the proximal tubule. A transepithelial chloride concentration gradient would develop between the tubular lumen and peritubular capillaries, which may drive proximal tubular sodium and fluid reabsorption (443). If a tubular lumen to peritubular capillary chloride concentration gradient is maintained, proximal tubular sodium and fluid reabsorption would be maintained as well (172; 174). Likewise, this hypothesis can also only partially account for isosmotic fluid reabsorption in proximal tubules.

Role of Aquaporin 1—Aquaporin 1 (AQP1) is a major water channel protein, which was cloned by Jung et al. in 1994 (256). The cloned AQP1 gene contains six putative transmembrane domains, but lacks cysteines at the known mercury-sensitive sites (256). The expression of the cloned AQP1 gene in Xenopus oocytes was found to induce 20-fold increase in osmotic water permeability. Northern blot and RNase protection assays demonstrated abundant mRNA expression in rat brain, and to less extent in the kidney and

other tissues (410). High levels of AQP1 expression were later localized in proximal tubules and the loop of Henle, where AQP1 may be physiologically responsible for up to 80% of water reabsorption from these nephron segments (331; 447; 517).

Studies in AQP1-knockout mice have provided new insights and perspectives on the important role of AQP1 in the regulation of water reabsorption in proximal tubules (331; 447; 517). Ma et al. showed that in membrane vesicles isolated from AQP1-knockout mouse kidneys, osmotic water permeability was decreased 8-fold compared with vesicles from wild-type mice (331). AQP1-knockout mice became severely dehydrated after water deprivation for 36 h, with serum osmolality increasing to 500 mOsm/kg H_2O and urine osmolality remained decreased (331). Using in vitro proximal tubule microperfusion and in vivo micropuncture, Schnermann et al. specifically determined the role of AQP1 in water reabsorption in AQP1-knockout mice (447). The authors demonstrated that transepithelial osmotic water permeability (Pf) in isolated S2 segments of proximal tubules from AQP1 knockout mice was markedly decreased, compared with wild-type mice. Spontaneous fluid absorption rates in AQP1-knockout mice were decreased to approximately 50% of wild-type. Further free-flow micropuncture studies showed that the percentage of fluid absorption in proximal tubules was decreased in AQP1-knockout mice (26 ± 3% vs. 48 ± 2%, $p<0.01$) (447). Vallon et al. compared osmolalities in micropuncture fluid samples collected from late proximal tubules and confirmed marked luminal hypotonicity in proximal tubules of AQP1-knockout mice (Fig. 13) (517). Taken together, these results strongly suggest that AQP1 in proximal tubules play an important role in the regulation of proximal tubular fluid reabsorption,

MECHANISMS OF GLOMERULO-TUBULAR BALANCE

Glomerulo-tubular balance

A constancy of electrolyte composition and fluid volume in the extracellular space is essential for survival of all mammals. Approximately 99% of filtered sodium and fluid load from the glomeruli is returned to the circulation by the renal tubular reabsorptive processes. Proximal tubules play a key role in the maintenance of the fine balance between the rate of glomerular filtration (GFR) and absolute proximal tubular reabsorption (APR) in response to spontaneous variations in GFR. This inherent property of proximal tubules in which APR is closely coupled to GFR has long been recognized as glomerulo-tubular balance (GTB) (184; 235; 523; 524; 539; 546; 549). Although the interest in studying this phenomenon appears to have decreased during last couple of decades, GTB remains one of the most important mechanisms whereby proximal tubular transport of sodium and fluid is regulated (184; 497; 546).

Historical evidence of GTB—The phenomenon of GTB has a long history in the renal physiology and pathophysiology, and excellent reviews on GTB have been published in detail elsewhere (156; 184; 497; 546). The evidence for the existence of proportionality between the rate of GFR and APR was reported as early as 1941 (523; 524). The classical micropuncture study by Walker et al. demonstrated for the first time that *"… at least two-thirds of the fluid are reabsorbed. This fluid reabsorption is an isosmotic process, accomplished without producing any increase in osmotic pressure of the fluid remaining within the tubule; …"* (523). These investigators also observed a parallel relationship between glomerular and proximal tubular function during spontaneous changes in GFR and concluded that *"… the percentage rather than the amount of reabsorption remained constant; …"*. This was followed by Wesson et al. who appeared to first use the expression of GTB in their article entitled "*The excretion of strong electrolytes*" (541). In his 1951 landmark monograph *"The Kidney: Structure and Function in Health and Disease"*, Homer Smith further introduced and extended the concept of GTB (474). Smith referred to GTB as a

physiological phenomenon involving the entire nephron population as an integration of glomerular filtration and proximal tubular reabsorption of sodium chloride, fluid, glucose, phosphate and sulphate etc. (474). However, most contemporary renal physiologists continue to focus GTB primarily to the relationship between GFR and absolute APR of sodium and fluid reabsorption.

Gold-standard micropuncture technique to study GTB—The concept of GTB as developed and advocated by Walker et al. (523), Wesson et al. (541), and Smith in the 1940s and 1950s (474) has led to extensive efforts to elucidate this phenomenon and underlying mechanisms. The early micropuncture findings by Walker et al. was subsequently confirmed by others in the 1960s and 1970s (114; 156; 159; 160; 316). Thus, in vivo micropuncture became the technique of choice to study proximal tubule transport and GTB in subsequent years. In fact, the technique remains a gold-standard tool for renal physiologists to elucidate this phenomenon in health and diseases today. The micropuncture technique has many advantages for studying GTB compared to other approaches. First, the tubular fluid can be collected directly from the end of a single proximal convoluted tubule via a fine glass micro-pipette for analysis of the changes of its compositions (156; 157; 514). Second, the structural and biochemical relationship between a proximal tubule, the interstitium and a peritubular capillary is well maintained during the collection of proximal tubular fluid. Third, perhaps more importantly agonists, hormones and their inhibitor(s) or blocker(s) may be applied directly into the tubular lumen or the peritubular capillary to study their roles in the regulation of proximal tubular transport and the cellular mechanisms (167; 200; 418). However, the micropuncture technique may also have some limitations. Proximal straight tubules of superficial nephrons and the entire proximal tubular segments in mid-cortical and juxtamedullary nephrons are inaccessible to in vivo micropuncture collection of the tubular fluid (156; 157; 514). This limitation is significant, because there are clear structural and functional heterogeneities between superficial and juxtamedullary nephrons (246; 248; 249; 291; 291; 336; 551). Thus the observations and conclusions obtained using this technique on a single proximal convoluted tubule of a single superficial nephron may not necessarily be applicable to all proximal tubules in the kidney. The other limitation is that the technique is so technically challenging and laborious that very few investigators in the world have the required expertise and resolve to continue to use the technique in their research (40; 269; 325; 399; 498; 514). This technical challenge may in part contribute to the diminished interest in studying GTB today. Recent generation of diverse transgenic mice with knockout, knockin, or overexpression of a particular gene appear to have revived the interest in using the in vivo micropuncture technique to study the physiological roles of these genes in mice (40; 206; 269; 325). Nevertheless, to accurately and reliably perform in vivo micropuncture experiments in superficial proximal tubules of the mouse kidney is even more technically challenging. It is not surprising that some of unexpected observations have been reported between micropuncture studies in the rat and mouse kidneys (40; 206; 269; 325). In spite of these limitations, in vivo micropuncture will remain the gold standard approach to study single proximal tubule function.

Indirect approaches to evaluate GTB in the entire kidney—Since GTB is a phenomenon only occurred under euvolemic conditions in the intact kidney, isolated perfusion of proximal tubules may not be suitable for studying the phenomenon of GTB. To determine whether or not GTB occurs in the entire kidney, several indirect approaches have been proposed. However, their usefulness or validity in evaluating GTB in the entire kidney is often controversial. For example, Leyssac proposed a simple occlusion time and transit time technique for measurement of absolute proximal tubular reabsorption in anesthetized rats (56; 305). But the assumptions and validity of the technique have been questioned (156; 157). Other indirect methods include the renal clearance of phosphate, calcium, solute-free

water clearance during maximal water diuresis to determine total proximal reabsorption of sodium and water in the kidney. But these substances are either reabsorbed or secreted in or beyond proximal tubules, and therefore not ideal for studying GTB (454).

We and others have attempted to use the lithium clearance technique to indirectly estimate absolute proximal reabsorption and thus GTB in the 1980s and 1990s (66; 196; 197; 202; 582; 587; 589). The theoretical assumption and validity of this method are primarily based on the observations that the concentration of endogenous lithium is negligible in humans and rodents, and that the reabsorption of exogenous lithium by proximal tubules of the kidney occurs in parallel with sodium and water (Fig. 14) (449; 494; 496). These include proximal convoluted and straight tubules. No significant lithium secretion or reabsorption was observed beyond the end of proximal tubules (209; 449; 483; 494; 496). It has been suggested that the lithium clearance technique may obtain information on the entire kidney proximal tubule function as reliable as the gold standard in vivo micropuncture technique on a single proximal convoluted tubule in rats with normal sodium intake (463; 495). It is cautioned, however, that some investigators have questioned the validity of the lithium clearance technique for estimating absolute proximal reabsorption in the entire proximal tubule function (288; 374), because lithium reabsorption in distal nephrons may occur under the conditions of sodium depletion or restriction (271; 288). In spite of this limitation, the lithium clearance technique has been used as an indirect tool to determine the roles of various humoral factors in the regulation of proximal tubule function and GTB in animals and humans (66; 75; 338; 386; 414; 438; 476; 576).

Mechanisms regulating glomerulo-tubular balance

Although GTB has been demonstrated consistently in rats, it still remains a puzzle how proximal tubules adjust their transport capacity to the physiological changes in GFR. It is well recognized that GTB is present in euvolemic but not in volume-expanded animals. If proximal tubules are isolated from the kidney and perfused in vitro, GTB is either impaired or abolished. This characteristic of GTB has led to the development of several hypotheses to explain the phenomenon of GTB, which include: a) peritubular physical factors (274; 364), b) intraluminal factors (274), and c) humoral factors (51; 183; 274; 364; 547). These factors are reviewed and discussed below (Fig. 15).

Role of peritubular physical factors

Peritubular capillary and interstitial oncotic pressure—The coupling of sodium, solute and fluid reabsorption from the lumen of proximal tubules into the lateral intercellular compartment may be mediated or regulated by a combination of active sodium transport, intercellular hypertonicity (102; 113), intraluminal hypotonicity (172; 441), or axial anion asymmetry (321; 442). Thereafter, the reabsorbate is either taken up by peritubular capillaries or leaks back into the tubular lumen via tight junctions due to paracellular back leak of solutes and fluid. The direction of solutes and fluid movement is then determined by the reabsorptive pressure, which is the balance of peritubular capillary and intrarenal interstitial oncotic pressure and hydrostatic pressure. Specifically, peritubular capillary oncotic and interstitial hydrostatic pressure promote fluid reabsorption from the intrarenal interstitium into peritubular capillaries, whereas peritubular capillary hydrostatic and interstitial oncotic pressure reduce fluid reabsorption by forcing fluid and solutes to leak back into the tubular lumen. In addition to peritubular physical forces, absolute fluid absorption in proximal tubules is also regulated by peritubular capillary reabsorptive coefficient, a product of effective reabsorptive area, hydraulic permeability, and tight junctions of proximal tubules.

Historically, the determinants of peritubular physical factors have been proposed as the dominant, if not sole, mechanism controlling proximal tubular fluid reabsorption, and hence the major mediator of GTB (32; 33; 64; 304; 419; 505). Indeed, a perfect GTB was demonstrated in studies using aortic artery constriction or release to alter peritubular physical factors (157; 163; 234; 429), or changes in peritubular and interstitial oncotic pressure during and after intra-aortic infusion of colloid-free, isooncotic or hyperoncotic solutions (62; 64; 172; 283; 419). Nevertheless, conflicting findings have also been reported in studies using similar microperfusion techniques (32; 214; 218). Thus, the role of peritubular and interstitial oncotic pressure in modulating GTB is still not well understood.

Peritubular capillary and interstitial hydrostatic pressure—The effects of peritubular capillary and interstitial hydrostatic pressure on absolute proximal tubular reabsorption and GTB were extensively studied throughout the 1970s to 1980s by altering hydrostatic pressure within peritubular capillaries and the renal interstitium due to alteration of blood pressure, constriction or dilatation of afferent and efferent arterioles, saline volume expansion and increased renal venous pressure (33; 93; 156; 182; 274; 430; 505; 546). Acute volume expansion or increase in renal perfusion pressure was closely associated with an increase in peritubular and interstitial hydrostatic pressure, resulting in a decrease in absolute proximal reabsorption and impairment of GTB (171; 430; 546). If the increases in renal perfusion pressure and therefore, hydrostatic pressure in peritubular capillaries and the renal interstitium were prevented by aortic constriction before volume expansion, GTB would be maintained. By contrast, GTB would be impaired if the aorta was clamped during or after acute volume expansion (139; 234; 258). It is now well understood that pressure diuresis and natriuresis occur largely due to increases in peritubular capillary and interstitial hydrostatic pressure, which impairs proximal tubular reabsorption and disrupts GTB.

Role of intraluminal factors

Flow-dependent fluid reabsorption—Flow-dependent fluid reabsorption in proximal tubules remains a well-recognized phenomenon today. Wiederholt et al. first showed that absolute proximal reabsorption changed in direct proportion to tubular flow or perfusion rate. These authors observed a constancy of proximal tubular fluid to plasma inulin concentration ratio, under conditions in which proximal tubular flow rate was altered without changes in single nephron GFR or peritubular physical factors (545). This phenomenon was later confirmed by many others (32; 69; 174; 184; 527), providing evidence of flow-dependent of proximal tubular fluid reabsorption.

The mechanisms by which the changes in absolute proximal tubular flow induce parallel changes in proximal tubular fluid absorption remain incompletely understood (527). One of the most recognized hypotheses is that glomerular-borne factors such as filtered sodium bicarbonate, glucose, organic acids, amino acids, and unidentified humoral factors act on proximal tubules (174; 184; 270). This hypothesis suggests that when the proximal tubular flow rate is increased, more glomerular-borne factors will be presented to the proximal tubular epithelium, which will stimulate proximal tubular reabsorption proportionally. For instance, Bartoli and Earley perfused proximal convoluted tubules with an ultrafiltrate of rat plasma and demonstrated flow-dependent fluid reabsorption, but not during perfusion of a Ringer solution alone (32). Haberle et al. perfused proximal tubules with proximal tubular fluid harvested previously and demonstrated a perfect GTB, which disappeared when the same tubule was perfused with an artificial fluid (184). These early elegant studies strongly suggested that natural glomerular filtrates contain glomerular-borne factors that regulate GTB by stimulating sodium and fluid reabsorption in proximal tubules.

However, the nature of glomerular-borne factors still remains to be determined. One of possible glomerular-borne factors may be HCO_3^-. Mathisen and coworkers used ethacrynic acid to inhibit proximal tubular carbonic anhydrase and reported a direct proportionality between HCO_3^- and absolute proximal fluid reabsorption (340). Green et al. perfused proximal tubular lumen with HCO_3^--Ringer solution and obtained 80% effective GTB (174). Other potential glomerular-borne factors may include organic solutes such as glucose, lactate, alanine, or citrate. Removal of these organic solutes from proximal tubular perfusates impaired GTB by almost 45–75%, whereas addition of these solutes in the perfusates increased absolute proximal reabsorption (30; 70; 174). These studies suggest that glomerular-borne factors may at least account for up to one-third of a perfect GTB.

An alternative intraluminal factor may involve the so-called tubular geometry. Gertz et al. suggested that GTB is closely associated with the tubular geometry or diameter (156). Indeed, decreased proximal tubular diameter induced by aortic constriction or increased proximal tubular diameter induced by ureteral occlusion was accompanied by parallel changes in absolute proximal reabsorption (424). Alternatively, absolute proximal tubular reabsorption was shown to be proportional to the cross-sectional diameter or area (448). However, the hypothesis of the tubular geometry was not supported by many others (72; 355; 429). Thus it appears that flow-dependent fluid reabsorption in proximal nephrons may be associated with glomerular filtered load or constituents of proximal tubular fluid rather than the diameter of proximal tubules.

Recently, it has been suggested that solitary (or primary) cilia of proximal tubular epithelia may play a role in flow-dependent fluid reabsorption in proximal tubules of the kidney, therefore in GTB (216; 285). Primary cilia are microtubule-based organelles that extrude from the cell surface such as the brush border membranes of epithelial cells (216). In cultured proximal tubule cells, the cilia may sense the fluid-mechanical stimuli to regulate the trafficking of apical membrane proteins, G protein-coupled receptors (GPCRs), or transcriptional factors between the cilia, cytoplasm and nucleus (216; 285). However, the presence and ultrastructure of primary cilia and their potential role in the regulation of proximal tubular transport have not been studied.

Roles of systemic and intrarenal humoral factors—Glomerulotubular balance was recognized between the 1970s and 1980s as an intrinsic physiological process that is regulated by either peritubular physical factors, (64; 234; 419; 505) or intraluminal factors (32; 33; 184; 214; 218; 270). This process requires little if any external neural or humoral influences. However, neither peritubular and interstitial physical factors nor intraluminal factors alone, or in combination, was firmly established as the sole mechanism(s) responsible for GTB (184; 546). Through the 1980s and the early 1990s, we reasoned that humoral mediators which have direct actions on GFR and sodium and fluid reabsorption in proximal tubules may play additional and important roles in the regulation of GTB. Among these humoral factors or mediators, ANG II (202; 527; 582; 587), atrial natriuretic peptide (105; 107; 196; 197; 332; 376; 398; 519; 589), endothelin 1 (201; 292; 293; 314; 560), and dopamine (11; 104) appear to directly or indirectly affect GFR and absolute proximal reabsorption and therefore GTB. This section of review focuses primarily on the roles of these systemic and intrarenal humoral factors or mediators in the regulation of absolute proximal reabsorption and GTB.

Roles of ANG II and its G protein-coupled receptors

Expression and localization of the major components of the renin-angiotensin system (RAS) in proximal tubules: Among various systemic and intrarenal humoral mediators, angiotensins, especially ANG II, play important roles in the regulation of GFR and proximal

tubular reabsorption of sodium and water (99; 186; 193; 276; 368; 528; 590). All major components of the RAS, including the substrate angiotensinogen (239; 275; 276; 371; 491), the rate-limiting enzyme renin (239; 276; 491), the angiotensin 1-converting enzyme (ACE) (86; 205; 584; 585) are expressed in proximal tubules of the kidney (Fig. 16). Thus ANG II can be formed not only systemically, but also locally in the kidney (77; 78; 250; 345; 346; 369; 372; 518). There is new evidence, however, that angiotensinogen expressed in the liver may be the primary source of angiotensinogen and ANG II in the kidney (341), Matsusaka et al. demonstrated that liver-specific knockout of angiotensinogen nearly abolished plasma and renal angiotensinogen protein and renal tissue angiotensin II (341). This study strongly suggests that under physiological conditions, hepatic angiotensinogen plays a dominant role in the generation of systemic and renal angiotensinogen and ANG II. However, increased local angiotensinogen expression in proximal tubules may partly contribute to high intrarenal or intratubular ANG II levels in ANG II-induced hypertension (373).

Angiotensin II acts on three different GPCRs, AT_{1a}, AT_{1b} and AT_2, in rodents, which are expressed in the apical and basolateral membranes of proximal tubules (Fig. 16) (82; 205; 391; 577; 578; 586). In humans, ANG II acts on two GPCRs, AT_1 (AT_{1a}) and AT_2, because humans do not express AT_{1b}. Recent studies using AT_{1a} receptor mutant mice showed that deletion of AT_{1a} receptors selectively from proximal tubules of the kidney is associated with significant decreases in proximal tubular reabsorption and basal blood pressure (177; 307). ANG II can be metabolized by aminopeptidases APA and APN to form ANG III and ANG IV, which are also biologically active in proximal tubules via AT_1/AT_2 or AT_4 receptors, respectively. (13; 189; 190; 308; 393; 579). Alternatively, ANG II can be degraded by ACE2 to form ANG (1–7), which activates ANG (1–7) or Mas receptors (88; 134; 180). ANG II and its major metabolites have been shown to alter proximal tubular transport and therefore may serve as mediators of GTB (90; 146; 189; 395; 486). The scope of this section focuses mainly on the roles of ANG II and its receptors.

Effects of ANG II on single nephron GTB: Although ANG II is well recognized to be a powerful regulator of sodium, bicarbonate and fluid reabsorption in proximal tubules (99; 186; 193; 276; 368; 590), few studies have tested the hypothesis whether ANG II is directly involved in the regulation of GTB. Leyssac appears to be the 1st investigator to suggest that angiotensin (probably refer to ANG II) regulates GTB in the mid 1960s by specifically and directly inhibiting fluid reabsorption in proximal tubules (306). Horster et al. subsequently determined whether angiotensin regulates proximal sodium reabsorption and came to a completely different conclusion that angiotensin did not have any direct effect on proximal tubular sodium reabsorption (220). Burg and Orloff investigated GTB in isolated, perfused rabbit proximal tubules in vitro (72). In that study, angiotensin was added into the bath rather than the lumen at the concentration of 2.5 μM and fluid reabsorption in proximal tubules was not significantly changed from the control (72). The authors concluded that *"… On the basis of the evidence, it appears unlikely that angiotensin is directly involved in this fashion in glomerulotubular balance. The possibility remains, however, that glomerulotubular balance might be regulated by a feedback system involving a hormone other than angiotensin."* Finally, Ichikawa and Brenner performed in vivo micropuncture studies to determine the role of efferent arteriolar tone in the regulation of proximal tubular fluid reabsorption and GTB in the rats (234). These authors observed that the subtype-nonselective ANG II antagonist saralasin reduced SNGFR and absolute proximal reabsorption proportionally possibly by altering the efferent arteriolar tone (234). In volume-depleted Munich-Wistar rats, Liu and Cogan reported that saralasin caused a small increase in SNGFR and parallel decreases in bicarbonate and chloride reabsorption in proximal convoluted tubules, implying an impairment of GTB (319). Thus whether ANG II regulates GTB remains incompletely understood.

Effects of ANG II and ANG III on the whole-kidney GTB: Using the whole-kidney integrative approach, we tested the hypothesis that ANG II or ANG III modulates GTB in anesthetized rats by altering GFR and increasing proximal sodium and fluid reabsorption (Fig. 17) (202; 582; 587). In our studies, the effects of ANG II and ANG III on GTB were evaluated by altering the whole-kidney GFR with the ACE inhibitor enalaprilat to suppress endogenous ANG II formation, and subsequently by replacing equimolar exogenous ANG II or ANG III. Simultaneous changes in absolute and fractional proximal reabsorption were determined by the lithium clearance method as an indirect marker of proximal sodium and fluid reabsorption in the entire kidney (494). We demonstrated that the diuresis and natriuresis induced by enalaprilat were due to the decreases in absolute and fractional proximal tubular reabsorption of sodium and fluid and the disruption of GTB to 48% of a perfect GTB (202; 582; 587). We further found that subsequent replacement of exogenous ANG II or ANG III largely restored GTB impaired by enalaprilat to 90% of a perfect GTB. Impairment of GTB was also observed in anesthetized rats treated with the AT_1 receptor antagonist losartan (587). These results may be interpreted to indicate that endogenous ANG II and ANG III may exert a direct stimulatory action on proximal tubular sodium and fluid reabsorption, and may act as a modulator of GTB by coupling the glomerular filtration and absolute proximal reabsorption. In contrast to our early studies (202; 582; 587), however, Carey et al. have suggested that ANG III may be the predominant agonist for AT_2 receptors in proximal tubules of the kidney, activation of which induces natriuresis via a GMP-dependent mechanism (268; 392; 393).

The conclusion that GTB may be modulated by ANG II is supported by the diverse effects of ANG II via AT_1 receptors in cultured proximal tubular cells, isolated perfusion of proximal convoluted tubules in vitro, as well as in free-flow micropuncture of proximal convoluted tubules in vivo (99; 186; 193; 276; 368; 528; 590; 591). In vitro, we have shown that ANG II stimulates the expression and activation of NHE3 in cultured rabbit and mouse proximal tubule cells (309; 311; 312). Both in vitro isolated perfusion and in vivo micropuncture studies have established that ANG II exerts biphasic effects on proximal tubular reabsorption with fentomolar concentrations stimulating whereas with nanomolar concentrations inhibiting proximal tubular transport (152; 200; 317; 453; 528; 529). In vivo, we have recently demonstrated in ANG II-infused rats that at the pressor dose, ANG II induced natriuresis by inhibiting phosphorylation or activation of NHE3 proteins (Fig. 6), whereas the non-pressor dose of ANG II stimulated activation of NHE3 in freshly isolated proximal tubules via protein kinase Cα (Fig. 7) (313). Both exogenous and endogenous ANG II also stimulates bicarbonate (59; 153; 575) and phosphate reabsorption (428), increases Na^+-K^+-ATPase activity (562), gluconeogenesis (175), and ammoniagenesis (92) in proximal tubules. These diverse effects of ANG II will promote Na^+/H^+ exchange, Na^+/glucose and Na^+/amino acid cotransport on the apical membranes, while increasing Na^+/HCO_3^- cotransport and Na^+/K^+-ATPase activity on the basolateral membranes (59; 153; 575). Hence, the stimulation by ANG II (and ANG III) of Na^+/HCO_3^-, and other Na^+-dependent solute cotransport may subsequently create a luminal hypotonicity and a lateral intercellular hypertonicity environment for promoting proximal tubular sodium and fluid reabsorption. Furthermore, by its preferential vasoconstrictive actions on efferent arterioles, ANG II and ANG III may also create a favorable peritubular physical force, i.e., increased oncotic pressure and decreased hydrostatic pressure, for peritubular capillary uptake of sodium and fluid into the circulation.

Roles of dopamine and its GPCRs

Dopamine synthesis in proximal tubules: Dopamine is best known as a catecholamine and neurotransmitter, but is now widely recognized to play an important paracrine role in the regulation of proximal tubular sodium transport in the kidney and arterial blood pressure

homeostasis (Fig. 18) (so see the review on Dopamine for a comprehensive review on the topic) (81; 233; 253; 570; 572). Dopamine is synthesized not only in noradrenergic and dopaminergic nerves in the central and peripheral nervous systems but also in the kidney. All major components of the entire dopamine system have been reported especially in proximal tubules (81; 572). How dopamine is synthesized, metabolized, and trafficking in proximal tubules of the kidney is still not fully understood. Dopamine synthesis in neurons involves hydroxylation of tyrosine by tyrosine hydroxylase to L-dihydroxyphenylalanine (L-DOPA), followed by decarboxylation via aromatic amino acid decarboxylase. However, tyrosine hydroxylase is not expressed in proximal tubules, which means dopamine may not be synthesized via the tyrosine hydroxylase (81; 572). There is also no evidence that L-DOPA is synthesized by proximal tubule cells, and instead its presence within proximal tubular cells is dependent mainly on the glomerular filtrate and taken up by proximal tubule cells via an apical membrane sodium transporter (81; 253; 410). The uptake of L-DOPA by the proximal tubule cells appears to increase during high salt loading, but the mechanisms involved remain poorly understood (81; 253; 390; 410; 456). Nevertheless, this suggests that dopamine synthesis is increased by high salt intake, therefore increased dopamine synthesis in proximal tubules may in part be responsible for high salt-induced natriuresis. Following its synthesis from L-DOPA in proximal tubules, dopamine is thought to be degraded by catechol-*o*-methyl-transferase and monoamine oxidase A or secreted into either interstitial or luminal fluid compartment, where dopamine activates either apical or basolateral membrane GPCRs (81; 253; 572), Recently, a novel flavin adenine dinucleotide-dependent amine oxidase, or renalase, has been identified in the kidney (327; 556). Renalase has been shown to efficiently metabolize catecholamines including dopamine, epinephrine, and norepinephrine (111; 556). Mice with renalase-knockout are hypertensive, suggesting that renalse may play a physiological role in proximal tubule transport and blood pressure regulation (111; 112).

Dopamine GPCRs in proximal tubules: The roles of dopamine in the regulation of proximal sodium reabsorption, urinary excretion and blood pressure are mediated by multiple GPCRs (Fig. 19) (81; 253; 566; 570). Dopamine GPCRs belong to the super family of G protein-coupled hepta-helical membrane receptors, and include at least five distinct members based on their molecular, structural and pharmacological properties (81; 253; 570; 572). Dopamine receptors are further classified into two subfamily groups, the D_1-like and D_2-like sub-families. The D_1-like group includes two members, D_1 (or D_{1A}) and D_5 (D_{1B}), whereas the D_2-like sub-family has three members, D_2, D_3 and D_4. The G protein-coupled signaling for the D_1-like and D_2-like dopamine receptors is strikingly different in that activation of the D_1-like receptors by dopamine stimulates adenylate cyclase by coupling to the stimulatory G protein, $G_{s\alpha}$, whereas activation of the D_2-like receptors inhibits adenylate cyclase by coupling to the inhibitory G_i protein (81; 253; 570; 572). Although all five members of dopamine receptors have been localized in the kidney, only D_1-like (D_{1A} and D_{1B}) and D_3 of the D_2-like dopamine receptors have been demonstrated in proximal tubules (382; 383; 390; 487; 557). Light and high resolution electron microscopic immunohistochemical studies have localized D_3 dopamine receptors in both apical and basolateral membranes of proximal tubules (81; 572). However, it remains poorly understood how apical/basolateral membrane and intracellular/nuclear dopamine receptor expression, localization or distribution are physiologically regulated by high salt intake, pressure natriuresis, and ANG II-dependent hypertension. High resolution electron microscopic immunohistochemistry or in situ hybridization should be ideal approaches to further investigate dopamine GPCRs in proximal tubules. .

Effects of dopamine on proximal tubule function and blood pressure homeostasis: Although whether dopamine and its receptor signaling directly regulate GTB in the kidney

has not been studied, it has long been recognized that intravenous or intrarenal administration of dopamine induces renal vasodilatation, diuresis and natriuresis, thereby resulting a decrease in arterial blood pressure (81; 253; 570; 572). While the effects of exogenous dopamine on renal hemodynamic responses including GFR and RBF remain inconclusive, dopamine does induce significant diuresis and natriuresis, when it was systemically or intrarenally administered (81; 229). Alternatively, the effects of dopamine on urinary sodium excretion of water and sodium could also be deduced from studies in which animals were treated with different dopamine receptor agonists or antagonists (81; 191; 229; 402; 533). If dopamine induces significant diuresis and natriuresis independent of the glomerular filtered load, this strongly suggests that dopamine inhibits proximal tubular sodium transport, since the majority of dopamine GPCRs are expressed or localized in proximal tubules. However, not all dopamine-induced diuresis and natriuresis are due to the inhibition of proximal tubular sodium and fluid reabsorption. In proximal tubules, the inhibitory effects of dopamine are primarily mediated by the D_1-like receptors to inhibit Na^+/K^+-ATPase and/or NHE3 activity, whereas the D_2-like receptors may act synergistically with the D_1-like receptors to either increase or decrease sodium reabsorption (81; 89; 533; 572). Activation of the D_1-like receptors localized in apical membranes by dopamine leads to the inhibition of NHE3 activity via stimulation of adenylyl cyclase, cAMP production and protein kinase A, while stimulation of basolateral membrane D_1 receptors inhibits Na^+/K^+-ATPase activity through activation of protein kinase C (55; 81; 533; 572).

New insights in the role of dopamine in dopamine GPCR transgenic mice: A significant role of D_1 (D_{1A}) receptors in the regulation of blood pressure was studied by Albrecht et al. (4). Mice with D_{1A} receptor knockout (D_{1A}R-KO) showed markedly elevation of basal systolic and diastolic blood pressures without significantly altering cAMP accumulation in renal tubules or urinary sodium excretion (4). The absence of changes in basal urinary sodium excretion and intrarenal cAMP accumulation in D_{1A}R-KO mice is unexpected. This suggests that dopamine may not play an important role in the regulation of basal renal function, but may become important under pathophysiological conditions such as sodium excess. Nevertheless, the ability of dopamine to increase renal cAMP production, induce sodium excretion, and inhibit NHE activity is decreased in D_{1A}R-KO mice. D_{1A}R-KO mice also develop fatal growth defects and died shortly after weaning age unless their diet is supplemented with hydrated food (4; 121). Alternatively, there may be compensatory responses to other dopamine GPCRs following genetic deletion of D_{1A} receptors. D_3 dopamine receptors are also expressed in proximal tubules and they are expected to regulate sodium excretion and blood pressure, because they negatively interact with ANG II and/or AT_1 receptors (381; 383; 569; 571). Indeed, Jose and associates generated D_3R-KO mice and demonstrated that D_3R-KO mice developed renin-dependent hypertension, also accompanied by insignificant changes in basal urinary sodium excretion (18). By contrast, in a different study D_3R-KO mice showed no significant differences from wild-type mice in urinary sodium excretion and blood pressure under basal conditions and during high salt-diet, salt-loading or volume expansion (482). Thus, the ideal approach may be to generate D_{1A}R-KO or D_3R-KO mice selectively in proximal tubules or to use in vivo micropuncture to study proximal tubular sodium transport responses in wild-type and dopamine receptor mutant mice. Nevertheless, it is estimated that the inhibition of NHE3 and Na^+/K^+-ATPase activities in proximal tubules and perhaps in more distal tubules by endogenous dopamine may be responsible for up to 50% of the basal urinary sodium excretion in the kidney (81; 253; 570; 572). Although the effects of dopamine and the receptors involved in GTB have not been studied, it is likely that dopamine, via interaction with ANG II AT_2 receptors and dopamine D_1 receptors, may physiologically impairs GTB and lower basal blood pressure

by inhibiting proximal tubular sodium and fluid reabsorption in animals and humans (162; 394).

Roles of atrial natriuretic factor (ANF) and natriuretic peptide receptors—In 1961, de Wardener and associates observed that intravenous infusion of saline led to a marked diuresis and natriuresis independent of changes in RBF, GFR and plasma aldosterone level (108). These investigators hypothesized that in addition to the already known GFR and aldosterone, a "third factor" might be involved in the regulation of renal sodium excretion. This observation sparked a great deal of interest and unsuccessful attempts to identify such a natriuretic factor in following years. It was two decades later when de Bold and colleagues first demonstrated that intravenous injection of atrial extracts cause a potent and rapid diuresis and natriuresis in anesthestized rats, which was named atrial natriuretic factor (ANF) or peptide (ANP) (105; 107). The discovery of de Bold et al. was soon confirmed by many others (58; 65; 76; 148). The molecular biology and cardiovascular and renal hemodynamic actions of ANF have been comprehensively reviewed elsewhere (105; 106; 165; 332; 376; 397; 398). Although many renal physiologists or nephrologists have recently lost interest in further studying the physiological and pathophysiological roles of ANF in the kidney and other tissues, it may still be relevant to briefly review the effects and mechanisms of ANF in the regulation of proximal tubular sodium and fluid reabsorption and GTB.

Effects of ANF on glomerular hemodynamics: In the kidney, ANF receptors are abundantly expressed in the glomeruli and proximal tubules in the cortex and the inner stripe of the outer medulla and inner medulla (Fig. 20) (85; 347; 458). The principal actions of ANF are to induce marked diuresis and natriuresis, but the mechanisms by which it increases urinary sodium and water excretion were quite controversial during 1980s to 1990s (165; 332; 376). A careful review of the ANF research field for last three decades since its discovery reveals at least two major hypotheses, with one being predominantly of the hemodynamic nature and the other involving inhibition of sodium and fluid reabsorption in proximal tubules (76; 98; 195; 228; 318; 332). While the effects of ANF on RBF have been inconsistent, its effects on GFR appear to be well recognized with the exception when crude atrial extracts or low doses of synthetic ANF were administered (75; 76; 332). Increases in glomerular filtered load of sodium and water may exceed the reabsorptive capacity of proximal and distal tubules, thereby leading to diuresis and natriuresis. However, pronounced diuresis and natriuresis still occurred in response to low doses of ANF in anesthetized animals without any detectable increases in GFR (27; 107; 362; 477; 594). These results strongly suggest that direct actions of ANF on renal tubular transport of sodium and fluid may be indicated.

Effects of ANF on proximal tubular sodium and fluid reabsorption: In addition to the diverse renal hemodynamic effects of ANF, there are also conflicting observations on the effects of ANF on the tubular transport of sodium and fluid reported by many renal physiologists. ANF has been shown to inhibit sodium reabsorption in distal tubules including cortical and medullary collecting ducts (65; 379; 478; 479; 568). However, in vitro microperfusion studies later found no direct effects of ANF in the medullary collecting duct (137; 138), or in the loop of Henle (287; 408). Since fractional sodium excretion was consistently demonstrated during ANF administration with or without changes in GFR, which cannot be entirely attributed to the inhibition of sodium reabsorption in distal nephron segments, a direct or indirect action of ANF on proximal tubules should be explored. Indeed, up to 65% of glomerular filtered sodium and fluid are reabsorbed by proximal tubules, any inhibition of proximal tubular reabsorption of sodium and fluid by a few percentages will likely result in a significant increase in the end proximal tubular delivery and thereby

urinary sodium and water excretion. This occurs especially if the distal tubules do not adequately compensate by reabsorbing more sodium and fluid delivered from the end of proximal tubules. For example, Burnett et al showed that ANF significantly increased fractional lithium and phosphate excretion in dog (74). Itabashi and associates demonstrated that ANF infusion caused increases in end-proximal tubular delivery of sodium and free water clearance in isolated perfused rat kidney (242). Finally, Hammond et al. showed that ANF impaired Na^+-dependent phosphate symporter and Na^+/H^+ antiporter activity in brush border membranes of rat proximal tubules (188). Interestingly, ANF had no effects on transepithelial volume flux or potential differences in isolated perfused rabbit proximal tubules (9; 35). The reasons underlying these conflicting reports on the renal tubular effects of ANF remained unresolved until Harris et al., who used split-droplet micropuncture technique to study whether ANF has a direct effect on proximal tubular transport (198). These investigators demonstrated for the first time that although ANF alone does not directly inhibit proximal reabsorption when it was perfused into peritubular capillaries, it significantly inhibited ANG II-induced increased proximal tubular reabsorption in a dose-dependent manner (198). These results were confirmed by Garvin two year later in isolated perfused proximal straight tubules (151). These results suggest that under physiological conditions, ANF may interact with ANG II in proximal tubules by antagonizing the stimulatory effects of endogenous ANG II on proximal tubular sodium and fluid reabsorption and therefore modulate GTB. The study of Harris et al. may at least explain why ANF does not have direct effects in isolated perfused proximal tubules (9; 35), loops of Henle (287; 408), and collecting tubules in vitro (137; 138).

Effects of ANF on GTB: We have investigated whether ANF inhibits proximal tubular sodium and fluid reabsorption and impairs GTB in anesthetized rats in late 1980s. We infused both low and high doses of synthetic ANF intravenously and simultaneously determined both renal hemodynamic and proximal tubular responses to ANF using the lithium clearance technique (196; 197; 199; 589). At low doses (0.1–5 ng/min), ANF induced diuresis and natriuresis without concomitant changes in GFR (197). At higher doses (30 ng/kg/min), ANF markedly increased both GFR and the magnitude of diuresis and natriuresis (196). Thus, while GFR was increased by 33% during ANF administration, absolute APR was increased by only 10%. Consequently, GTB was reduced to 30% of a perfect GTB (196; 197). In parallel experiments, we infused the pancreatic hormone glucagon, which is a known to induce glomerular hyperfiltration in the kidney, to raise GFR to the level seen during ANF infusion, and surprisingly found a proportionally increase in APR and a well-maintained GTB (196). In further studies, we investigated the interactions between ANG II and ANF on the whole-kidney proximal tubular reabsorption in anesthetized rats (Fig. 21) (589). We first treated the rats with the ACE inhibitor enalaprilat to suppress endogenous ANG II formation before ANF was infused intravenously. The effects of ANF on APR and GTB were prevented in rats pretreated with enalaprilat. These whole-kidney studies on the effects of ANF on APR and GTB are consistent with the shrinking split-droplet micropuncture study of Harris et al in rat proximal convoluted tubules (198) or in isolated perfused proximal straight tubules as reported by Garvin (151). The other indirect evidence supporting our observations includes that ANF-induced increases in fractional lithium and phosphate excretion were abolished by combined administration of an ACE inhibitor and ANG II (420; 421; 438). However, it should be pointed out that Liu and Cogan failed to demonstrate a proximal tubular effect of ANF when it was administered at a pharmacological dose (5 μg/kg as a bolus dose followed by a constant infusion rate of 0.5 μg/kg/min) (318). These differences may only be further resolved in the future by using transgenic mice with genetic deletion of ACE (206; 269), AT_{1a} receptor for ANG II (177; 299; 307), natriuretic peptide receptor A (NPRA) and B (NPRB) for ANF (397; 398) selectively in proximal tubules of the kidney.

Roles of endothelin-1 and ET_A and ET_B receptors—Endothelin-1 (ET-1) is known as one of the most potent vasoactive polypeptides initially derived from cultured porcine endothelial cells (560), but it is now well recognized to be synthesized or expressed in the kidney including proximal tubules (278; 280). Endothelin-1 belongs to the mammalian ET gene family, which includes two additional members, ET-2 and ET-3 (278; 280). The molecular biology, tissue-specific expression or production, and its physiological and pathophysiological roles in the regulation of salt and fluid balance and therefore blood pressure has recently been comprehensively reviewed by Kohan et al. (278; 280). This section therefore only devotes to the potential roles of ET-1 and its receptors in the physiological regulation of proximal tubular function and GTB.

Production of ET-1 in proximal tubules—It is important to emphasize that very low levels of ET-1 are present in the circulation under physiological situations and therefore ET-1 may be viewed as a local tissue paracrine or autocrine peptide (280; 457; 462; 560). The evidence that proximal tubules express and synthesize ET-1 primarily came from molecular biology and immunohistochemical studies. For example, there is evidence that ET-1 mRNA is expressed in cultured proximal tubules cell lines, including rabbit proximal tubule cells (207; 277) and human proximal tubule cells (387). By contrast, ET-1 mRNAs are either expressed (91; 314) or not expressed in rat proximal tubules (507; 509). Although immunohistochemical staining of ET-1 was detected in proximal tubules (548), these studies may only serve as an indirect evidence for proximal tubular production of ET-1 under physiological conditions. It may be necessary to determine the physiological levels of ET-1 concentrations in freshly isolated proximal tubules.

Expression and localization of ET-1 receptors in proximal tubules—Two classes of ET-1 receptors, ET_A and ET_B, have been molecularly cloned in humans and other mammals (2; 12; 128; 222; 315; 367; 384; 436; 437). The human ET_A receptor gene encodes 427 amino acids (2; 222), whereas the human ET_B receptor gene encodes 442 amino acids, respectively (367; 384; 436). The ET_A receptor has much higher affinity in binding to ET-1 than to ET-2 and ET-3 (2; 222), whereas the ET_B receptor appears to bind three ET peptides equally (367; 384; 436). Both ET receptors belong to the GPCR family and have been shown to involve several G proteins, including G_i, G_s, G_q and $G_{\alpha 12/13}$ (125; 272; 280; 315; 367; 384; 436; 437). Depending on the tissues or cells, activation of both receptors by ET-1 induces a variety of signaling responses (208; 279; 280; 412; 445). In the kidney, mRNAs for ET_A and ET_B receptors are widely expressed in different cells, including glomerular mesangial cells, vascular smooth muscle cells, proximal and distal tubular epithelial cells and inner collecting duct cells (280). Low levels of specific ET-1 and ET-3 receptor binding have been demonstrated in microdissected proximal tubular segments (490; 508), whereas both ET_A and ET_B receptor immunostaining were localized in proximal tubules of the rat kidney (538; 558; 559). Using in vitro and in vivo autoradiography, we and others have localized ET-1 receptor binding to the glomeruli, cortical inter-glomerular regions corresponding to proximal tubules, inner stripe of the outer medulla, and inner medulla (109; 110; 281; 282; 581; 583). Using ET_A receptor-selective antagonist BQ123 or ET_B receptor-selective agonist sarafotoxin 6C (S6C) as a binding displacer/inhibitor, we demonstrated that most of intrarenal ET-1 receptor binding is of the ET_B receptor (109; 110; 581; 583; 588). However, in vitro autoradiographic studies suggest that levels of ET-1 or ET_B receptors are much lower in proximal tubules, than those in the glomeruli, inner stripe of the outer medulla, and inner medulla in the rat kidney (Fig. 22).

Effects of ET-1 on proximal sodium and fluid reabsorption and GTB—Although both ET-1 synthesis and its receptor expression are relatively lower in proximal tubules, ET-1 appears to have diverse effects on proximal tubular sodium and fluid transport in the

kidney (280). Depending on the experimental settings or tissue preparations, two different modes of ET-1-induced effects have been reported. In vitro, ET-1 appears to exert positive or stimulatory effects, which are associated with increases in proximal tubular sodium and fluid reabsorption. For example, ET-1 increases the activities of NHE3 via an autocrine action (176; 292; 293; 314) and Na^+/HCO_3^- symporter in rabbit renal cortical vesicles (127) or opossum kidney proximal tubular cells (OKP) (525), and Na^+/P_i cotransporter in rat renal cortical slices (176). ET-1 also induces activation and/or phosphorylation and exocytic insertion of NHE3 in OKP cells via ET_B receptors and activation of protein kinase C (PKC) and cAMP-dependent protein kinase A (PKA) (94; 403; 404). Furthermore, increased activities of NHE3, Na^+/HCO_3^- symporter, and Na^+/P_i cotransporter in proximal tubular cells are associated with enhanced proximal tubular sodium and fluid reabsorption. The stimulatory effects of ET-1 in proximal tubule cells in vitro were elicited at nM of concentrations, which are probably above physiological levels of ET-1 in proximal tubules. However, it is quite common that higher concentrations of ET-1 or any other agonists would be required to induce biological effects in the in vitro preparations or cultured cells.

Although there have been more than 20,000 publications on ET-1 and ET_A and ET_B receptors since ET-1 was discovered more than two decades ago, there is limited information on whether ET-1 and its receptors regulate proximal tubular sodium and fluid reabsorption in the kidney in vivo or in isolated perfused proximal tubules in vitro (147; 150; 201; 405; 432). Using the lithium clearance technique, we intravenously infused low doses of ET-1 (1 and 10 ng/kg/min) in anesthetized rats, which did not alter the whole-kidney GFR (201). We demonstrated that ET-1 induced transient increases in blood pressure followed by sustained hypotension and decreased renal vascular resistance, accompanied by 5-fold increases in fractional water and 10-fold increases in fractional sodium excretion (201). Interestingly, we found that the end-proximal tubular delivery as estimated by the lithium clearance technique doubled and fractional sodium reabsorption was decreased by ~20% by ET-1 infusion. APR also fell significantly indicating an impairment of GTB by ET-1. These findings were subsequently confirmed in a different lithium clearance study by Perico et al. who also demonstrated that ET-1 (150 pmol, i.v.) induced marked diuresis and natriuresis primarily by decreasing both APR and fractional proximal tubular reabsorption of sodium (405). Thus these two reports were the first demonstration of an inhibitory effect of low concentrations of ET-1 on proximal tubular sodium and fluid transport and GTB in the rat kidney in vivo. By contrast, in healthy human subjects ET-1 did not have any effect on APR, when it was infused at a dose that significantly increased blood pressure, caused renal vascular constriction, and induced marked anti-diuresis and anti-natriuresis (480). In an in vivo micropuncture study in which ET-1 was administered intraluminally at 10^{-7} M, APR was increased by more than 3-fold whereas fractional proximal tubular sodium reabsorption was increased by 30% (432). Whether ET-1 exerts such profound stimulatory effects on proximal tubular reabsorption in the kidney remains controversial, since pharmacological concentrations of ET-1 were used (280; 432). Similarly, the mechanisms by which ET-1 inhibits proximal tubular sodium and fluid reabsorption in the rat kidney are also not well understood. However, it has been shown that ET-1 inhibited fluid and bicarbonate reabsorption in isolated perfused rat proximal straight tubules by decreasing Na^+-K^+-ATPase activity (150). Furthermore, activation of ET_B receptors by an ET_B receptor agonist in proximal tubules of the WKY rat kidney also inhibits Na^+-K^+-ATPase activity (565).

PROXIMAL TUBULAR FUNCTIONS AND GLOMERULO-TUBULAR BALANCE IN GENE-TARGETED ANIMALS

Over the last two decades, gene silencing or deletion has been increasingly used to generate unique animal models in which a gene encoding a particular enzyme, protein, GPCR, or transporter is silenced or deleted globally throughout the body or in a cell- or tissue-specific

manner. These novel animal models has provided a powerful tool to further study the proximal tubular function and determine the genetic and signaling mechanisms by which the proximal tubular function is regulated. However, some interesting but unexpected findings and/or insights on the proximal tubular function and GTB have emerged during recent years. Several examples are briefly reviewed below.

NHE3

NHE3 is the major Na^+/H^+ exchanger expressed in proximal tubules of the kidney (48; 118; 389; 500) and small intestines of the digestive system, and is responsible for the majority of sodium reabsorption in proximal tubules (5; 14; 352; 451). One would expect an imbalance between the glomerular filtered load and urinary excretion of sodium in mice with deficiency of the NHE3 gene. In these mutant mice, absolute reabsorption of fluid and bicarbonate in proximal tubules was reduced by more than 60% in NHE3-knockout mice (*Nhe3*−/−) (325; 451; 530). This suggests that the end-proximal tubular fluid and sodium delivery should be increased by a similar extent into the distal nephrons, and may induce marked diuresis and natriuresis, because the distal nephrons are only responsible for reabsorbing about 30% of the filtered load. However, urinary water and sodium excretion was reduced rather than increased in *Nhe3*−/− mice (325; 451; 530). This is because NHE3 is also expressed in abundance in small intestines and global deletion of NHE3 in these mice not only markedly impairs fluid and sodium reabsorption from proximal tubules but also from small intestines. There is a marked fluid and sodium wasting from the digestive system due to fluid and sodium retaining inside the lumen of intestines and moderate to severe diarrhea (325; 451; 530). Further studies on transgenic rescue of the NHE3 gene in small intestines led to improvement of fluid and sodium wasting from the digestive system (380; 550). Thus severe fluid and sodium wasting in the gut may stimulate compensatory responses to retain fluid and sodium from proximal tubules and the kidney by reducing single nephron and whole-kidney GFR (325).

ACE

ACE is expressed in abundance in apical membranes of proximal tubules (Fig. 15B), and play an important role in the regulation of proximal tubular transport of fluid and sodium by converting ANG I to ANG II (130; 194; 205; 206; 269; 372; 584; 587). Previous studies in anesthetized rats or in vivo micropuncture studies using ACE inhibitors confirmed the important roles of ACE and by implication, endogenous ANG II (194; 205; 372; 584; 587). To determine the role of ACE in renal function, Hashimoto et al. performed in vivo micropuncture on two lines of ACE-KO mice, in which ACE expression in the kidney was markedly reduced (ACE1/3) or eliminated (ACE2/2), respectively (206). In ACE1/3 mice, total GFR and SNGFR and fractional proximal reabsorption were similar to those of wild-type mice, In ACE2/2 mice, total GFR and SNGFR were significantly reduced while fractional proximal tubular reabsorption was increased significantly (206). These authors concluded that the chronic lack of ACE, and presumably endogenous ANG II generation, in the proximal tubule was not associated with sustained proximal fluid transport defects (Fig. 23) (206). Similar results were reported by Kesseler et al. in mice with or without expression of renal ACE (14). These results again suggest that in the absence of ANG II-stimulated proximal tubular transport, other vasoactive systems may compensate for the loss of the effects induced by ACE or ANG II in proximal tubules, therefore maintaining GTB.

ANG II and/or AT_1 (AT_{1a}) receptors

In contrast to ACE-KO mice, AT_1 (AT_{1a}) receptors in proximal tubules appear to play an important role in the regulation of proximal tubular reabsorption and blood pressure in transgenic mouse models. Gurley et al. generated transgenic mice with deficiency of AT_{1a} receptors selectively in proximal tubules, and demonstrated that ANG II in the epithelium of

the proximal tubule plays a critical and nonredundant role in determining the basal level of blood pressure. Abrogation of AT_{1a} receptor signaling in the proximal tubule alone reduced proximal fluid reabsorption and altered expression of key sodium transporters, modified pressure-natriuresis and protected the animals against hypertension (177). Li et al. used a proximal tubule specific, androgen-dependent promoter construct (KAP2) to generate mice with either over-expression of a constitutively active AT_{1a} receptor transgene or depletion of endogenous AT_{1a} receptors (307). Androgen administration to female transgenic mice caused a robust induction of the transgene in the kidney and increased baseline blood pressure. In the receptor depleted mice, androgen administration to females resulted in a Cre recombinase-mediated deletion of AT_{1a} receptors in the proximal tubule and reduced blood pressure (307). Using the in vivo intrarenal adenoviral gene transfer approach, we expressed an intracellular cyan fluorescent fusion of ANG II (ECFP/ANG II), selectively in proximal tubules of the rat and mouse kidneys with a proximal tubule-specific SGLT2 gene promoter (Fig. 24) (310). In our study, systolic blood pressure was increased in ECFP/ANG II-transferred rats, whereas fractional sodium and lithium excretion was reduced significantly. These suggest that intracellular ECFP/ANG II expression selectively in proximal tubules of the kidney led to increased basal blood pressure by increasing proximal tubular sodium reabsorption. The effects of ECFP/ANG II on blood pressure were blocked by losartan and prevented in AT_{1a} receptor knockout mice (Fig. 25). Thus our results provide evidence that proximal tubule-selective transfer of an intracellular ANG II fusion protein increases blood pressure by activating AT_{1a} receptors and increasing sodium reabsorption in proximal tubules (310). Taken together, AT_1 (AT_{1a}) receptors in proximal tubules appear to play an important role in mediating both extracellular and intracellular ANG II-regulated proximal tubular reabsorption and blood pressure.

SUMMARY AND CONCLUSIONS

In summary, the kidney no doubt plays a central role in the maintenance of a delicate extracellular electrolyte and fluid balance and blood pressure homeostasis largely through the function of proximal tubules. Proximal convoluted and straight tubules appear to exert a more prominent role than other nephron segments by reabsorbing 65% to 70% of the entire glomerularly filtered load and most, if not all, of filtered amino acids, solutes and low molecular weight proteins. Proximal tubules also contribute to the regulation of body acid-base balance and glucose metabolism. Great progress has been made in almost all aspects of proximal tubular function, especially with recent advances acquired from studies using molecular biology, gene silencing, and transgenic approaches in proximal tubules of the kidney. However, some basic tenets of the proximal tubule including the ultrastructures, intrinsic properties of proximal tubular sodium and fluid transport, and the regulatory mechanisms involved remain surprisingly intact. These include nearly isosmotic transport of two-thirds of the glomerular filterd load, the proportionality of APR to GFR (or GTB), and the roles of apical membrane NHE3, basolateral membrane Na^+-K^+-ATPase and NBCe1-A, peritubular physical and intraluminal humoral factors. However, recent studies showed that global or proximal tubule-specific deficiency of a particular transporter protein, a GPCR, or a peptide hormone that has profound effects on proximal tubular transport may not lead to significant body sodium and fluid imbalance in transgenic animals, but may lead to lower basal blood pressure (206; 269; 325; 446; 517; 530). This is because the defects in the proximal transport function due to the knockout of a gene or protein of interest are alleviated by appropriate compensatory responses in dietary intake, the glomerular filtered load and distal nephron segments (446). When a transporter protein is deleted from the proximal tubule, the same transporter expressed in other nephron segments or other solute transporters in proximal and distal nephron segments respond by increasing their expression or activities. Thus the body can largely adapt to the changes in proximal tubule functional defects in order to maintain body salt and fluid balance.

Although our understanding of the proximal tubular function has greatly improved with the use of novel approaches, new agonists or inhibitors, and global or proximal tubule-specific gene-targeting animals, the proximal tubular function and its physiological regulatory mechanisms may still be further studied using complementary approaches in the future. First, the traditional approach using a particular pharmacological compound to target an enzyme, a protein kinase, or a GPCR etc., still has a place in studying a particular tubular transport mechanism in proximal tubule cell cultures, in vitro isolated perfused or in vivo micropuncture of proximal tubules. However, better inhibitors or antagonists which have fewer nonspecific effects need to be developed. Second, in vitro isolated perfused and in vivo micropuncture of proximal tubules remain the gold standard techniques to study the proximal tubular transport and underlying physiological mechanisms. Third, gene silencing of a particular transporter or protein using siRNAs is increasingly used in the cell culture studies, but its usefulness for elucidating proximal tubule-specific effects in animals remains to be confirmed. The question remains as to how a particular siRNA may be delivered specifically and efficiently to proximal tubules to knockdown a gene or protein expression. There are also major concerns on the off-target effects or nonspecific consequences of this gene-silencing approach (257). Fourth, it is no longer sufficient to use global knockout animals to study proximal tubule physiology, and novel animal models with proximal tubule-specific knockout or knockin should be developed. Finally, with recent advances in gene microarrays and proteomics, an integrative approach should be used to uncover or explore the complex signaling transduction pathways and their interactions responsible for the regulation of the proximal tubular function in health and disease. Together, future studies with these complementary and innovative approaches will no doubt provide further new insights and perspectives in our understanding how proximal tubular transport is regulated by humoral factors, and how proximal tubular transport contributes to blood pressure homeostasis, and therefore becomes a therapeutic target in the prevention and treatment of hypertension and progressive kidney diseases.

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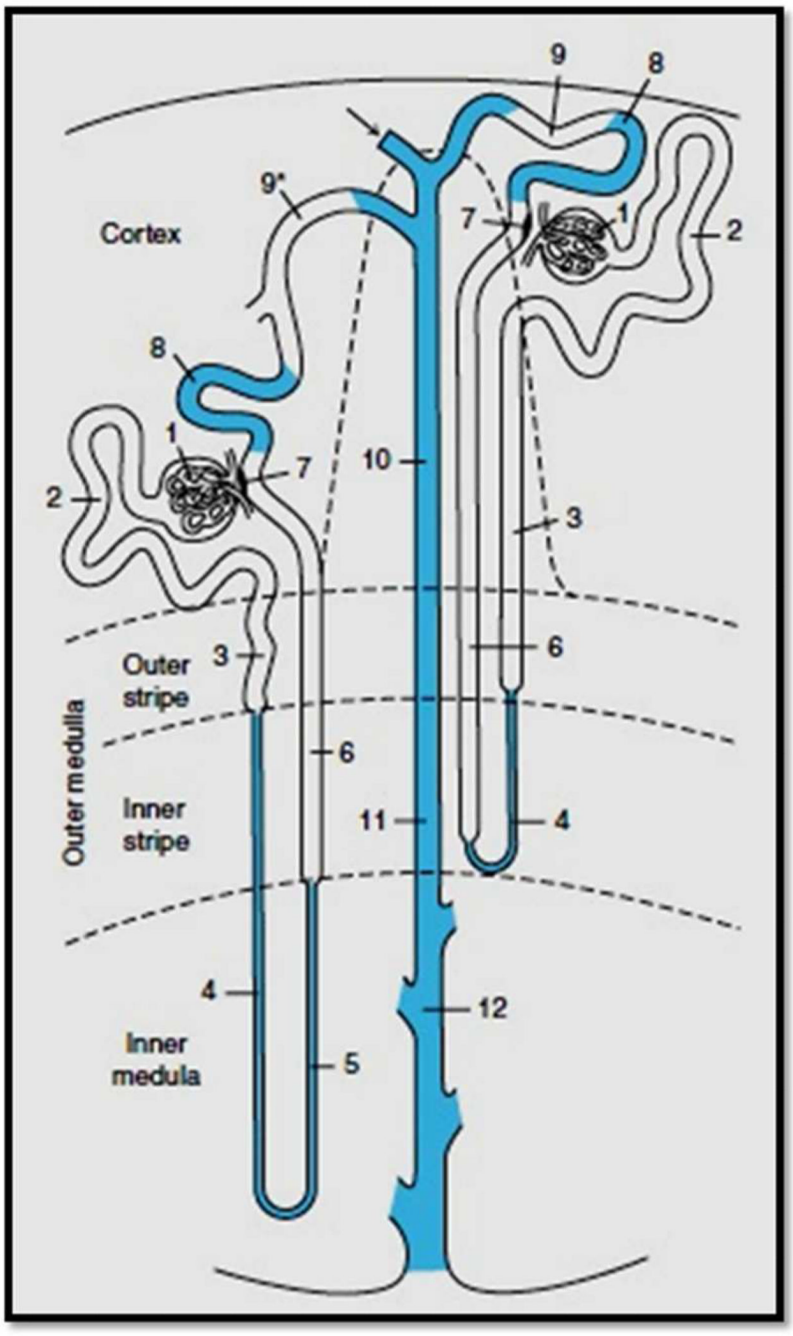

Figure 1.

Classification and localization of superficial (short-looped, upper) and juxtamedullary (long-looped, lower) nephrons, together with the collecting system. The cortical medullary ray is the part of the cortex that contains the straight proximal tubules, cortical thick ascending limbs, and cortical collecting ducts, delineated by a dashed line. 1, renal corpuscle (Bowman's capsule and the glomerulus); 2, proximal convoluted tubule; 3, proximal straight tubule; 4, descending thin limb; 5, ascending thin limb; 6, thick ascending limb; 7, macula densa (located within the final portion of the thick ascending limb); 8, distal convoluted tubule; 9, connecting tubule; 9*, connecting tubule of a juxtamedullary nephron that arches upward to form a so-called arcade (there are only a few of these in the human kidney); 10,

cortical collecting duct; 11, outer medullary collecting duct; 12, inner medullary collecting duct. Reproduced with permission from Kriz W, Bankir L. (290).

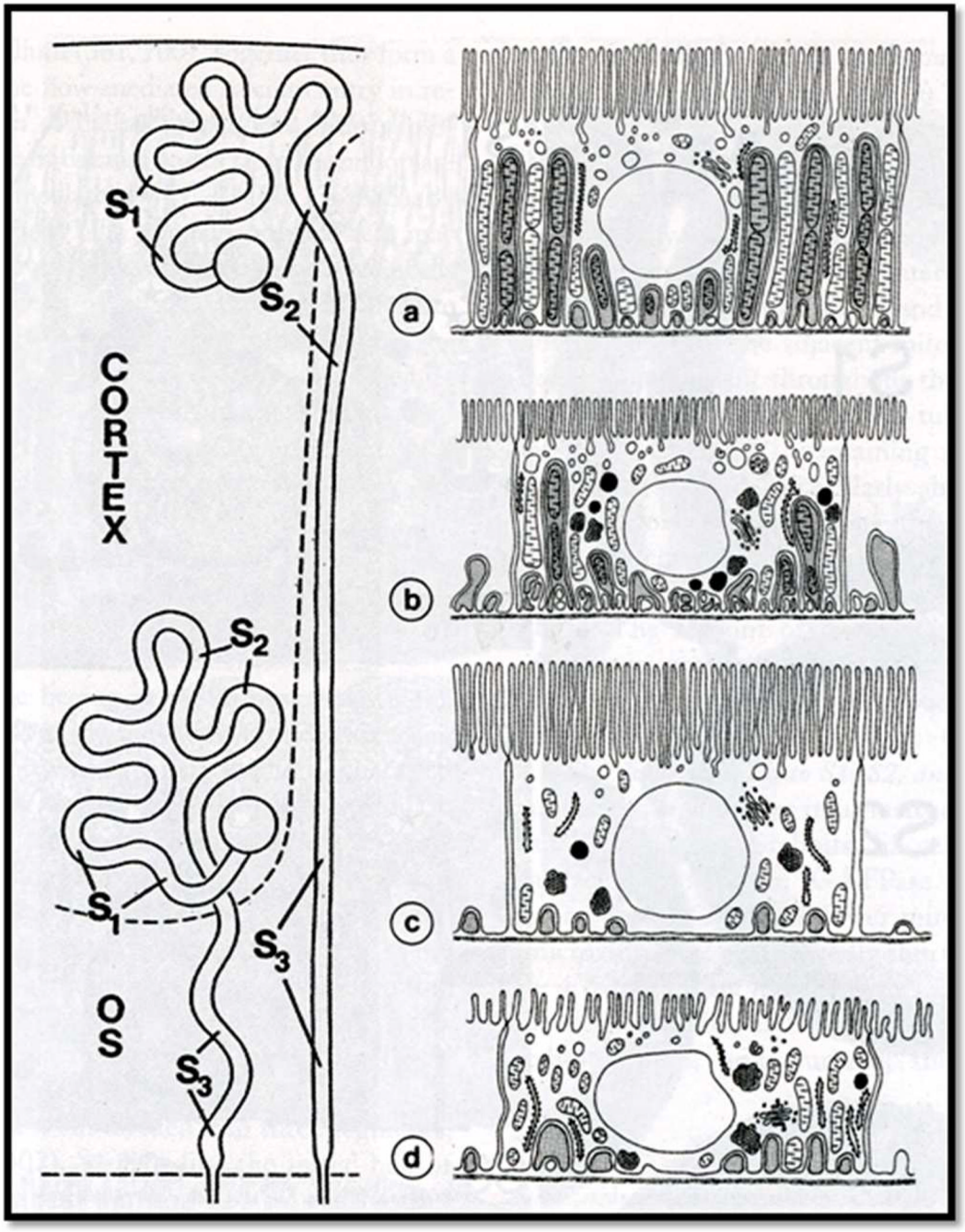

Figure 2.

Schematic location and ultrastructure of proximal tubular S_1–S_3 segments in superficial and juxtamedullary neprhons. For superficial nephrons, S_1 segments begin at the urinary pole of the renal corpuscle in the superficial cortex, transform gradually to S_2 segments within the labyrinth, and S_2 are transformed at different levels within the medullary rays. S_3 segments terminate at the border of the outer stripe (OS) to the inner stripe. For juxtamedullary nephrons, S_1 and S_2 segments start at the urinary pole of the renal corpuscle in the inner cortex, and S3 segments also terminate at the border of the outer stripe (OS) to the inner stripe. A): the S1 segment has the most extensive cellular interdigitation and dense brush border membranes. B): the vacuolar apparatus in the subapical cytoplasm, mitochondria,

ER, Golgi apparatus, lysosomes, and peroxisomes in proximal tubule cells. C): the rabbit has tallest brush border microvilli in proximal tubule cells. D): many other species shows shortest microvilli in proximal tubule cells. Reproduced from Kriz and Kaissling with permission (291).

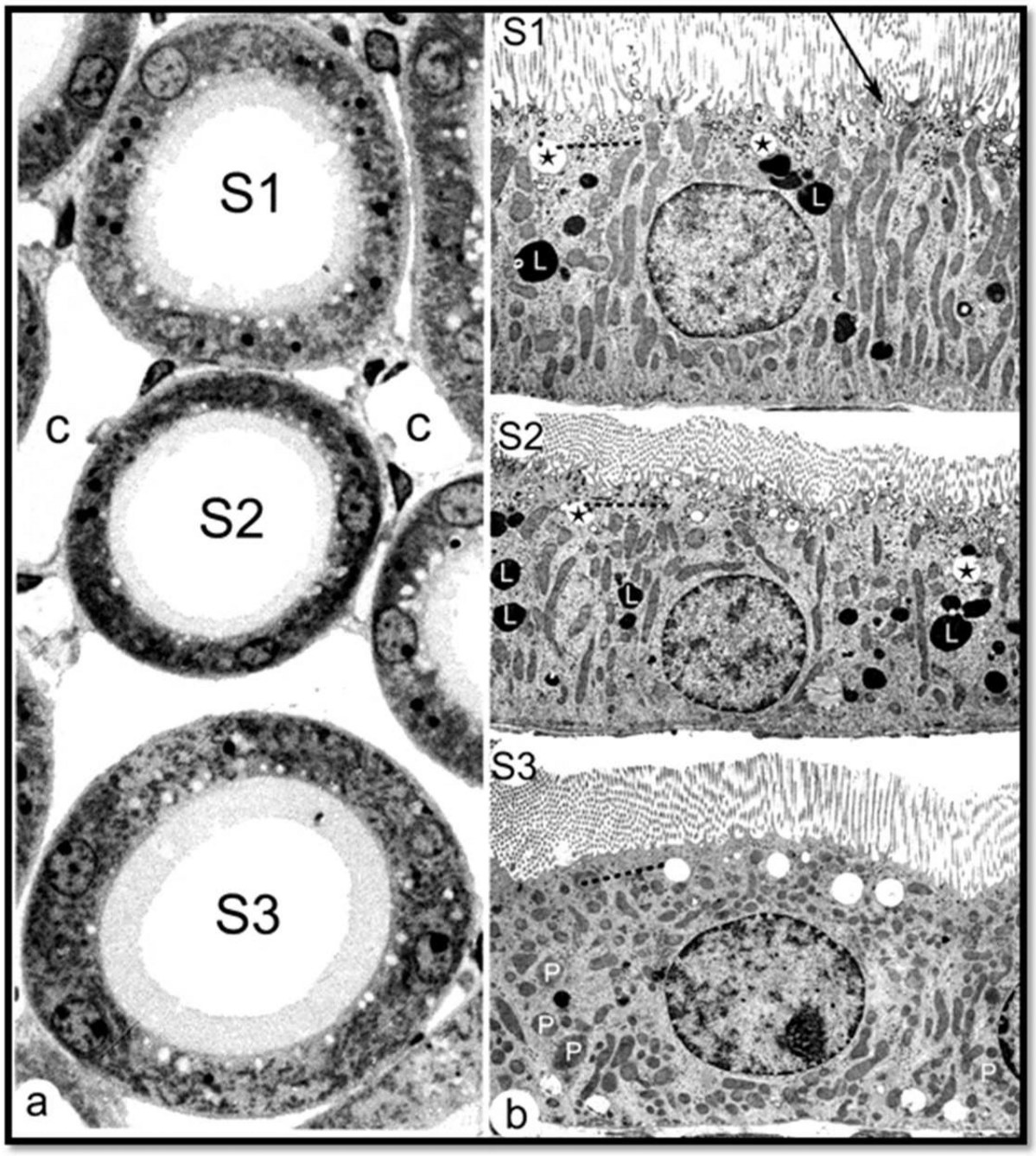

Figure 3.

Low resolution profiles and ultrastructures of proximal tubules in the rat kidney. A): profiles of S1, S2 and S3 segments of juxtamedullary proximal tubules with different brush border heights, cytoplasmic density, and outer diameters. Magnification: X ~1000. B): ultrastructures of S1, S2 and S3 proximal tubular cells in the rat kidney. Note that the mitochondria in S1 and S2 are located in lateral cell processes, whereas in S3 they are mainly scattered throughout the cytoplasm. The endocytic apparatus is the subapical cytoplasm is most prominent in S1 and S2 segments (broken lines), whereas endosomes (stars) and lysosomes (L) are localized deeper in the cytoplasm. There are few vacuolar apparatus and lysosomes present in the S3 segment, but peroxisomes (P) are more frequent

in this segment. C, capillaries. Magnification: X ~5400 from transmission electron microscopy. Reproduced from Kriz & Kaissling with permission (290).

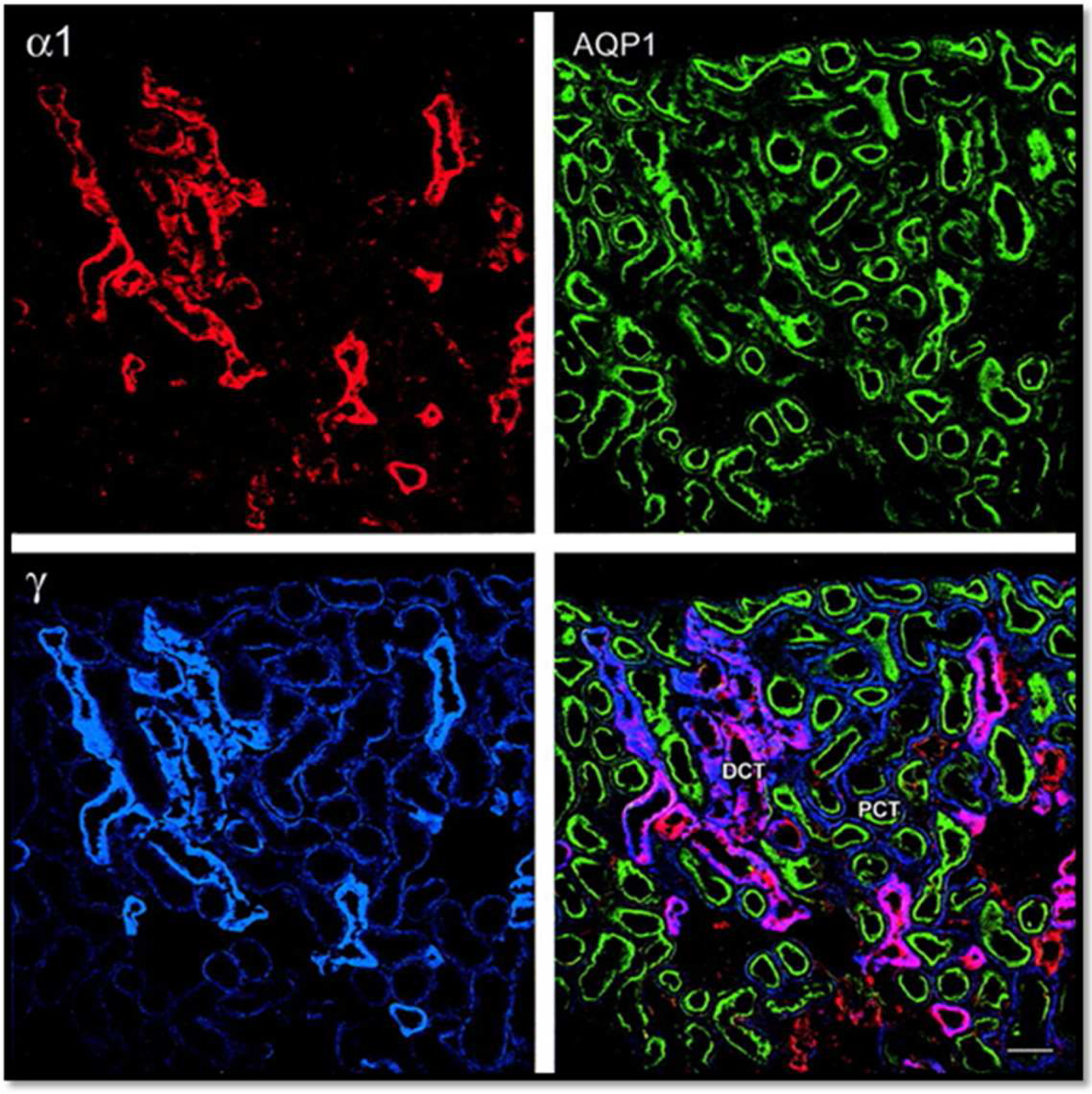

Figure 4.

Localization of Na^+-K^+-ATPase α1- and γ-subunits and aquaporin-1 (AQP1) in the renal cortex. AQP1 was used as a marker of proximal tubule. Kidney cortex was triple labeled with α1- (red, TSA-Cy3), AQP1 (green, FITC), and γ-subunit (blue, Cy5) antibodies. Proximal segments containing AQP1 stain were lightly labeled with α1- and γ-subunits (bottom right: merged image). Conversely, distal segments that were not labeled by the AQP1 antibody were brightly stained by α1- and γ-subunits (bottom right: merged image). Scale bar, 50 μm. Reproduced from Wetzel and Sweadner with permission (543).

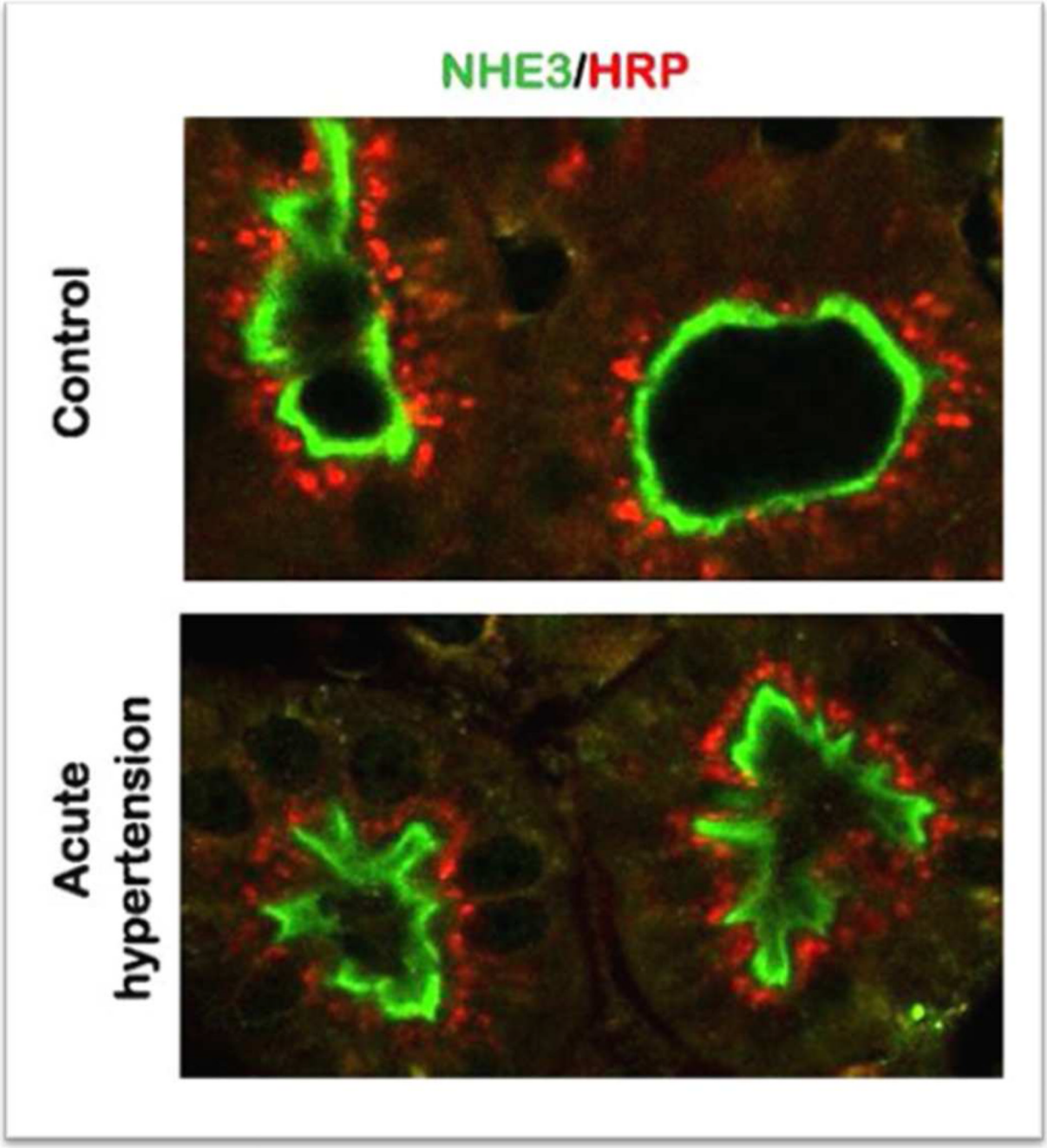

Figure 5.
Localization and redistribution of NHE3 during acute hypertension. The endocytic compartment of the proximal tubule was labeled by intravenous injection of horseradish peroxidase (HRP), and rats were sham operated (control), or blood pressure was increased for 20 min (acute hypertension). Kidneys were fixed in situ, sectioned, and double labeled with either polyclonal anti-NHE3 or monoclonal anti-HRP (red). NHE3 is retracted from the body to the base of the microvilli during acute hypertension, with no evidence that NHE3 moves into endocytic tracer HRP-labeled compartment. Reproduced from McDonough with permission (343).

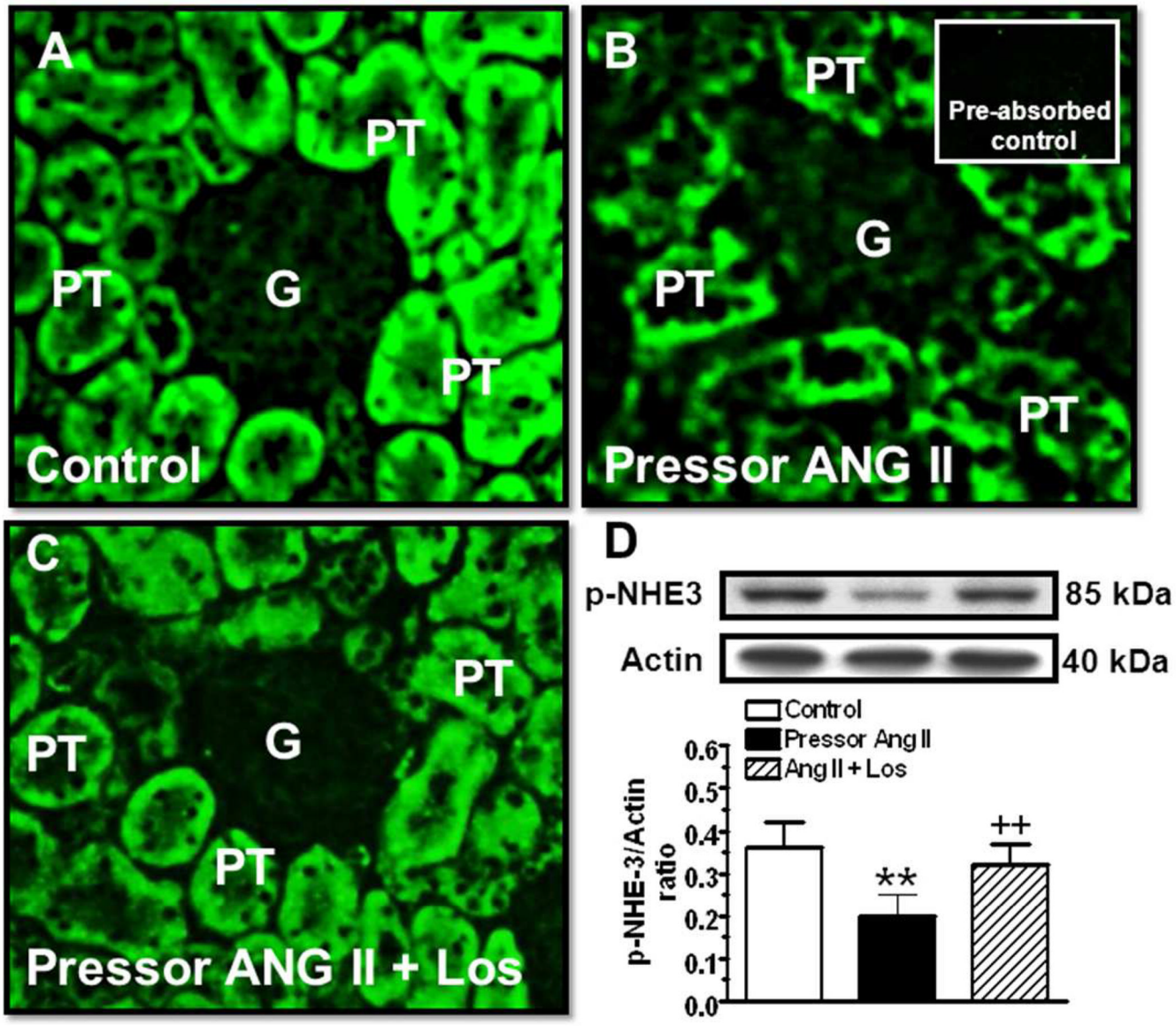

Figure 6.

Effects of 2 week infusion of a pressor dose of ANG II and concurrent losartan treatment on phosphorylated or activated NHE3 immunofluorescence staining (A–C, not quantitative) or phospho-NHE3 protein abundance in membrane fractions of proximal tubules of the rat kidney (semi-quantitative). 100 μg proteins were loaded in each lane of western blot gels. *p<0.05 or **p<0.01 vs. control; $^{\dagger\dagger}p$<0.01 vs. ANG II-infused rats. Reproduced from Li and Zhuo (313).

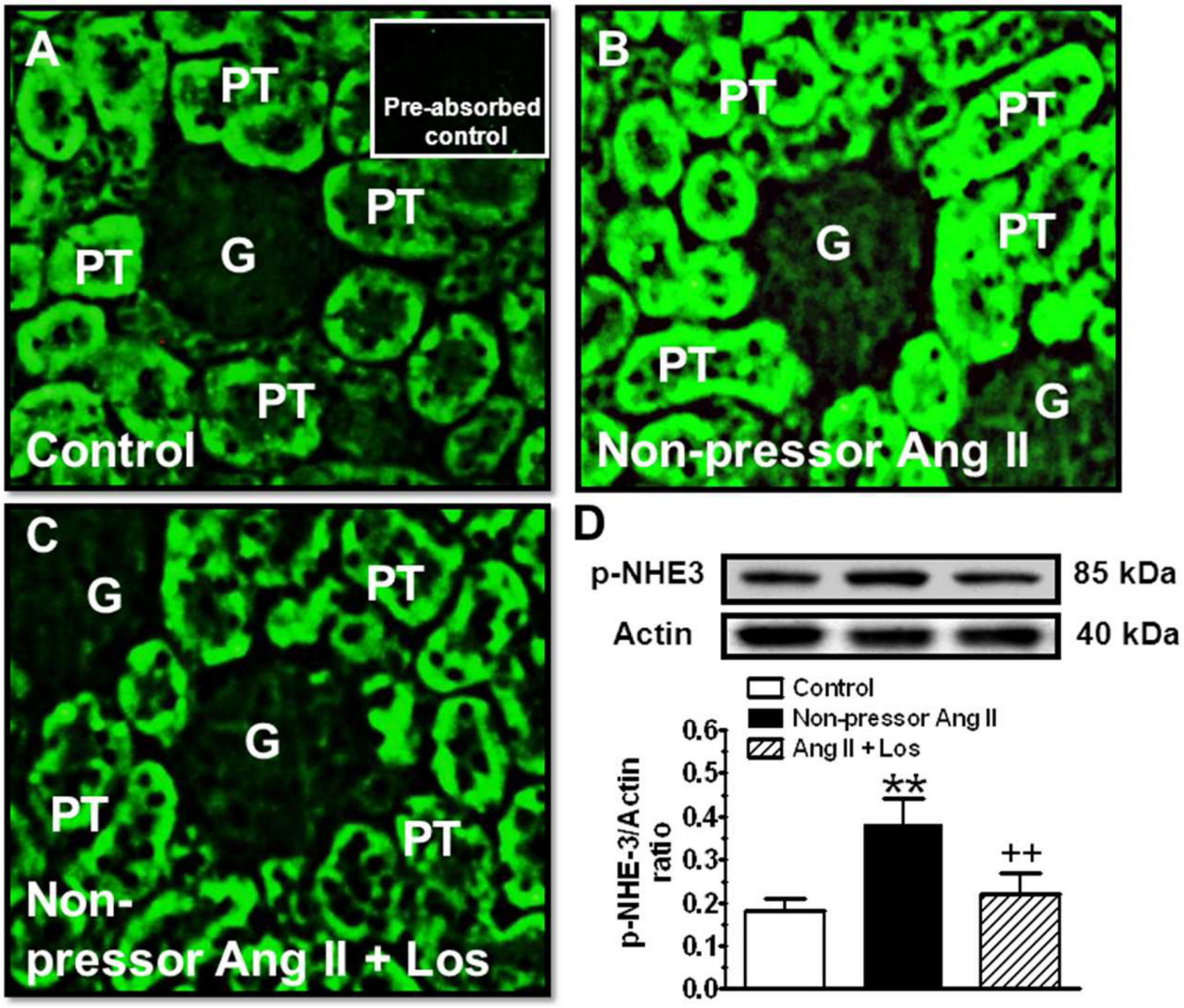

Figure 7.

Effects of 2 week infusion of the non-pressor dose of ANG II and concurrent losartan treatment on phosphorylated NHE3 immunofluorescence staining (A–C, not quantitative) or phospho-NHE3 protein abundance in membrane fractions of proximal tubules of the rat kidney (semi-quantitative). 100 μg proteins were loaded in each lane.of western blot gels. *p<0.05 or **p<0.01 vs. control; $^{\dagger\dagger}p$<0.01 vs. ANG II-infused rats. Reproduced from Li and Zhuo (313).

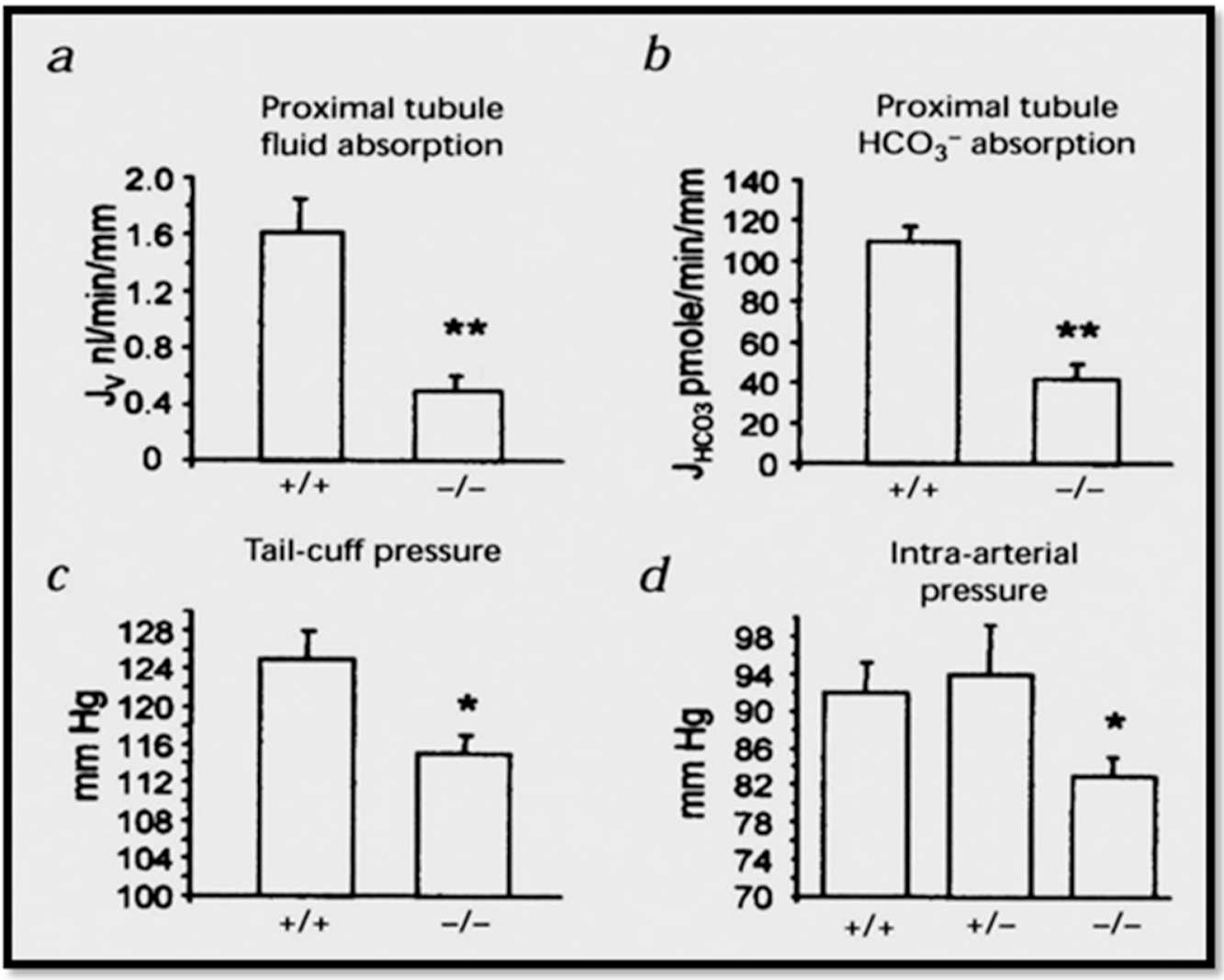

Figure 8.

Effects of global NHE3 gene knockout on proximal tubule fluid and bicarbonate absorption and blood pressure in adult *Slc9a3*$^{+/+}$ (WT) and *Slc9a3*$^{-/-}$ (NHE-3 knockout) mice. ***a,b***, *In situ* microperfusion of proximal convoluted tubules revealed that fluid *(a)* and HCO_3^- *(b)* absorption were sharply reduced in *Slc9a3*$^{-/-}$ tubules (n = 14) relative to *Slc9a3*$^{+/+}$ tubules (n = 12). ** $P < 0.001$; J_v, fluid absorption; J_{HCO3}, HCO_3^- absorption. ***c***, Blood-pressure measurements using the tail-cuff method showed that systolic pressure was significantly reduced in awake *Slc9a3*$^{-/-}$ mice (*$P < 0.05$, n = 4 for each genotype). ***d***, Blood-pressure measurements using a femoral artery catheter showed that mean arterial pressure was reduced (*$P < 0.05$) in anaesthetized *Slc9a3*$^{-/-}$ mice (n = 12) compared with both *Slc9a3*$^{+/-}$ (n = 7) and *Slc9a3*$^{+/+}$ (n = 10) mice. Values for all analyses are mean s.e.m. Reproduced from Schultheis et al. (451).

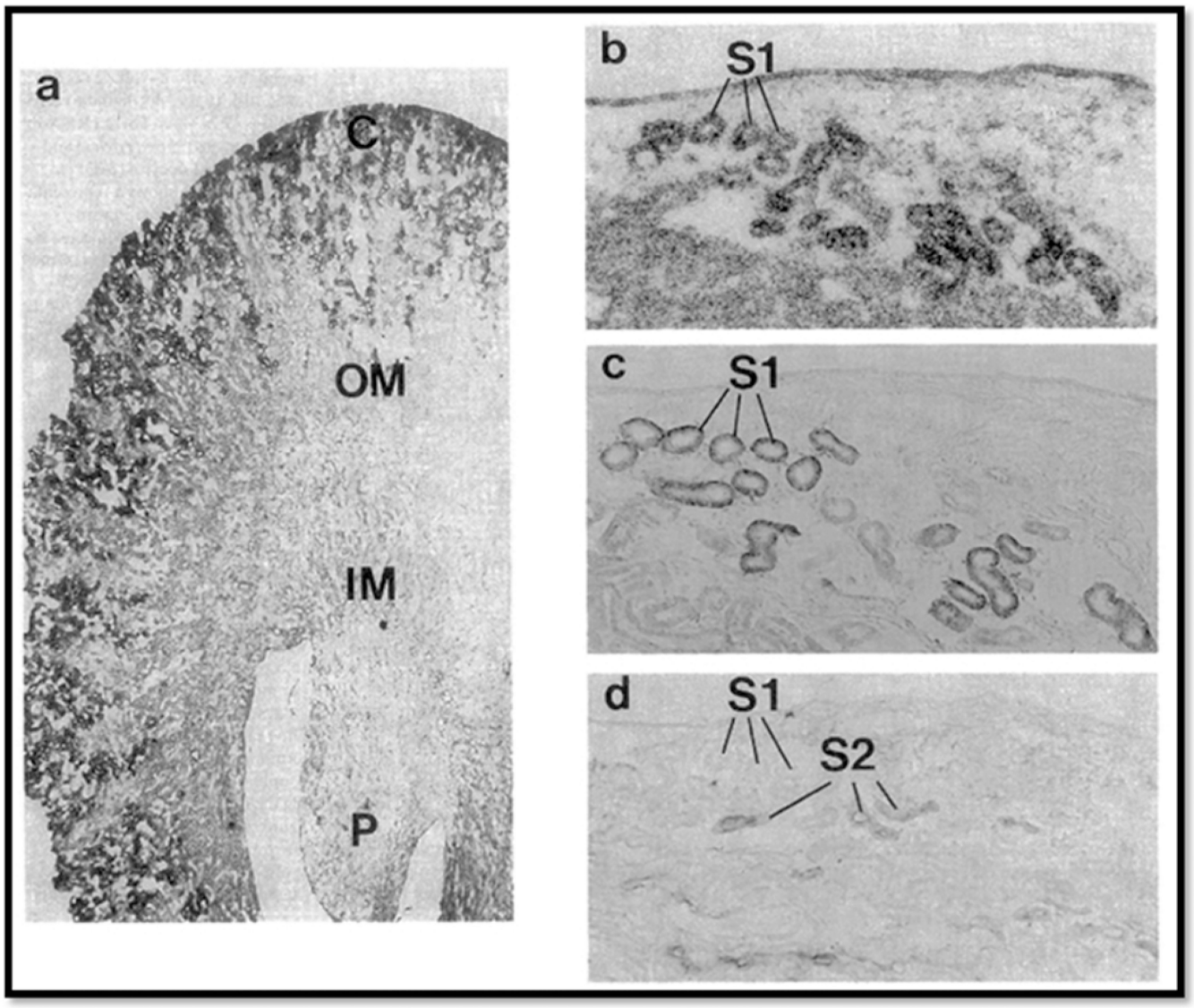

Figure 9.

Localization of the sodium and glucose cotransporter 2 (SGLT2) mRNAs in the kidney tubules by in situ hybridization. (a) Low power micrograph showing the pattern of hybridization of Hu 14 antisense cRNA probe (35S-labeled) to rat kidney cryosections. A strong hybridization is detected over tubules in the cortex (C), whereas the signal is absent in outer medulla (OM), inner medulla (IM), and papilla (P). (b–d) Sequential 5 μm sections of rat kidney cortex hybridized with Hu14 antisense cRNA probe (b) or stained with antibodies against the S1 segment specific marker GLUT2 (c) or carbonic anhydrase IV (d), which is specific for S2 segments of proximal tubules and the thick ascending limbs of Henle's loop. A strong hybridization signal is evident in b and is localized over tubules that show a basolateral staining for GLUT2 (indicated as SI in c). In contrast, carbonic anhydrase IV positive tubules (indicated as S2 in d) do not contain a Hu14 hybridization signal. The S3 segment-specific anti-ecto ATPase antibody did not stain tubules in the field corresponding to b and ecto-ATPase-positive tubules detected in other areas of the kidney did not contain Hu14 hybridization signal (not shown). Bar, 0.4 mm (a) and 0.1 mm (b–d). Reproduced from Kenai et al. with permission (259).

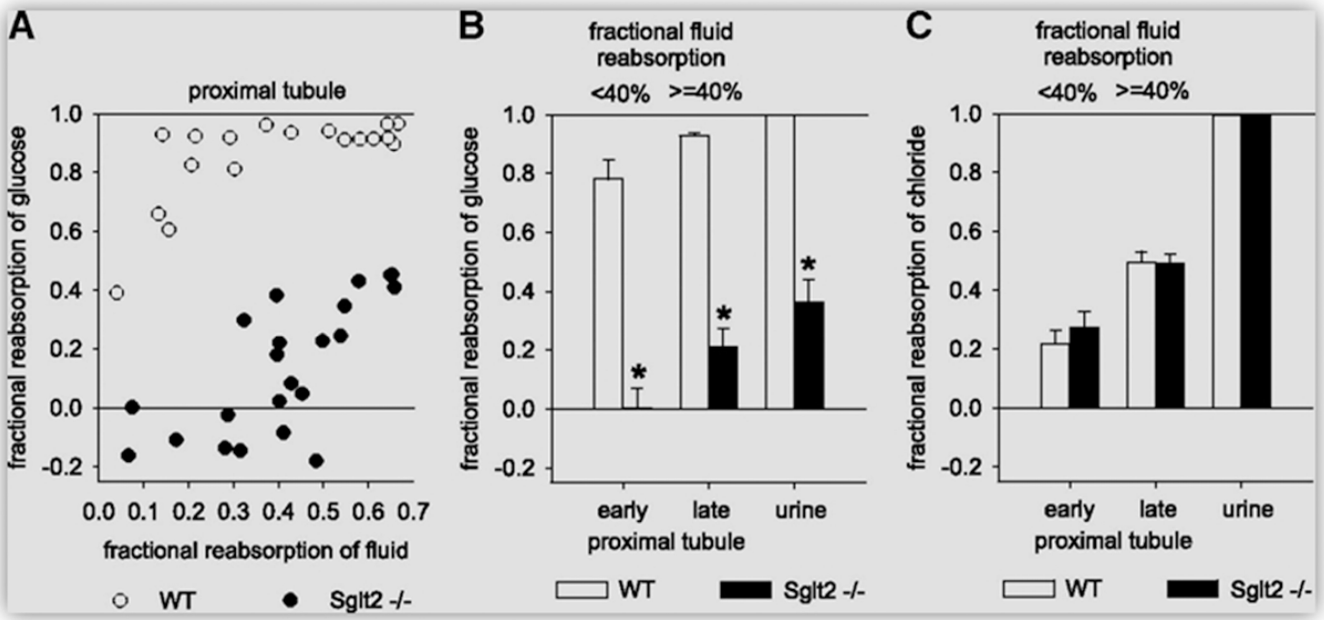

Figure 10.

Effects of SGLT2 knockout on glucose reabsorption in the early proximal tubule of SGLT2$^{-/-}$ mice, as revealed by in vivo micropuncture studies under anesthesia. (A) Free-flow collections of tubular fluid are performed along accessible proximal tubules at the kidney surface to establish a profile for FR-glucose *versus* FR-fluid. (B and C) Mean FR-glucose (B) and fractional reabsorption of chloride (C) for early (FR-fluid <40%) and late (FR-fluid ≥40%) proximal tubular collections and up to the urine (n = 18 to 23 nephrons in four to five mice). *P < 0.001 *versus* WT mice. Reproduced from Vallon et al. with permission (516).

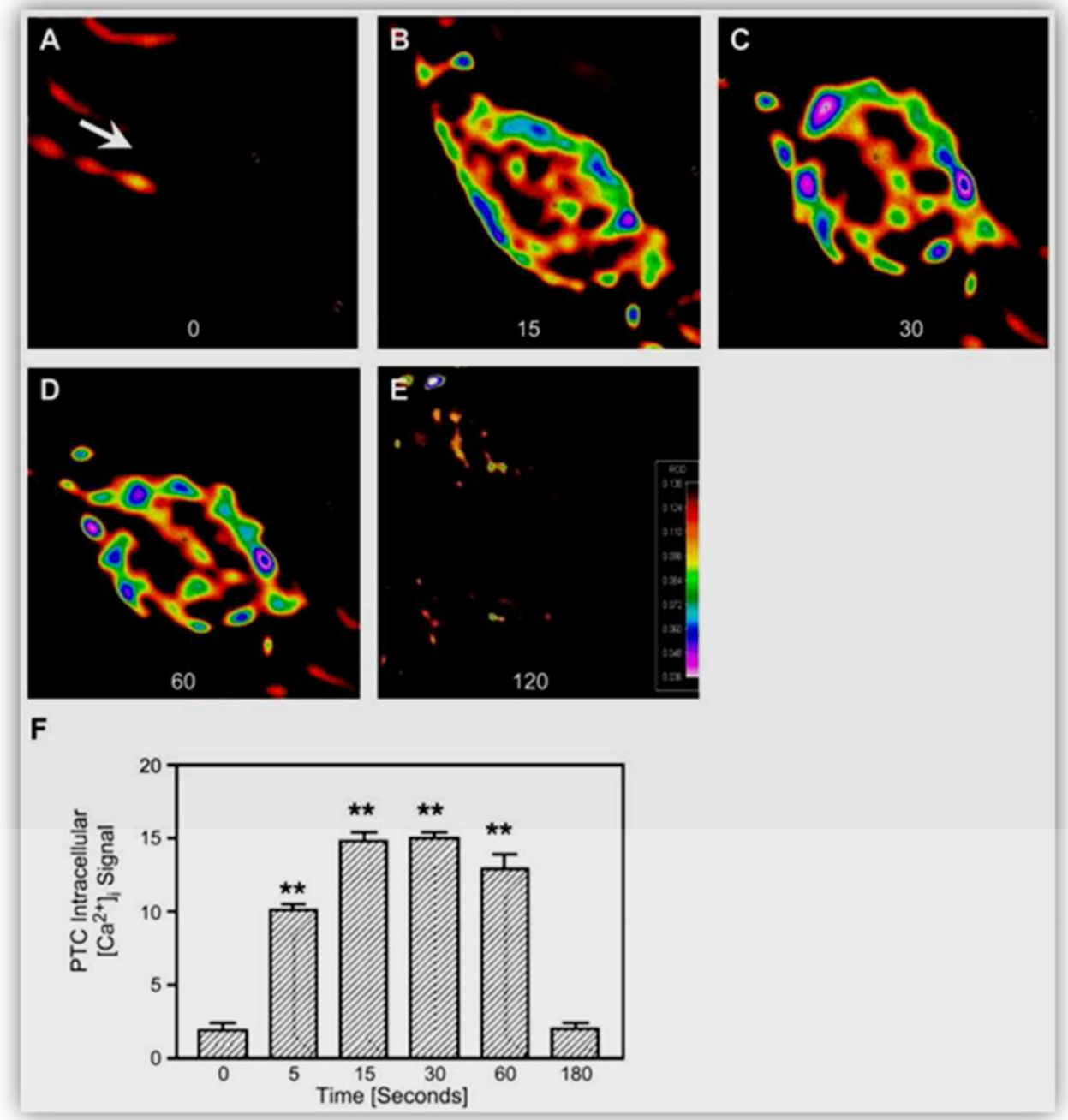

Figure 11.

A–E: effect of intracellular microinjection of ANG II (1 nM, ~70–100 fl) on $[Ca^{2+}]_i$ responses in single proximal tubule cells at baseline (0 s) and 15, 30, 60, and 120 s after microinjection of Ang II in the cells. *F*: relative levels of $[Ca^{2+}]_i$ signaling before and after microinjection of Ang II. Red represents the highest level of $[Ca^{2+}]_i$ responses, whereas black is the background. $^{**}P < 0.01$ vs. basal. Reproduced from Zhuo et al. with permission (592).

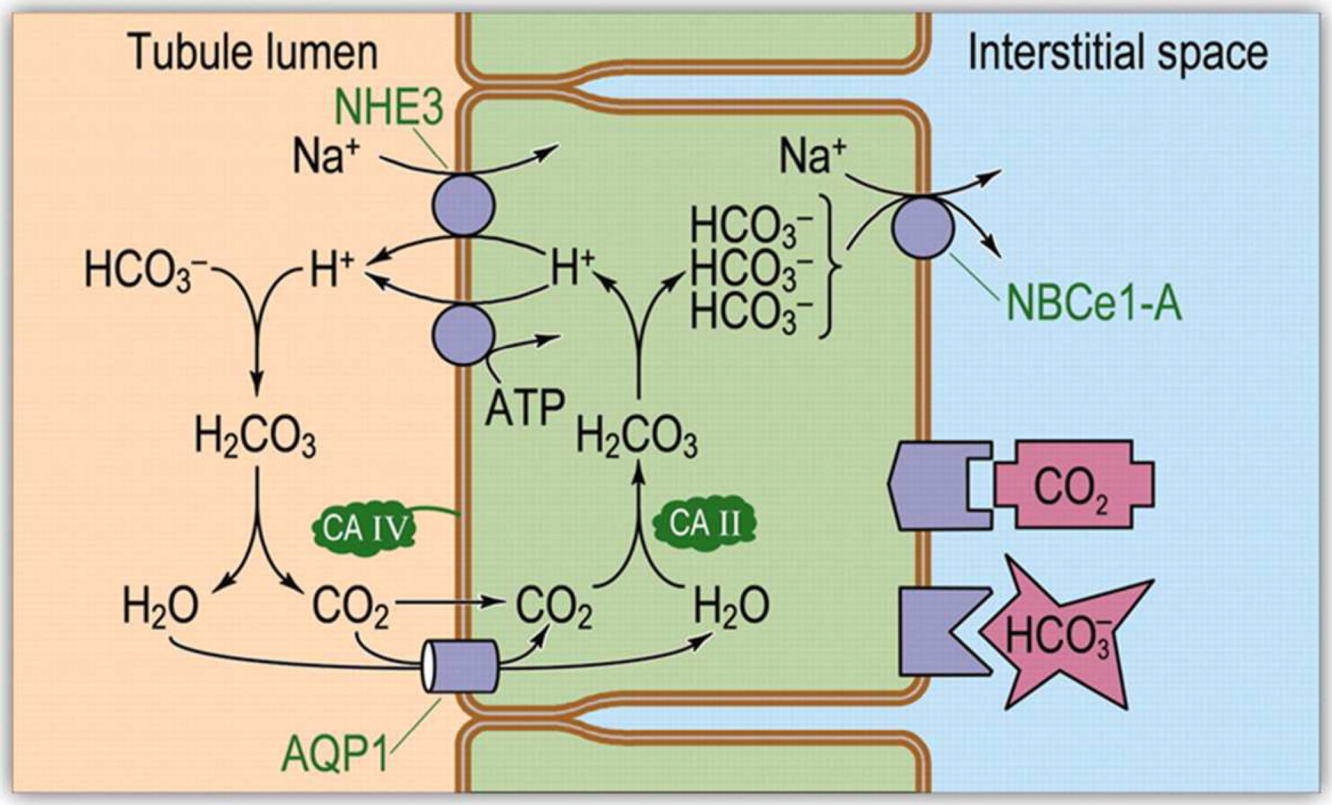

Figure 12.

Model of acid-base transport in the proximal tubule (PT). The PT reabsorbs HCO_3^- by using active-transport processes to secrete H^+ into the tubule lumen and titrating HCO_3^- to CO_2 and H_2O. Thus, HCO_3^- reabsorption requires CO_2 uptake across the apical membrane. Once inside the cell, CO_2 and H_2O recombine to regenerate HCO_3^-, which exits across the basolateral membrane. NHE3, Na-H exchanger 3; AQP1, aquaporin 1; CA II and CA IV, carbonic anhydrases II and IV; NBCe1-A, electrogenic Na/HCO_3 co-transporter 1, splice variant A. Reproduced from Boron with permission (59).

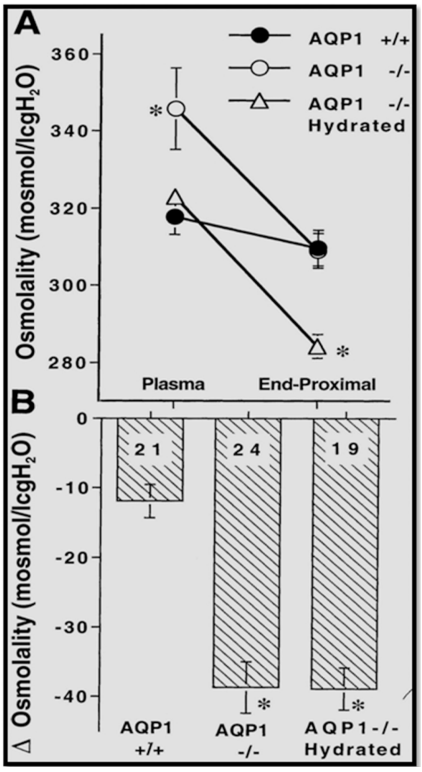

Figure 13.

Osmolality in plasma and late proximal tubular (LPT) fluid in aquaporin-1 (AQP1)-knockout (−/−) and wild-type (+/+) mice. Values are means ± SE and are shown for AQP1 +/+ (n = 21 nephrons in 4 mice), AQP1 −/− (n = 24/5), and hydrated AQP1 −/− mice (n = 19/3). *A*: relationship between absolute values of osmolalities in plasma and late proximal tubule fluid (where SE bars cannot be seen, they are smaller than the symbol used). *B*: transtubular osmotic gradients, i.e., the osmolality differences (e) between plasma and LPT. * $P < 0.001$ compared with AQP1 +/+ mice. Reproduced from Vallon et al. with permission (517).

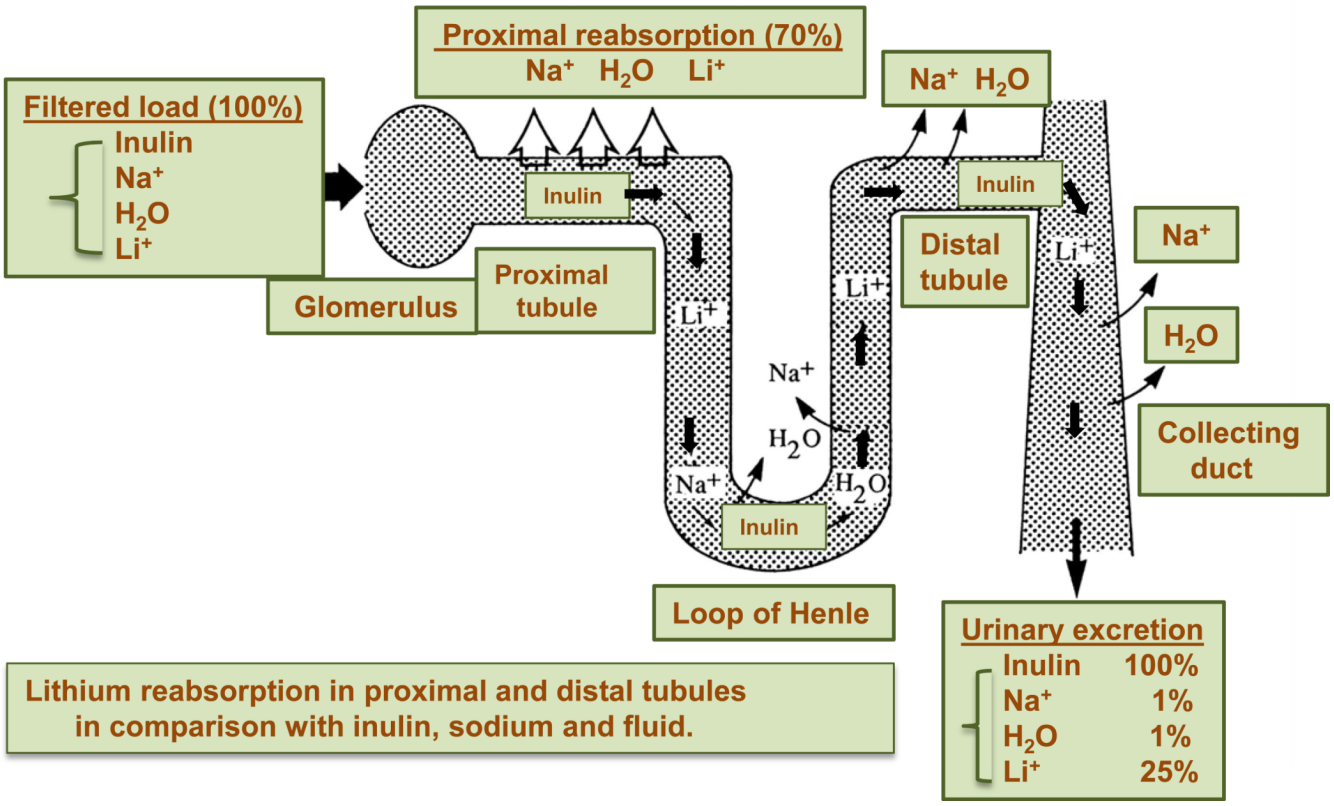

Figure 14.

Normal renal handling of lithium reabsorption in proximal tubules in comparison with those of inulin, sodium and water in rodents and humans with a normal sodium intake. Data are drawn from Refs. (449; 463; 495; 496).

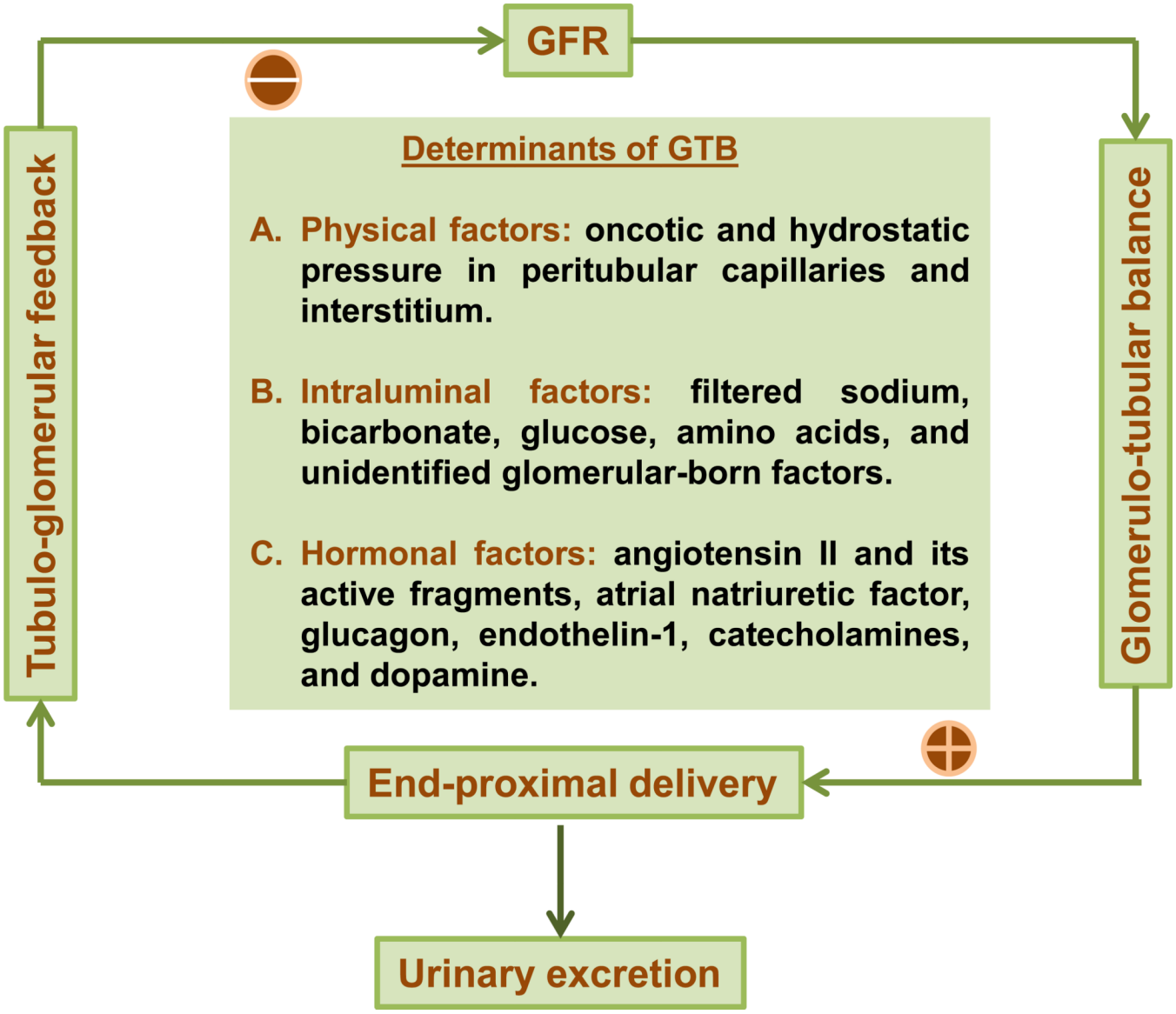

Figure 15.
A schematic diagram showing physical, intraluminal and humoral factors that regulate glomerulotubular balance (GTB). ⊕, increase. ⊘, decrease.

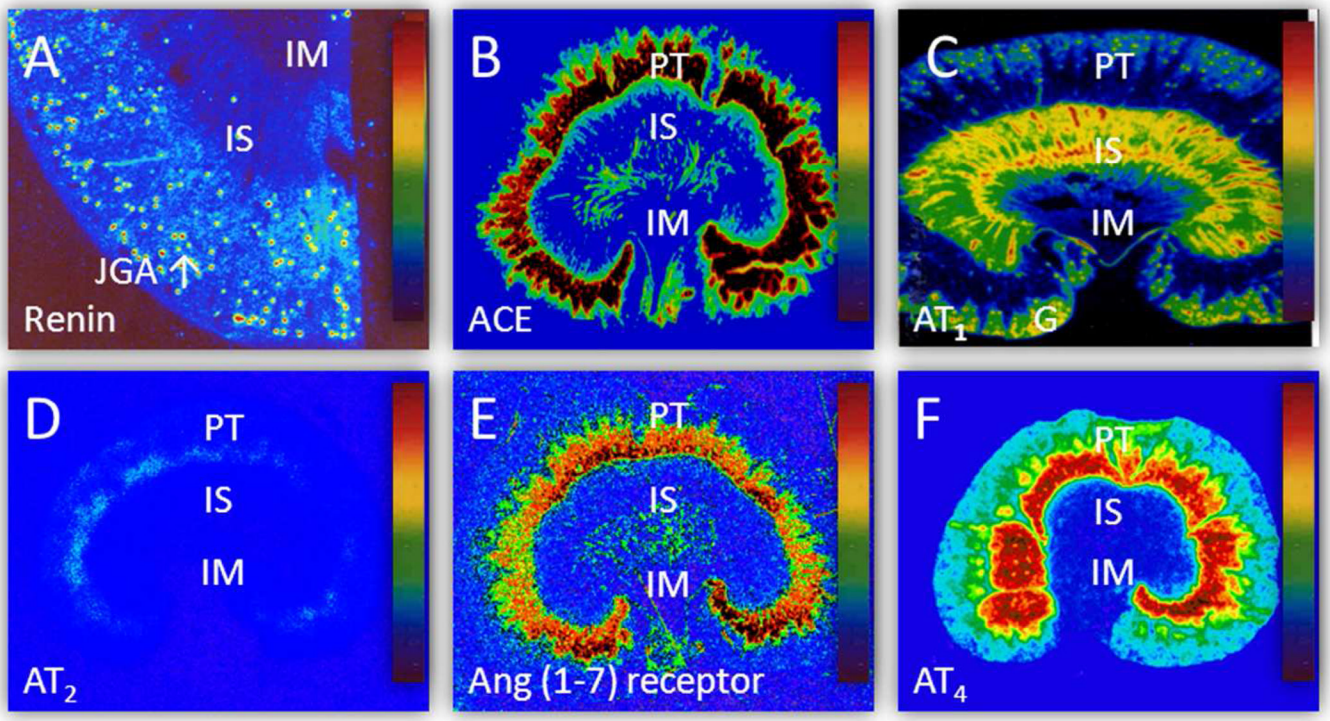

Figure 16.

In vitro autoradiographic mapping of: (A) active renin binding in justaglomerular apparatus in the dog kidney pretreated with sodium depletion using the radiolabeled renin inhibitor, ^{125}I-H77, (B) angiotensin I-converting enzyme binding in proximal tubules of the rat kidney using ^{125}I-351A, (C) AT_1 receptor in the presence of the AT_2 receptor blocker PD123319 or (D) AT_2 receptor binding in the presence of the AT_1 receptor blocker losartan using ^{125}I-[Sar^1,Ile^8]-ANG II, (E) ANG (1–7) receptor binding in the rat kidney using ^{125}I-ANG (1–7) as the radioligand, and (F) ANG IV receptor binding in the rat kidney using ^{125}I-ANG (3–8). The levels of binding are indicated by color calibration bars with red representing the highest, whereas blue showing the lowest levels of enzyme or receptor binding. G: glomerulus. IM: inner medulla. IS: inner stripe of the outer medulla. JGA: juxtaglomerular apparatus. P: proximal tubule. Reproduced from Zhuo and Li with permission (591).

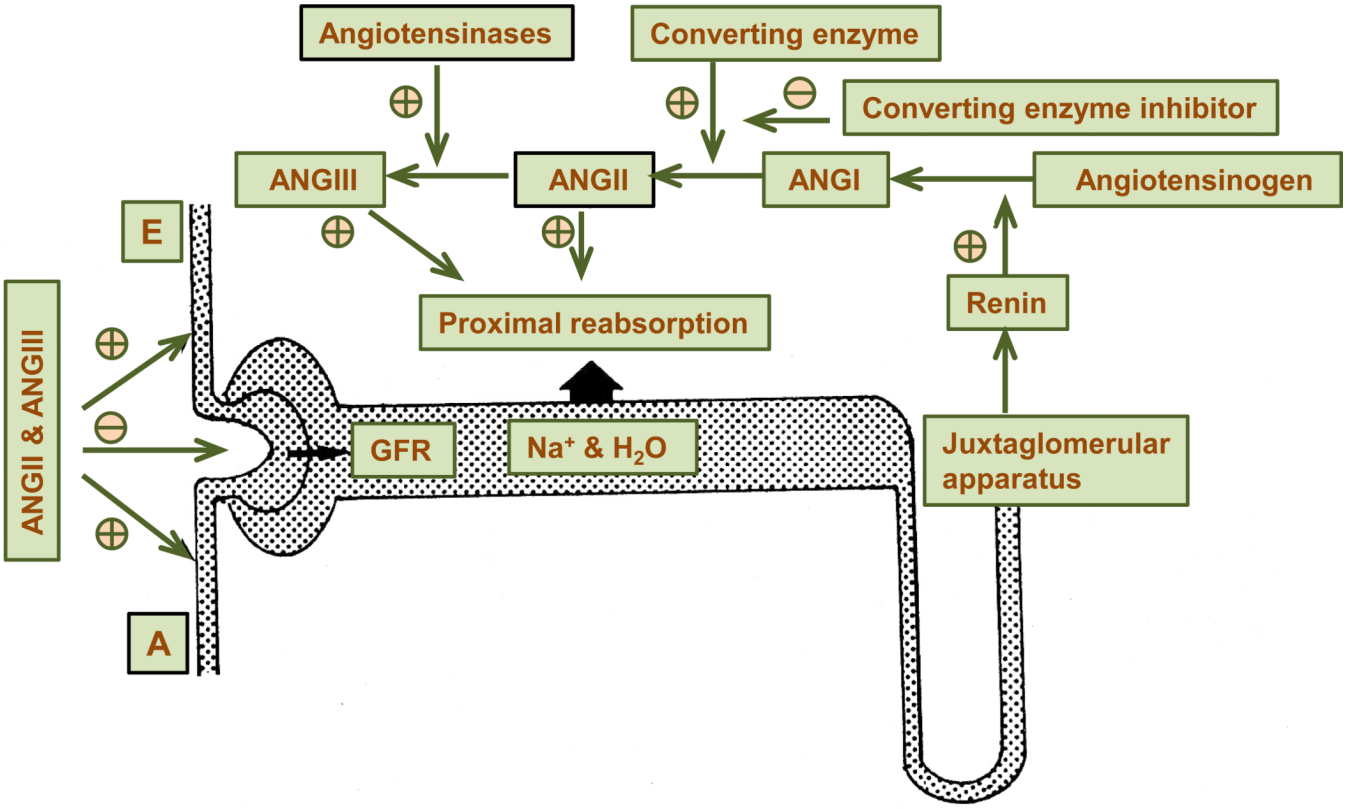

Figure 17.
A schematic representation of local generation of ANG II in proximal tubules of the kidney and its role in the regulation of proximal tubular reabsorption and glomerulotubular balance (GTB). ⊕, stimulation. ⊘, inhibition.

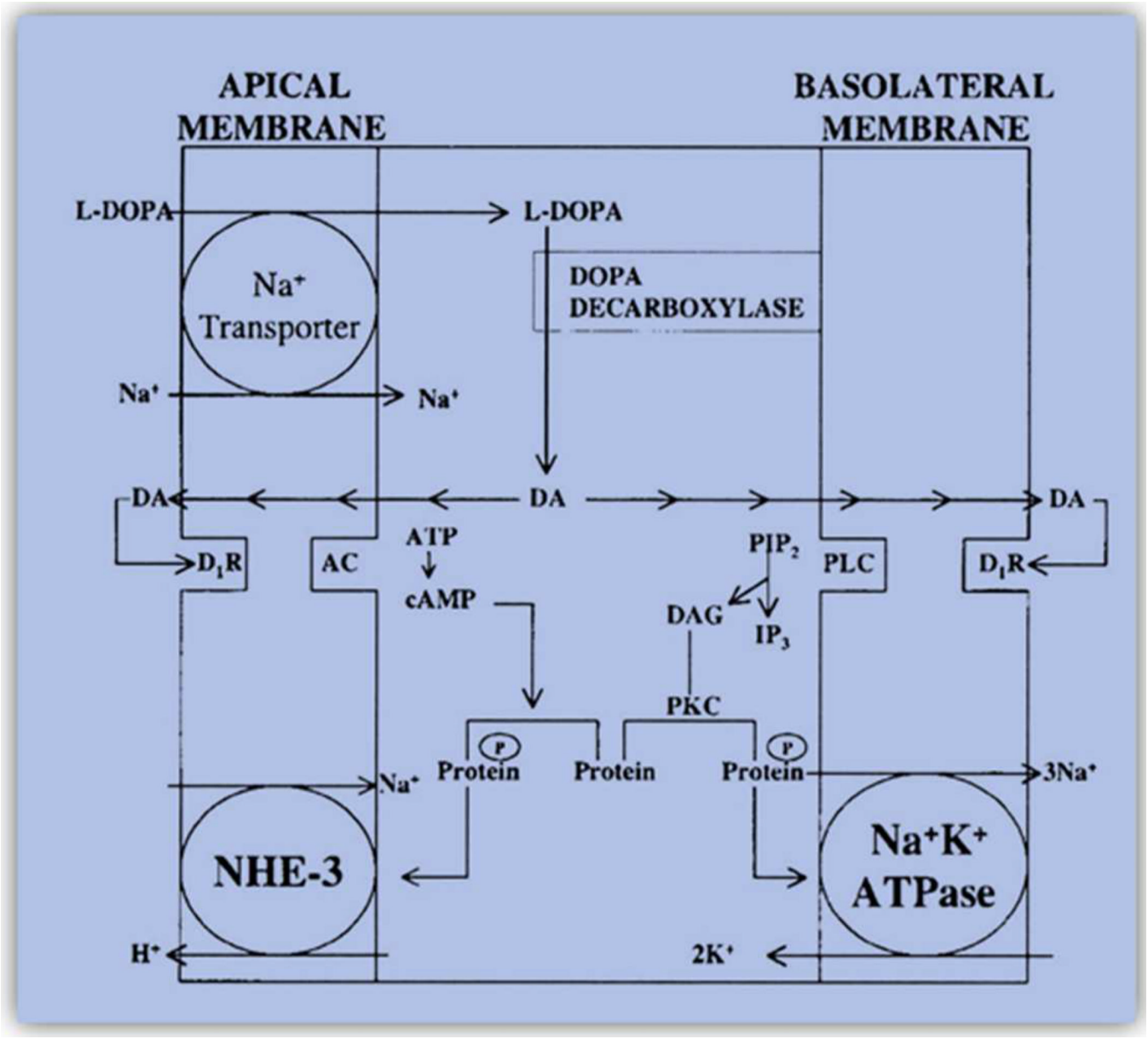

Figure 18.

Schematic depiction of dopamine formation and cell signaling mechanisms activating sodium transport across the proximal renal tubule cell. DA indicates dopamine; D_1R, dopamine D1 receptor; PLC, phospholipase C; DAG, diacylglycerol;and AC, adenylyl cyclase. Reproduced from Carey with permission (81).

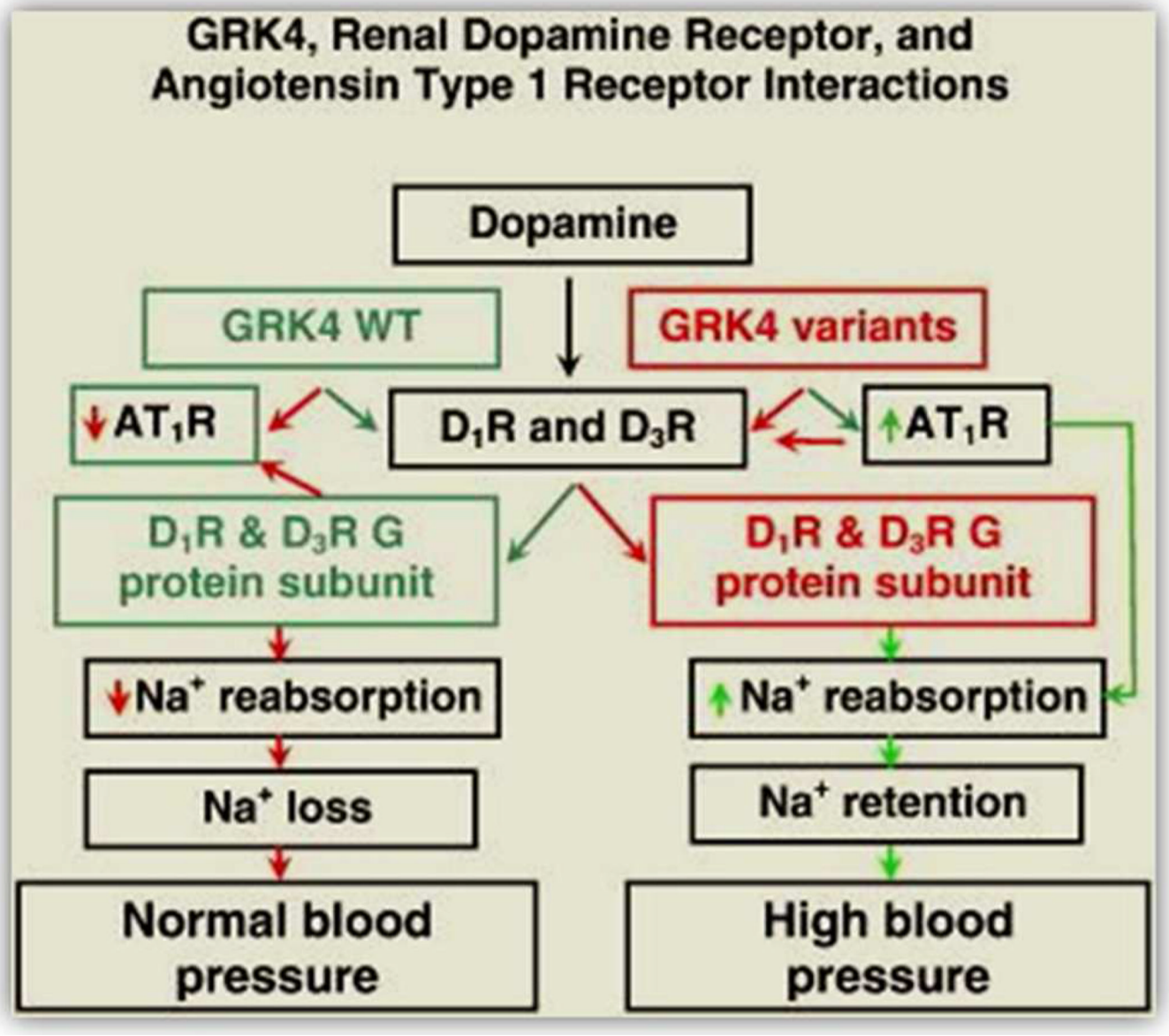

Figure 19.

A schematic diagram showing GRK4 and renal dopamine and ANG II type 1 receptor interactions to regulate renal tubular transport and blood pressure homeostasis. During conditions of moderately increased NaCl intake, the renal D_1R is stimulated by dopamine produced in the kidney. The D_1R or D_3R, whose coupling to G protein subunits is regulated by G protein-coupled receptor kinase type 4 (GRK4), inhibits sodium reabsorption in several nephron segments. This results in an increase in sodium excretion and maintenance of normal blood pressure. GRK4 wild-type (GRK4 WT) also negatively regulates AT_1R transcription. The decrease in AT_1R expression, caused by GRK4 WT, facilitates the inhibitory effect of D_1R on renal sodium transport. In essential hypertension, constitutively active variants of GRK4 not only uncouple D_1R and D_3R from G protein subunits, but also increase AT_1R transcription in the kidney. These effects impair the ability of the kidney to excrete the excess sodium load, resulting in sodium retention, and ultimately hypertension. Green box = normal coupling of D_1R and D_3R to G protein subunits, Red box = uncoupling

of D_1R and D_3R from G protein subunits. Green arrows = stimulatory, Red arrows = inhibitory. Reproduced from Jose with permission (254).

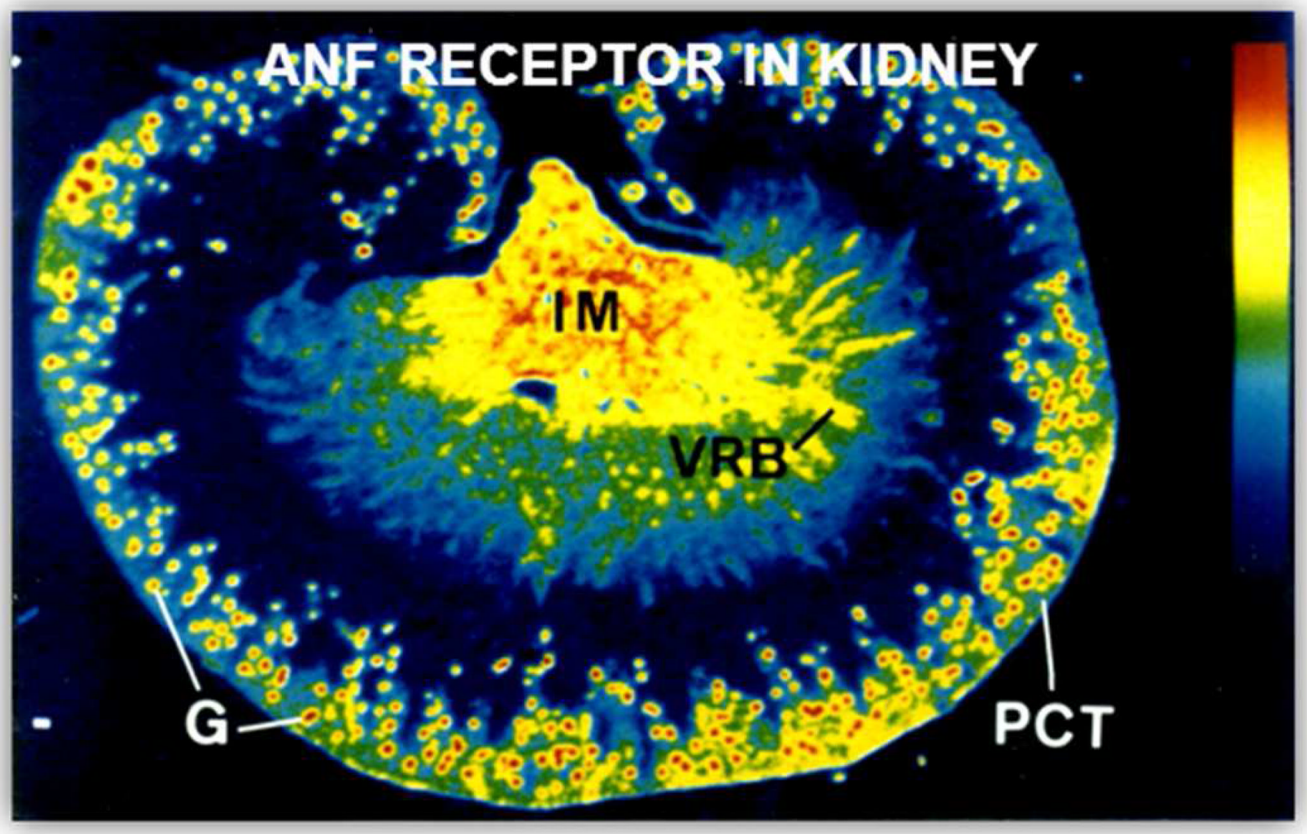

Figure 20.

The intrarenal distribution of ANF receptors in the rat kidney, as visualized by quantitative in vitro autoradiography using [^{125}I]-labeled ANF as the radioligand. High levels of ANF receptor binding occur in the glomeruli (G) and the inner medulla (IM), whereas moderate levels of ANF binding are seen in the proximal convoluted tubules (PCT) and inner stripe of the outer medulla (VRB). Red represents highest whereas black the lowest levels of ANF receptor binding. Reproduced from Zhuo and Mendelsohn with permission (583).

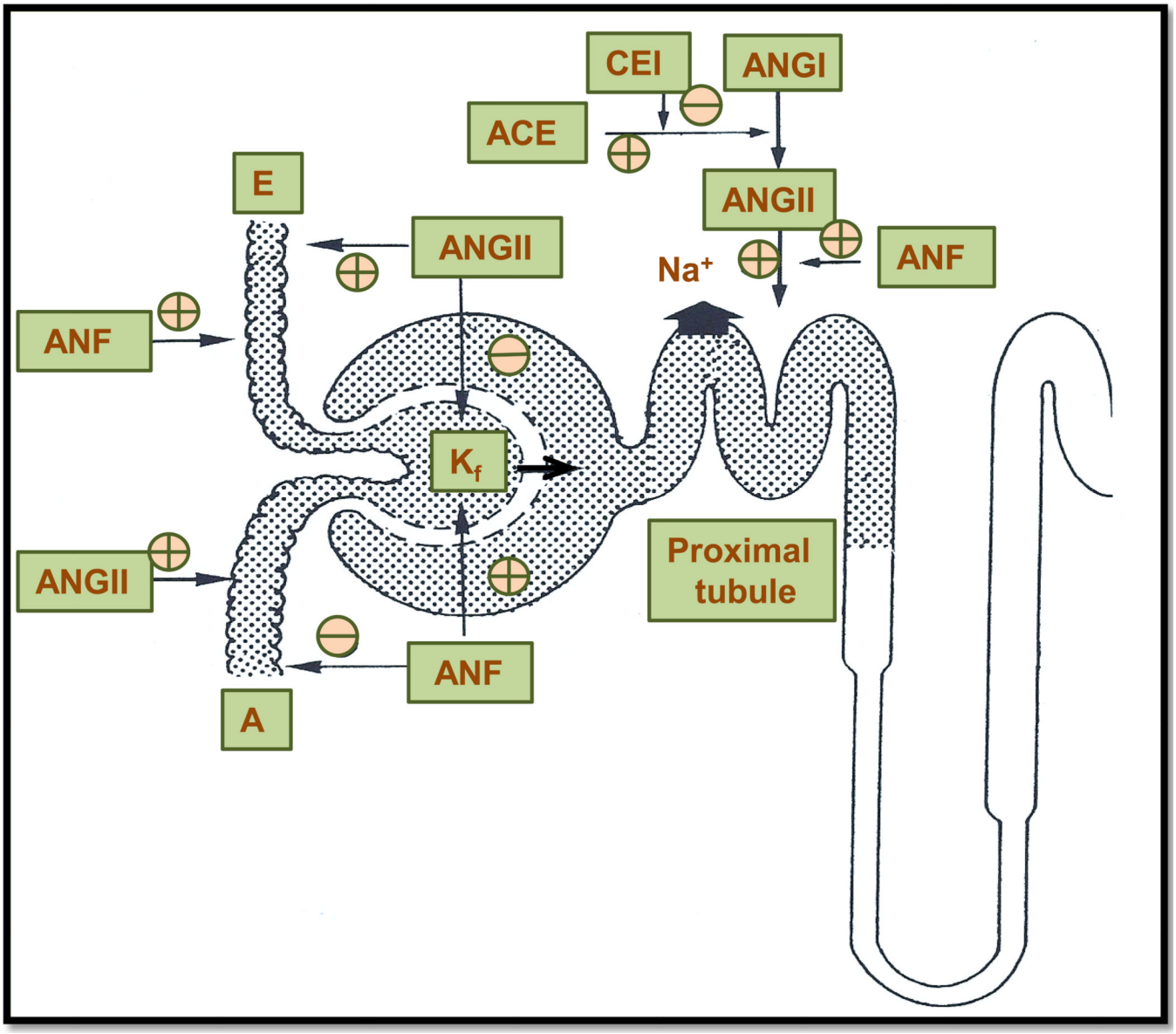

Figure 21.

Schematic representation of potential multi-level interactions between ANF and ANG II to regulate renal hemodynamics and proximal tubular transport of sodium and fluid in the kidney. A, afferent arteriole. E, efferent arteriole. AI, ANG I. AII, ANG II. CE, converting enzyme. CEI, converting enzyme inhibitor. K_f, ultrafiltration coefficient. ⊕, stimulation or increase. ⊘, inhibition or decrease.

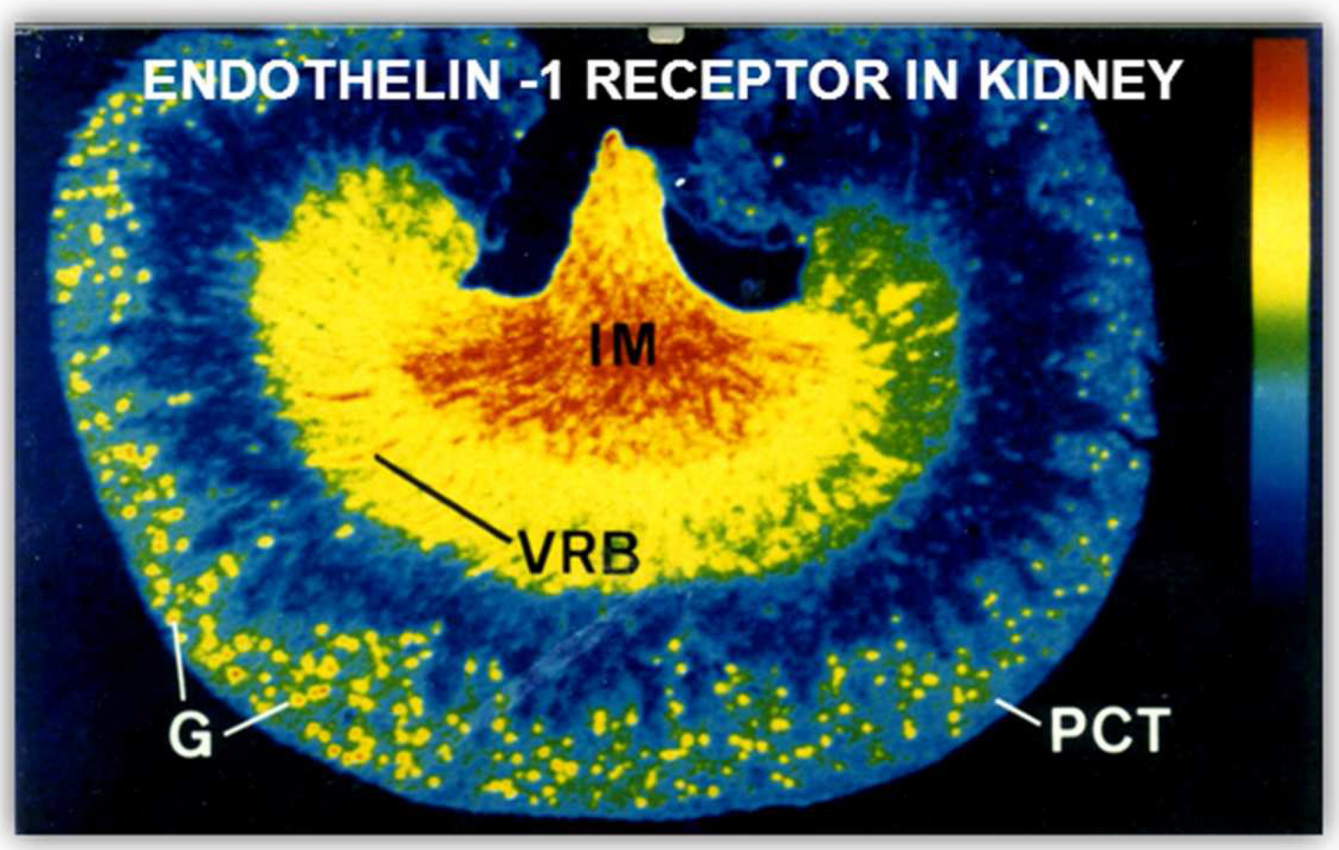

Figure 22.

The intrarenal distribution of endothelin 1 (ET-1) receptors in the rat kidney, as visualized by quantitative in vitro autoradiography using [^{125}I]-endothelin 1 as the radioligand. High levels of ET-1 receptor binding occur in the inner medulla (IM) and glomeruli (G), whereas moderate levels of ET-1 binding are seen in the proximal convoluted tubules (PCT) and inner stripe of the outer medulla (VRB). Red represents highest whereas black the lowest levels of ET-1 receptor binding. Reproduced from Zhuo and Mendelsohn with permission (580; 583).

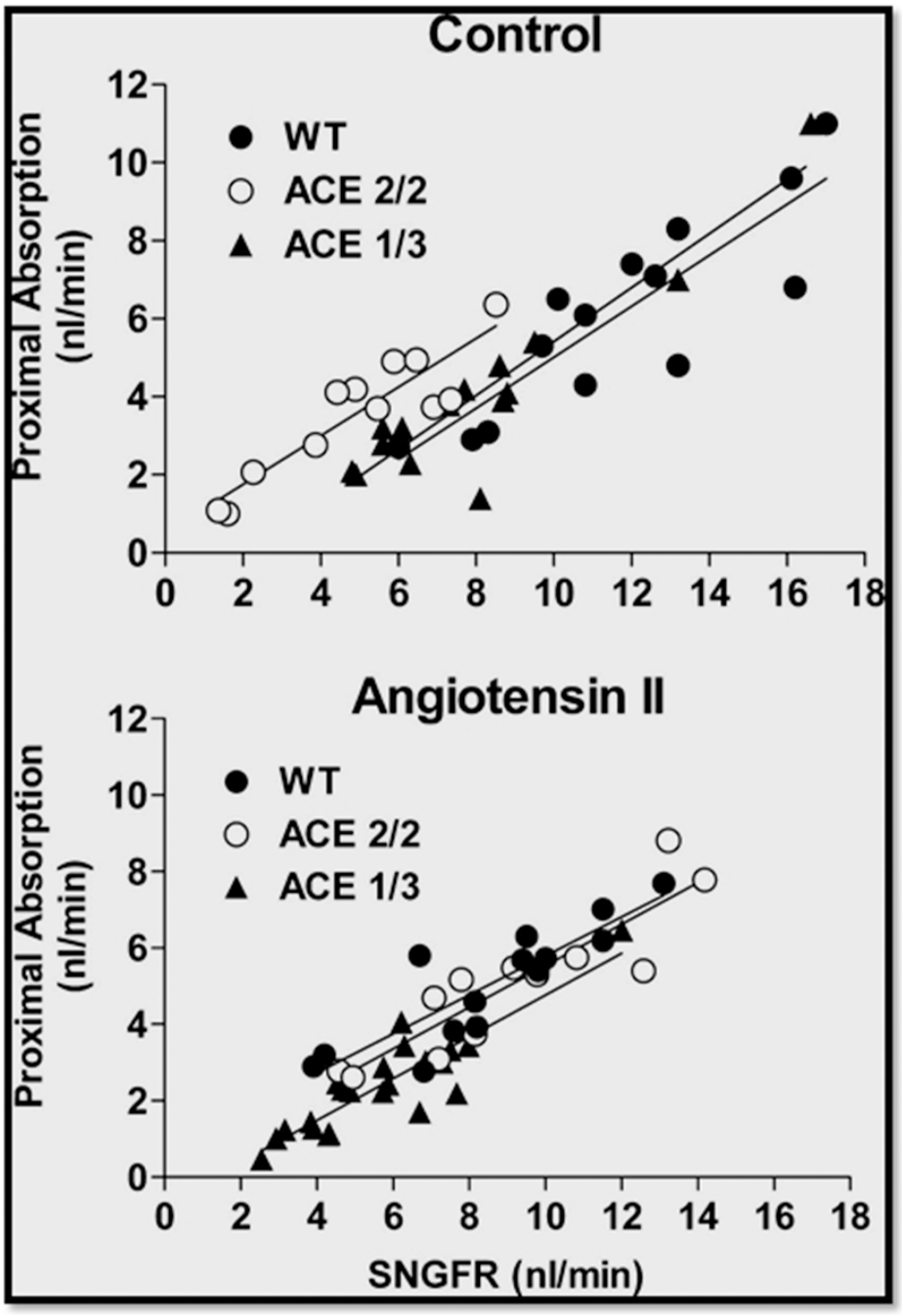

Figure 23.
Relationship between the rates of single nephron GFR (SNGFR) and proximal tubular fluid reabsorption of WT, ACE 2/2, and ACE 1/3 mice during control (*top*) and during angiotensin II infusion (*bottom*). Lines are linear regression lines calculated for the range of the data. Reproduced from Hashimoto et al. with permission (206).

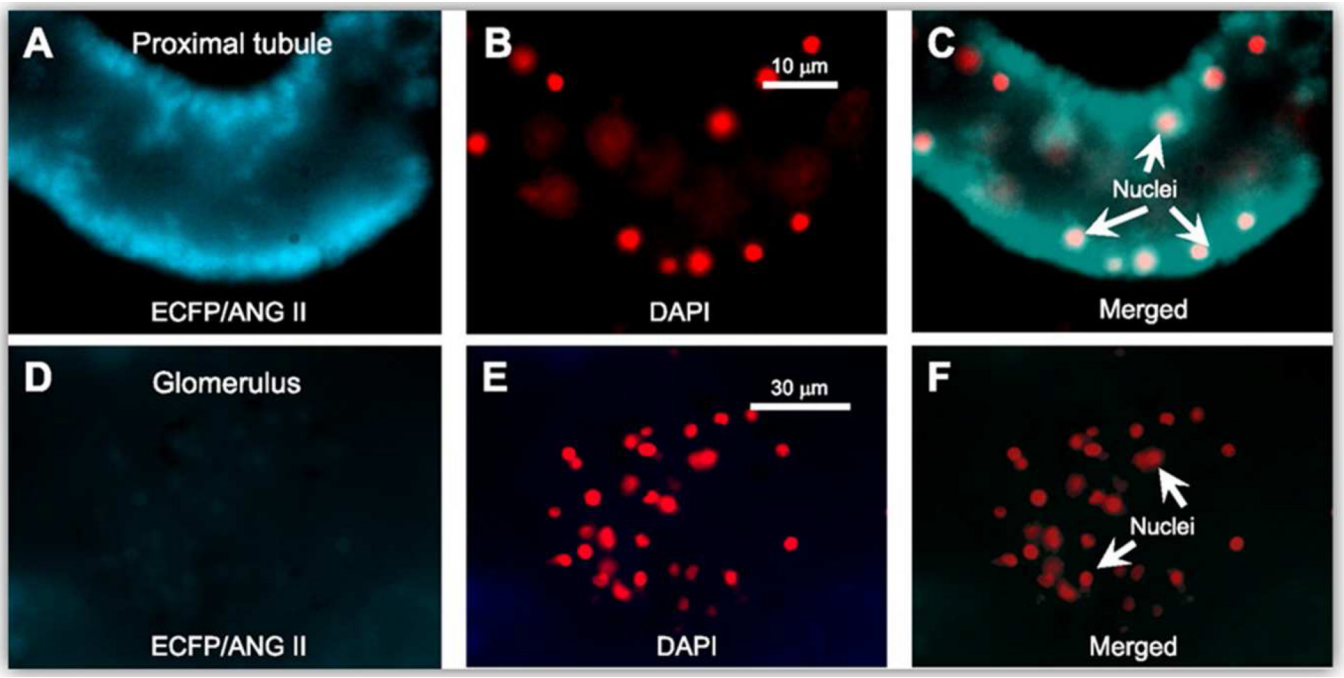

Figure 24.

Expression of an intracellular cyan fluorescent fusion of ANG II, ECFP/ANG II, selectively in freshly isolated proximal tubules of the rat kidney 2 weeks after intrarenal ECFP/ANG II transfer. The SGLT2 gene promoter was used to drive ECFP/ANG II expression selectively in proximal tubules of the kidney. Bars = 10 μm for the proximal tubule or 30 μm for the glomerulus. Reproduced from Li et al. with permission (310).

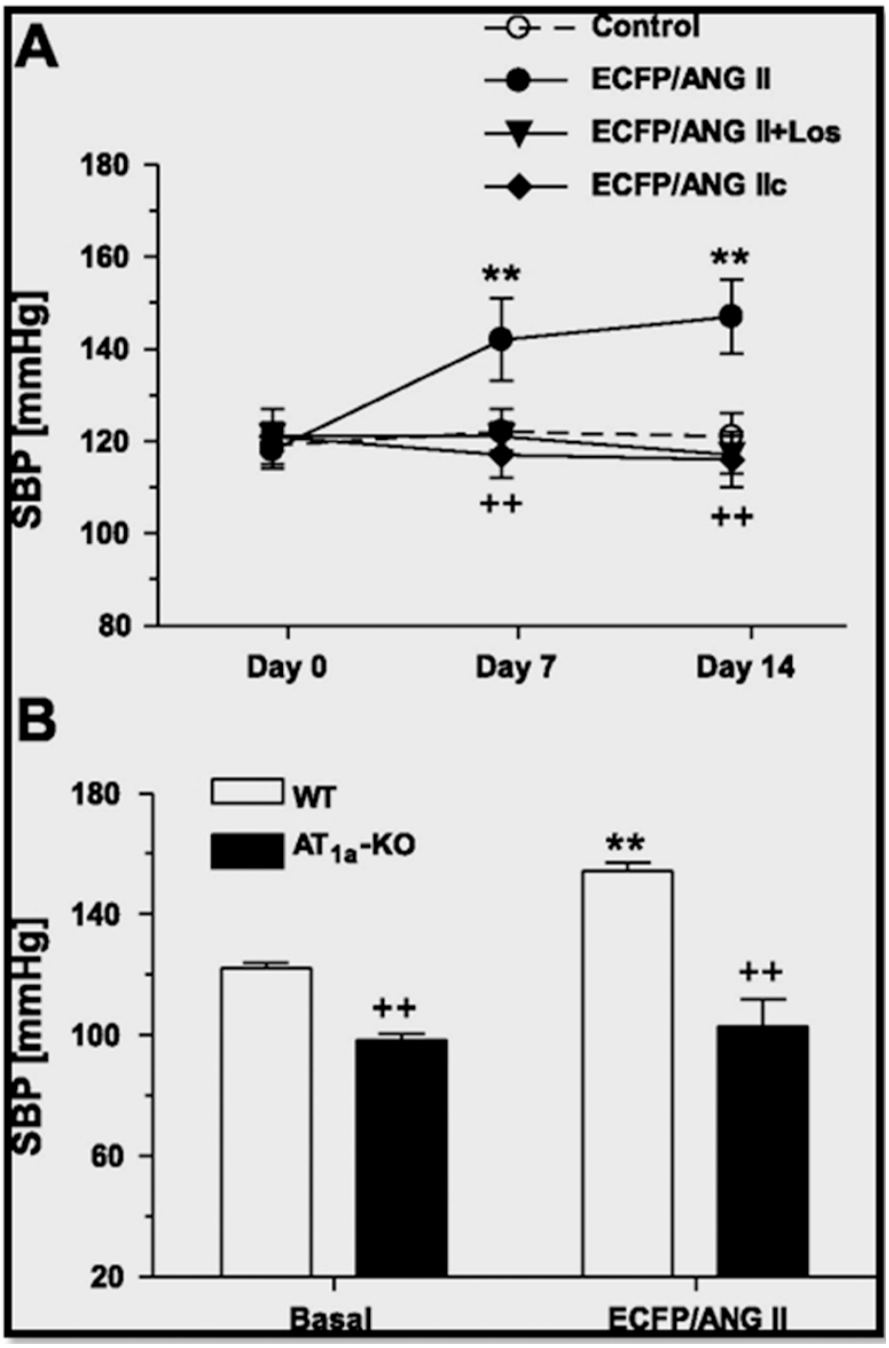

Figure 25.

Effects of proximal tubule-specific transfer of ECFP/ANG II or its scrambled control, ECFP/ANG IIc, with or without losartan treatment on systolic blood pressure in rats (SBP; *A*) or ECFP/ANG II transfer in wild-type or AT_{1a}-KO mice (*B*). *$p< 0.05$ or **$p< 0.01$ vs. basal SBP. $^{+}p< 0.05$ or $^{++}p< 0.01$ vs. SBP in ECFP/ANG II-transferred rats. $^{\#}p< 0.05$ or $^{++}p< 0.01$ vs. SBP in wild-type mice at basal or 2 weeks after intrarenal ECFP/ANG II transfer. Reproduced from Li et al. with permission (310).

Table 1

Nephron numbers in the kidneys of representative animals and humans, as estimated by different counting techniques.

Species	Gender	Number of nephron	*N*	Method	Reference(s)
Dog					
Beagle	♂/♀	~ 589,000	5	Stereology	Horster et al., 1971
	♂/♀	379,000 ± 40,000	10	Disector/fractionator	Basgen et al., 1994
	♂/♀	376,000 ± 108,000	10	MRI	Basgen et al., 1994
Mouse					
C3H/HeJ	♂	20,220 ± 684	24	Adaptor/imaging	Murawski et al., 2010
C57BL/6J	♂	21,085 ± 779	24	Adaptor/imaging	Murawski et al., 2010
Rabbit					
New Zealand white	♀	188,542 ± 7,206	14	maceration	Tendron et al., 2003
English cross-bred	♀	160,803 ± 11,838	6	dissector	Maduwegedera et al., 2007
Rat					
F344	♂	27,131 ± 1,668	5	Direct counting	Szabo et al., 2008
Lewis	♂	34,512 ± 1,549	5	Direct counting	Szabo et al., 2008
SD	♂	31,764 ± 3667	7	Fractionator	Bertram et al., 1992
SD	♂	33,786 ± 3,753	5	MRI	Beeman et al., 2011
SD	♂	35,132 ± 3,123	4	Stereology	Heilmann et al., 2011
SD	♂	32,785 ± 3,117	4	MRI	Heilmann et al., 2011
SHR	♂	36,970 ± 1,352	10	Fractionator	Schulz et al., 2008
Wistar Fromter	♂	27,028 ± 1,322	7	Fractionator	Schulz et al., 2008
Human					
American					
African	♂/♀	959,306 ± 328,602	21/16	Stereology	Hughson et al., 2003
African	♂	~706,752	12	Stereology	Zimanyi et al., 2009
Caucasian	♂	~620,000	?	Stereology	Nyengaard & Bendtsen 1992
Caucasian	♂/♀	869,959 ± 286,006	15/4	Stereology	Hughson et al., 2003
Caucasian	♂	~872,317	12	Stereology	Zimanyi et al., 2009
Australian					
Aborigine	♂/♀	~683,174	11/6	Stereology	Hoy et al., 2006
Non/aborigine	♂/♀	~885,318	21/3	Stereology	Hoy et al., 2003

Species	Gender	Number of nephron	*N*	Method	Reference(s)
European White	♂/♀	730,000 ± 300,000	39	MRI	Fulladosa et al., 2003

Table 2

Ultrastructural heterogeneity of proximal nephrons in mammalian kidneys including humans.

Characteristics	S1	S2	S3	References
Location	Superficial/mid-cortex	Mid-cortex	Inner cortex & OSOM	Maunsbach 1966
				Madsen et al., 2007
				Kriz & Kaissling, 2008
Brush border membrane				
Size	Taller & wider	short	shorter	Maunsbach 1966
Endocytic compartment				
	Most prominent	Less prominent	Least prominent	Maunsbach 1966
				Madsen et al., 2007
Microvilli	Abundant	less abundant	Least abundant	Welling & Welling, 1975
Vasuolar-lysosomal system				
	Well-developed	Less developed	Least developed	Madsen & Park, 1987
Golgi apparatus	Well-developed	Less developed	Least prominent	Madsen et al., 2007
Megalin	Most abundant	Abundant	less abundant	Kerjaschki et al., 1984
				Christensen & Birn, 2001
NHE3	Abundant	Present	Least abundant	
Alkaline phosphatase				
	Present	Present	Present	Heidrich HG et al., 1972
Aminopeptidases	Abundant	Present	Less prominent	Madsen et al., 2007
Basolateral membrane				
Invagination	Extensive	less extensive	Least entensive	Madsen et al., 2007
Lateral process	Extensive	Less prominent	Absent	Madsen et al., 2007
Mitochondria	Elongated	Small	Smaller	Madsen et al., 2007
Na^+/K^+-ATPase	Abundant	Less abundant	Present but lower	Ernst 1975
				Kashgarian et al., 1985
Peroxisomes	Present	Present	Present	Maunsbach 1966
				Maunsbach 1966

Abbreviations: NHE3, the sodium and hydrogen exchanger or antiporter 3. OSOM, the outer stripe of the outer medulla.

Table 3

Functional heterogeneity of proximal nephrons in superficial and juxtamedullary cortex in mammalian kidneys.

Characteristics	Superficial nephron pars convolute	Juxtamedullary nephron pars convoluta	References
Absolute proximal reabsorption	Lower	Higher	Jacobson 1979
Fractional proximal reabsorption	Similar	Similar	Jacobson 1979
Na^+/HCO_3^- reabsorption	Smaller	Greater	Jacobson 1979
Na^+ permselectivity	More permselective Early	Absent	Maddox & Gennari 1987; Jacobson & Kokko, 1976
Cl^- permselectivity	More permselective Late	Less permeable	Maddox /Gennari 1987
HCO_3^--to-Cl^- permselectivity	Smaller	Greater	Schafer et al., 1978
Hydraulic pressure	Similar	Similar	Schafer et al., 1978
Lumen-negative electrical Potential difference	Absent	Persisted	Jacobson 1979
NHE3 expression	Abundant	Prominent	Biemesderfer et al., 1992 & 1997
NaP_i-cotransporter expression	Greater	Lower	Madjdpour et al., 2004
NBC expression	Lower	Higher	Abuladze N et al 1998
$Na^+/HCO3^-$ cotransport	Lower	Higher	Abuladze N et al 1998
PT reabsorptive response to RPP	Decreased	Decreased	Roman 1988
PT reabsorptive response to ANF	Unaltered	Increased	Haas & Knox, 1989

Abbreviations: ANF, atrial natriuretic factor. $Na^+/HCO3^-$, sodium bicarbonate. NBC, sodium and bicarbonate cotransporter. NaP_i, sodium and phosphate cotransporter. PT, proximal tubule. RPP, renal perfusion pressure.