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REVIEWS

Role of Hormones in Regulating Sodium Transporters in the Kidney: Modulation of Phosphorylation, Traffic, and Expression

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Abstract—The review focuses on the key sodium transporters involved in maintaining water–salt balance in the kidney. The topography of sodium transporters is discussed. Specifics of the hormone-dependent regulation, including phosphorylation, traffic, and expression, are considered for particular transporters. Special attention is paid to direct intracellular regulators of the transporter function. The role that dopamine plays as a natriuretic factor in modulating the function of various transporters is described.

Keywords: hormones, sodium, sodium transporters, dopamine, kidney

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Maintaining the electrolyte content and fluid volume in the extracellular space at constant levels is of immense importance in mammals. As is well known, approximately 99% of sodium and water filtered by glomeruli returns in circulation via reabsorption, which takes place in renal tubules.Humoral factors are necessary for regulating water and sodium reabsorption. The set of such factors and mediators includes, first of all, angiotensin II (ATII), atrial natriuretic peptide (ANP), dopamine (DA), and endothelin 1 (ET-1), which directly or indirectly affect sodium transporters [1]. The review considers the humoral regulation of the sodium transporter function at various levels.

Topography of Sodium Transporters in the Nephron

Sodium reabsorption is known to be the most efficient in the proximal nephron (especially, the proximal tubule and the loop of Henle), while the distal convoluted tubule and medullar collecting duct contribute no more than 5–10% to the total sodium reabsorption [2]. Sodium transporters act to ensure sodium reabsorption in various parts of the nephron. Each of the transporters has distinct expression topography. The proximal tubule shows expression of a Na^+/H^+ exchanger (isoform NHE-3), Na^+/HCO_3^- cotransporter (NBC-1), Na^+/glucose cotransporters (SGLT1 and SGLT2), Na^+/PO_4^{3-} cotransporter (NPt2), and Na^+/amino acid cotransporter. A $Na^+/K^+/2Cl^-$ cotransporter is found in the thick ascending limb of the loop of Henle. The collecting duct expresses a Na^+/Cl^- cotransporter (NCC), epithelial sodium channel (ENaC), and Na^+/H^+ exchanger (isoform NHE-1). It is of interest that the adenosine triphosphate (ATP)-dependent exchanger Na^+/K^+-ATPase occurs in all segments of the nephron, being the most abundant in the thick ascending limb of the loop of Henle and the proximal tubule. A polar location in various segments of the nephron is characteristic of all transporters. NHE-3, NKCC2, NCC, and ENaC occur on the apical membrane, while NHE-1, Na^+/K^+-ATPase, and NBC-1 are found on the basolateral membrane. All transporters are regulated by a complex network of hormones and, therefore, secondary messengers, which are involved in the molecular cascades triggered as a result of hormone interactions with respective receptors [2, 3]. The transporter functions can be modulated at several levels, including

(1) phosphorylation/dephosphorylation of a transporter by enzymes,

(2) the regulation of transporter traffic,

(3) the expression regulation at the mRNA or protein level.

The role of various protein kinases in modulating transporter activity has been studied most extensively, while little is known on why changes occur in the transporter function, including changes in expression, phosphorylation, or traffic.

Although a broad range of humoral signals affect the function of sodium transporters, several common points are possible to isolate in their regulation. The set includes certain enzymes that mediate the hormonal signal and directly interact with a transporter (see below).

Direct Regulators of the Sodium Transporters Function

An enzyme of particular interest is salt-inducible kinase (SIK), which is involved in regulating the Na^+/K^+-ATPase function and acts predominantly in the proximal tubule and the thick ascending limb of the loop of Henle. SIK was initially identified in the adrenals of rats fed a high-Na^+ high-K^+ diet for one week. Three SIK isoforms are known. In humans, the SIK genes are on chromosomes 21 (SIK1) and 11 (SIK2 and SIK3). SIK belongs to the 5-AMP-activated protein kinase (AMPK) family and is an 86-kDa monomeric protein with three main domains. SIK has been demonstrated to affect the function of the sodium–potassium pump in experiments with opossum kidney cells. An increase in intracellular Na^+ concentration increases the Ca^{2+} influx through the Na^+/Ca^{2+} exchanger (NCE1) and thus activates Ca^{2+}/calmodulin-dependent protein kinase 1 (CAMK1). CAMK1 undergoes phosphorylation and activates SIK1 associated with Na^+/K^+-ATPase. As a result, SIK1 stimulates the Na^+/K^+-ATPase function by acting indirectly through protein phosphatase 2A (PP2A). PP2A is a component of a multiprotein complex that additionally includes SIK1, Na^+/K^+-ATPase, and protein phosphatase methylestherase 1 (PME-1). In normal conditions, PME-1 is demethylated and inactivates PP2A. Once SIK1 is activated by CAMK1, SIK1 phosphorylates PME-1 to cause its dissociation from the multiprotein complex. In turn, PP2A is methylated and thus activated by cell methylases and dephosphorylates the α1 subunit of Na^+/K^+-ATPase, increasing its catalytic activity [3].

Apart from SIK1, adducin plays an important role in maintaining the Na^+/K^+-ATPase function. It is a heterodimeric cytoskeletal protein and consists of α and β subunits. Adducin promotes the binding of spectrin to actin, binds with calmodulin, is a substrate of protein kinase C (PKC) and protein kinase A (PKA), and regulates Na^+/K^+-ATPase activity. A substitution of thymine (T) for guanine (G) in the coding region of *ADD1* changes tryptophan to glycine in the protein. Mutant adducin activates Na^+/K^+-ATPase in renal tubules and thereby facilitates sodium retention, triggering hypertension [4]. Milan hypertensive strain rats carry an α-adducin gene mutation similar to that found in the human gene. Studies with rats of this strain have shown that the mutation increases Na^+/K^+-ATPase activity and that the increase is associated with SIK1 activation [3]. Procino et al. [5] have studied the adducin-dependent mechanism of hypertension in the renal cortex and inner medulla; Mondini et al. [6] have used cultured distal convolute tubule cells of Wistar and Milan hypertensive rats for the purpose.

In the 1980s, Na^+/K^+-ATPase inhibitors similar to digitalis were found in circulation and shown to play a role in regulating sodium reabsorption in proximal tubules and total sodium transport in the kidney. Plant-derived substances structurally similar to ouabain, such as marinabufagenin, have recently been implicated in regulating the blood pressure and natriuresis. Moreover, an increase in concentration of these cardiotonic steroids (marinabufagenin) correlates with a higher sodium excretion in the kidney in some cases [7].

Serum- and glucocorticoid-dependent kinase 1 (SGK1) is another important enzyme that is involved in regulating the function of several sodium transporters in the kidney. A high SGK1 level in the kidney may contribute to hypertension and diabetic nephropathy [8]. SGK1 is a serine/threonine protein kinase and belongs to the protein kinase A/protein kinase G/protein kinase C (AGC) family. Expression of the SGK1 gene is stimulated by glucocorticoids, mineralocorticoids, androgens, the gonadotropin-releasing hormone, insulin, resistin, and other factors [9]. Transcription of the SGK1 gene is known to increase in response to osmotic stress mediated by stress-activated protein kinase 2 (SAPK2), which is also known as p38 [9]. Interleukin 6 stimulates SGK1 transcription by acting mostly through the JAK/STAT cascade. As for a nongenomic regulation, the transforming growth factor β (TGF-β) and insulin cause SGK1 phosphorylation through a signaling cascade including phosphatidylinositol 3-kinase (PI3K), 3-phosphoinositide-dependent protein kinases 1 (PDK1), and mTORC2 (mammalian target of rapamycin complex 2) [9].

There are data that SGK1 colocalizes with Na^+/K^+-ATPase in the renal epithelium. SGK1 has been shown to stimulate the Na^+/K^+-ATPase function in several species; similar results were obtained with cultured A6 cells, which originate from distal tubules of the kidney. The effect has not been associated with changes in sodium–potassium pump content in the plasma membrane or protein expression level [9]. Aldosterone stimulates SGK1 phosphorylation and upregulates expression of the α1 subunit at the protein level in the cortical collecting duct, distal convolute tubule, and proximal tubule [10].

In addition, SGK1 contributes to regulating NHE-3 in the proximal tubule. Chronic exposure (24 h) to insulin activates NHE-3 through the classical PI3K–SGK1 signaling pathway in the proximal tubule. The insulin effect on NHE-3 increases as a result of high SGK1 expression. In the case of a short-term (1–2 h) exposure to insulin, the effect on NHE-3 consists in increases in its activity, content in the apical membrane, and phosphorylation. The PI3K–SGK1-Akt and TC10 signaling cascades are potentially involved in these processes in acute insulin exposure [11]. In addition to SGK1, SGK2, which is another isoform of the enzyme, is expressed in the proximal tubule, but does not respond to glucocorticoids in contrast to SGK1. Experiments with SGK2 expression in cul-

tured opossum renal P cells have shown that SGK2 similarly increases NHE-3 activity and that the increase correlates with a higher level of NHE-3 expression on the cell surface [12].

There are data that coexpression of NKCC2 with SGK1 in a model system causes a sixfold increase in NKCC2-mediated sodium flux as compared with a control. The precise mechanism of NKCC–SGK1 interaction is still unknown [9].

SGK1 plays a key role in preventing ENaC ubiquitination in the distal tubule. ENaC is ubuquitinated by the E3 ligase Nedd4-2, which is encoded by *NEDD4L* according to the NCBI Gene database (https://www.ncbi.nlm.nih.gov/gene/23327). SGK1 acts as a Nedd4-2 antagonist, i.e., SGK1 binds and phosphorylates Nedd2-4, thus making its docking sites accessible to 14-3-3 proteins. The interaction of the 14-3-3 proteins with Nedd4-2 is thought to prevent Nedd4-2 binding with ENaC, and ENaC consequently accumulates in the plasma membrane [13]. Experiments with a model system have shown that ENaC activity increases as SGK1 expression increases in response to aldosterone in the distal tubule [8].

It is of interest that several deubiquitinating enzymes have been found to affect ENaC. The ubiquitin-specific protease Usp2-45 has been shown to deubiquitinate ENaC and to stimulate the ENaC-mediated Na^+ transport, the effect being nonadditive to that of SGK1. Ubiquitin C-terminal hydrolase (UCH) isoform L3, which is another deubiquitinating enzyme, provides for ENaC recycling and thereby also plays a role in regulating the ENaC density on the cell surface [2].

The SPAK/OSR1/WNK signaling pathway is of importance for a total transporter family. The relevant enzymes phosphorylate serine and threonine residues and thereby regulate the function of sodium transporters of the SLC12 family, which are expressed in the thick ascending limb of the loop of Henle and the collecting duct. It is of interest that the same residues are phosphorylated in NKCC1, NKCC2, and NCC, while other residues are phosphorylated in potassium–chlorine cotransporters (KCCs), which belong to the same family [14].

The functions of NKCC and NCC essentially depend on kinase–phosphatase balance. The relevant kinases include calcineurin, and the kinase set includes serine–proline–alanine-rich kinase (SPAK) and oxidative stress response kinase 1 (OSR1), which is encoded by the *OSR1* gene according to NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/130497). In turn, activities of these kinases are modulated by the WNK (with-no-lysine kinase) family. The WNK-family kinases are currently subject to intense research because their mutations in humans cause salt-dependent hypertension with hyperkaliemia, which is also known as pseudohypoaldosteronism type II, or Gordon's syndrome. There is evidence that OSR1 is involved in regulating the function of NKCC2 rather than the other transporters. A mutation of OSR1 has been found to decrease NKCC2 expression and to cause a phenotype characteristic of Batter's syndrome [14].

Carbonic anhydrase II (CA II) is another enzyme that plays an important role in the function of the NHE-3 and NBC-1 transporters. CA II is a cytosolic enzyme that converts CO_2 and H_2O to carbonic acid. Patients with mutations of CA2, which codes for CA II, develop metabolic renal tubular acidosis with dramatically impaired reabsorption of sodium and bicarbonate. In addition, the disorder has recently been associated with mutations of other genes, including *SLC4A4*, which codes for NBC-1; *SLC4A1*, which codes for the Cl^-/HCO_3^- exchanger AE1; and *ATP6B1*, which codes for the B1 subunit of H^+-ATPase [15, 16]. Proximal renal tubular acidosis due to NBC-1 defect may be accompanied by mental disorders, glaucoma, cataract, and pancreatic dysfunction because the exchanger is additionally expressed in the retina and pancreas [16, 17].

The above factors are common factors, which are involved in regulating several sodium transporters. Below we consider the specifics of the function of individual sodium transporters in various segments of the nephron.

Regulation of the Sodium Transporter Function

Basolateral Na^+/K^+-ATPase directly or indirectly regulates the total sodium reabsorption in proximal tubules [1]. The enzyme plays an important role in sodium reabsorption and provides a driving force for an inward flow of sodium and a pumping of potassium out of the cell via transporters located on the apical membrane in epithelial cells of the nephron [2]. Because the function of the sodium–potassium pump has been characterized more comprehensively as compared with other sodium transporters, its regulation is described below.

It is important to consider the specifics of the hormonal regulation of Na^+/K^+-ATPase in various segments of the nephron.

Dopamine is known to inhibit Na^+/K^+-ATPase activity in the proximal tubule, acting through PKA, which phosphorylates both the α1 subunit to suppress its function and the protein phosphatase 1 (PP1) inhibitor dopamine- and cAMP-regulated phosphoprotein (DARPP-32) to convert it to an active form. DARPP-32 inhibits PP1, and PP1 consequently ceases to dephosphorylate and thereby activate Na^+/K^+-ATPase [18]. Norepinephrine acts through the α1 adrenoreceptor to stimulate Na^+/K^+-ATPase activity, as has been demonstrated using [γ-^{32}P]ATP to evaluate the ATP hydrolysis rate by measuring radioactivity. The effect is mediated by activation of the cal-

cium/calmodulin-dependent protein phosphatase calcineurin, which dephosphorylates DARPP-32 and thereby activates PP1. Then PP1 dephosphorylates and thereby activates Na^+/K^+-ATPase. The mechanism of norepinephrine-dependent activation of the sodium–potassium pump is essentially opposite to the mechanism of dopamine action through PKA [19]. Another pathway leading to inhibition of the sodium–potassium pump involves cyclic guanosine monophosphate (cGMP) and protein kinase G (PKG) activation, as has similarly been demonstrated using [γ-^{32}P]ATP for ANP [20].

The signaling compounds considered below are still poorly understood in terms of the mechanism of their effect on the sodium–potassium pump. The arachidonic acid derivative 20-hydroxyeicosatetraenoic acid (20-HETE) acts through PKC to inhibit Na^+/K^+-ATPase activity in the proximal tubule [21]. Likewise, NO inhibits Na^+/K^+-ATPase in the thick ascending limb of the loop of Henle, as has been determined colorimetrically by measuring the phosphate resulting from ATP hydrolysis. The effect is seen upon a prolonged (>30 min) incubation of the thick ascending limb of the loop of Henle with NO and depends on the O_2^- content [22]. It is of interest that leptin receptors (short Ob-Ra and long Ob-Rb isoforms) have been found in the medullar collecting duct. An intraperitoneal injection of leptin to Wistar rats has been found to inhibit Na^+/K^+-ATPase activity (as measured colorimetrically by phosphate resulting from ATP hydrolysis) in the renal medulla and increases sodium excretion and urine production. Leptin has been assumed to act through the Ob-Ra receptor and PI3K to affect the Na^+/K^+-ATPase function in the kidney [23]. There are data that the endocannabinoid system functions in proximal tubules. Experiments with LLC-PK1 cells (immortalized epithelial cells originating from pig proximal tubules) have shown that the CB_1 endocannabinoid receptor may trigger two signaling cascades that oppositely affect Na^+/K^+-ATPase activity and that the transient receptor potential vanilloid type 1 (TRPV1) is potentially involved in this regulation. The CB_1 receptor agonist hemopressin has been found to act through the PKA-dependent pathway to inhibit Na^+/K^+-ATPase, while WIN, which is a synthetic agonist of the CB_1 receptor and TRPV1, acts through PKC to stimulate Na^+/K^+-ATPase activity (the pump function has been evaluated calorimetrically) [24].

As for the stimulating effect, the neuropeptide Y (NPY) acts through the Y2 receptor to increase Na^+/K^+-ATPase activity in the proximal tubule. NPY increases the intracellular concentration of calcium, which activates calcium/calmodulin-dependent protein kinase II (CaMKII), which stimulates the function of the sodium–potassium pump (as assayed with [γ-^{32}P]ATP). Protein phosphatase 2B (PP2B) is also involved in the signaling cascade stimulating the Na^+/K^+-ATPase function [25]. Activation of proteinase-activated receptor 2 (PAR2) increases Na^+/K^+-ATPase activity and affinity for sodium in the thick ascending limb of the loop of Henle, acting through the PLC/PKC/$ERK_{1,2}$ cascade, as has been established using [γ-^{32}P]ATP [26].

Estradiol is of interest in terms of the regulation of sodium–potassium pump expression at the protein level. On the one hand, estradiol has been reported to stimulate Na^+/K^+-ATPase activity through PI3K and protein kinase B (PKB) [27]. On the other hand, protein expression of the dephosphorylated α1 subunit of Na^+/K^+-ATPase in the thick ascending limb of the loop of Henle in ovariectomized rats is substantially higher than in intact females [28].

Prior to considering the transcriptional regulation of the Na^+/K^+-ATPase function, it is important to describe the structural specifics of the genes that code for the Na^+/K^+-ATPase subunits. The α1 and β1 Na^+/K^+-ATPase subunits are encoded by *ATP1A1* and *ATP1B1*, respectively. The β1-subunit amount is a limiting factor for α/β heterodimer formation in many cells. Hence, an increase in *ATP1B1* transcription exerts a greater effect on Na^+/K^+-ATPase at the cell level as compared with an increase in *ATP1A1* transcription. Higher levels of the β1-subunit mRNA are observed when prostaglandins E_1 and E_2 stimulate transcription of *ATP1B1*, which codes for the β1 Na^+/K^+-ATPase subunit. *ATP1B1* expression is controlled by promoter regulatory elements, which include three prostaglandin response elements (PGEs), a mineralocorticoil/glucocorticoid response element (MRE/GRE), and a thyroid hormone response element (TRE). Each of the elements is activated in response to the respective hormone. The cAMP response element binding protein (CREB) plays a central role in the transcriptional regulation. It should be noted that CREB is activated via phosphorylation by mitogen-activated protein kinase (MAPK) and Ca^{2+}/calmodulin-dependent protein kinase (CAMK) and, additionally, via PKA and PKC, which play a key role in regulating the pump function. Phosphorylated CREB binds to cAMP response elements (CREs) via its DNA-binding domain (bZIP), which is at the C end of the protein. A kinase-inducible domain (KID) is at the N end of CREB and harbors a PKA phosphorylation site, Ser133. Phosphorylated CREB or, more exactly, its bZIP binds with transducers of regulated CREB (TORCs), and the binding affects the interaction of CREB with the CREB-binding protein (CBP). The interaction with CBP activates CREB and increases the transcription rate of CREB-dependent genes. A feature of TORCs is their capability of affecting CREB regardless of its phosphorylation at Ser13. SIK plays an important role in regulating the process. A nuclear SIK form phosphorylates TORCs, thus

decreasing their affinity for CREB, and TORCs are transported into the nucleus. The likelihood of the events depends on the extent of SIK phosphorylation. *ATP1B1* is TORC sensitive in kidney cells. TORCs mostly stimulate *ATP1B1* transcription in cells of the proximal tubule, the greatest effect being exerted by TORC3 [3].

Other regulators are known to affect expression of the Na^+/K^+-ATPase subunit genes in addition to the hormones that have corresponding response elements in the gene promoters. For instance, experiments with cultured human renal tubule cells (HRTCs) originating from the cortex have shown that the C-peptide (a proinsulin fragment) upregulates expression of the α1 Na^+/K^+-ATPase subunit by acting through PKCδ, PKCε, and MAPK, which activate transcription of the gene for the ZEB factor, which has a binding site in the promoter of the α1-subunit gene in human and rat cells [29].

As for the regulation of the traffic of the sodium–potassium pump, angiotensin II (ATII) is known to activate PKCβ at low concentrations. The α1 Na^+/K^+-ATPase subunit is phosphorylated as a result, and Na^+/K^+-ATPase is incorporated in the plasma membrane [3]. Aldosterone has been reported to stimulate the transfer of the α1 subunit of Na^+/K^+-ATPase from the intracellular compartment to the basolateral membrane surface in the distal nephron, but the mechanism of the process remains unclear [30]. In contrast, dopamine and the parathyroid hormone cause endocytosis of Na^+/K^+-ATPase. Dopamine activates PKCζ, which phosphorylates the α1 Na^+/K^+-ATPase subunit. The protein 14-3-3 binds to the phosphorylated motif, facilitating the binding of PI3K to the neighbor proline-rich domain in the α1 subunit and thus leading to PI3K activation. Activated PI3K promotes the binding of adaptor protein 2 (AP-2) to the α1 subunit, and this binding is a key prerequisite to Na^+/K^+-ATPase endocytosis. AP-2 recruits clathrin, leading to the formation of clathrin-coated pits and endocytosis of the sodium–potassium pump [3]. The parathyroid hormone stimulates phosphorylation of the α1 Na^+/K^+-ATPase subunit via the ERK-dependent signaling cascade, which involves PKCα, Src kinase, phospholipase C (PLC), and phospholipase A2 (PLA2). The process results in Na^+/K^+-ATPase endocytosis via clathrin-coated vesicles [31, 32]. It is of interest to note that Kif5b is involved in regulating the transport of Na^+/K^+-ATPase-containing vesicles in the thick ascending limb of the loop of Henle and the distal convolute tubule. Kif5b is a kinesin-1 heavy chain isoform and is expressed, in particular, in the nephron. In addition, Kif5b stimulates the transport of mitochondria to the basolateral membrane, where the sodium–potassium pump is localized. The localization of Na^+/K^+-ATPase in the nephron is altered in mice with a Kif5b knockout in the kidney; i.e., the sodium–potassium pump is expressed in the apical membrane in the knockout kidney [33].

NKCC

Two NKCC isoforms, NKCC1 and NKCC2, are known, both belonging to the SLC12 transporter family [14]. As mentioned above, the bumetanide-sensitive sodium–potassium–chlorine cotransporter NKCC2 is expressed in the thick ascending limp of the loop of Henle. NKCC2 transports 80% of Na^+ and 100% of Cl^- in this segment of the nephron. The important role that NKCC2 plays in ion and water reabsorption is supported by the fact that a NKCC2 block with diuretics, such as furosemide, greatly increases the urine production [34].

The hormone effect on the transporters is mediated by secondary messengers. Among these, cAMP plays an important role by regulating the NKCC2 incorporation in the apical membrane in the thick ascending limb of the loop of Henle. In general, cAMP serves as a main intracellular stimulator of ion reabsorption in the ascending limp of the loop of Henle; its concentration increases in response to vasopressin, the parathyroid hormone, glucagon, calcitonin, and β-adrenoreceptor agonists, and the NKCC2 traffic is regulated accordingly. A decrease in any of the hormones exerts no effect on the function of the nephron segment because the other hormones continue stimulating reabsorption [35]. Vesicle-associated membrane protein 2 (VAMP2), which belongs to the soluble NSF attachment receptor (SNARE) family, mediates the cAMP-stimulated incorporation of NKCC2. Not only cAMP-dependent, but also constitutive traffic is known for NKCC2 and dependent on activity of VAMP3, another VAMP isoform [36]. A negative regulation is due to inhibition of adenylate cyclase or other steps of the cAMP-dependent pathways by angiotensin, prostaglandin E2 (PGE2), and endothelin [37]. Recent studies have shown that the alkaloid spilanthol inhibits both cAMP production and NKCC2 phosphorylation. Spilanthol is a major alkaloid of the plant *Acmella oleracea*, which is used in Brazilian traditional medicine as a diuretic, although scientific data supporting its physiological effect were scarce until recently [38].

In addition to cAMP, cGMP may be involved in regulating NKCC2. It is known that NO suppresses the NKCC2 function by acting through cGMP, which is degraded by phosphodiesterases (PDEs). ATII administration has been reported to increase the PDE5 level in smooth muscle cells, leading to a decrease in cGMP. Ramseyer et al. [34] have shown that the NO level in the thick ascending limb of the loop of Henle decreases in ATII-induced hypertension in male Sprague-Dawley rats and that the NKCC2 function is therefore not suppressed. NKCC

activity has been estimated by fluorescence of labeled sodium loaded into isolated renal tubules [34]. Jiandong Zhang et al. [39] have shown in mice knocked out in the interleukin-1 (IL-1) receptor that receptor activation stimulates salt retention in the kidney by suppressing NKCC2 activity via a NO-dependent mechanism.

Among all hormones that affect NKCC2, vasopressin acts as a key stimulator of its activity. Two regulatory mechanisms are known: a short-term regulation is based on changes in NKCC2 vesicular traffic, while a long-term regulation is due to an increase in expression of the NKCC2 gene *SLC12A1* [40, 41].

Apart from vasopressin, ATII stimulates expression of *SLC12A1* and its protein product in the kidney in rats with ATII-induced hypertension [42].

Phosphorylation/dephosphorylation of serine or threonine residues in the N- and C-terminal domains of the SLC12-family transporters is another mechanism that regulates their activities [14, 38].

Distorted ion transport due to lower NKCC2 activity in the thick ascending limb of the loop of Henle may cause hypotension, while higher sodium reabsorption in the thick ascending limb of the loop of Henle leads to hypertension. A mutation of *SLC12A1*, which codes for NKCC2, causes Batter's syndrome, which is characterized by hypotension, hypokalemia, metabolic alkalosis, and hypercalciuria [14].

NKCC1 is expressed on the basolateral membrane of cells of the collecting duct and is encoded by *SLC12A2*. Apart from the nephron, NKCC1 is expressed in mesangial cell and afferent arterioles. There is no information on a unique role of NKCC1 in the physiology of renal tubules in the available literature. However, there are data that renin secretion is elevated in NKCC1 knockout mice [14].

Thiazide-Sensitive Sodium–Chloride Cotransporter

Thiazide-sensitive sodium–chloride cotransporter (NCC) belongs to the SLC12 transporter family, like NKCCs, and is expressed on the apical cell membrane in the distal convolute tubule. Activity of the SLC12-family transporters depends on phosphorylation/dephosphorylation of serine and threonine residues in their N- and C-terminal regions. The NCC function is regulated by many stimuli involved in maintaining various physiological parameters, such as blood pressure, potassium concentration in the blood serum, and calcium excretion. The stimuli include ATII, aldosterone, vasopressin, insulin, norepinephrine, estradiol, progesterone, prolactin, and the parathyroid hormone [14, 41, 43]. All but one (parathyroid hormone) of these hormones stimulate C-terminal phosphorylation of NCC via the SPAK/OSR1 signaling pathway and thereby increase the transporter function [14]. The parathyroid hormone inhibits NCC activity. The effect is associated with a positive regulation of transient receptor potential vanilloid 5 (TRPV5) and a consequent increase in calcium reabsorption in the distal convolute tubule. It is of interest that the parathyroid hormone inhibits the NCC function through WNK4, which is capable of exerting both inhibiting and stimulating effects. The type of the WNK4 effect on NCC has been assume to depend on the intracellular Cl^- concentration. When Cl^- concentration decreases, WNK4 suppresses NCC activity [44].

As for the effect on transcription of *SLC12A3*, which codes for NCC, studies in lower vertebrates have shown that cortisol stimulates NCC expression in cover tissues [45]. Activation of the P2Y2 adenosine receptor by ATP or uridine triphosphate (UTP) inhibits NCC expression in distal convolute tubules of mice at both mRNA and protein levels [46].

Activation of NCC contributes to hypertension due to treatment with inhibitors of calcineurin, which acts as a phosphatase and an antagonist of the OSR1 and SPAK kinase. For instance, tacrolimus and cyclosporine induce NCC phosphorylation and activation, thus increasing salt reabsorption and causing hypertension. In clinical studies, NCC expression and phosphorylation in urinary exosomes of hypertensive patients receiving tacrolimus after kidney transplantation were higher than in patients with a normal blood pressure [14].

Three disorders are currently known to be due to NCC dysfunction.

First, Gitelman syndrome is associated with a loss-of-function *SLC12A3* mutation and is characterized by hypotension, hypokalemia, metabolic alkalosis, and hypocalciuria.

Second, SeSAME (Seizures, Sensorineural deafness, Ataxia, Mental disability, and Electrolyte imbalance) syndrome is due to an inactivating mutation of the K^+ channel gene *KCNJ10*. SeSAME syndrome is similar in clinical presentation to Gitelman syndrome, but additionally involves neurological disorders. Potassium channel dysfunction decreases the basolateral chlorine conduction in the distal convolute tubule, thus decreasing WNK–SPAK activity and, eventually, NCC activity.

Third, pseudohypoaldosteronism type II (PHII) is due to an increase in NCC activity. A higher NCC activity is currently thought to be the key factor that is responsible for hypertension, hyperkalemia, and metabolic alkalosis in PHII. Four different forms of PHII result from mutations of the genes for WNK1, WNK4, Kelch-like protein 3 (*KLHL3*), and Cullin 3 (*CUL3*). The two last proteins form a ubiquitin ligase complex and determine the NCC half-life via the ubiquitination mechanism [14].

ENaC

ENaC occurs on the apical membrane of cells of the cortical collecting duct and convolute tubule. ENaC belongs to the Deg/ENaC ion channel family and is a heteromeric protein complex. There are four ENaC subunits: α (encoded by *SCNN1A*); β (*SCNN1B*); γ (*SCNN1G*); and δ, which is not expressed in the kidney. The complex consists of two α, one β, and one γ subunits. [13].

Like with other ion channels, ENaC activity is regulated via several basic mechanisms, which modulate the ENaC content on the cell surface (vasopressin and aldosterone stimulate a redistribution of ENaC from the intracellular pool into the apical membrane [13]), ENaC conductance [2, 13], or expression of the subunit genes at the gene or protein level.

Because aldosterone regulates the ENaC traffic, ENaC is an important effector of the renin–angiotensin–aldosterone system (RAAS) and, therefore, plays a central role in sodium homeostasis and the regulation of the blood pressure. Aldosterone has additionally been found to stimulate expression of the genes for WNK, PI3K, Usp2-45, K-Ras small GTPase, etc. [2]. It is known also that ENaC function is regulated by endothelin, insulin, insulin-like growth factor 1 (IGF-1), epidermal growth factors, and arachidonic acid metabolites. Several small GTPases, such as K-Ras, RhoA, Rac1, and Rab11, have been reported to modulate the ENaC function, and even the small G-protein utilizes its own mechanism to regulate ENaC activity [2].

Vasopressin regulates not only the ENaC traffic, but also expression of the ENaC genes. Expression of all genes coding for the ENaC subunits is decreased in mice knocked out in adenylate cyclase VI, which mediates the vasopressin effect on ENaC [47]. An increase in expression of the ENaC α subunit and SGK1 mRNAs has been observed in human collecting duct cells incubated with TGFβ and glucose (a model of type 2 diabetes mellitus) [48].

Prolactin treatment has been reported to increase the transepithelial current through ENaC and to stimulate ENaC activity in A6 renal epithelial cells compared with control cells. The data have been obtained by the patch-clamp technique in the cell-attached configuration [49].

Ubiquitination and deubiquitination of ENaC are of interest. Liddle syndrome often develops when amino acid substitutions alter the PY motifs in the β and γ subunits and thereby distort the interaction of ENaC with Nedd4-2 [50] and, therefore, ENaC endocytosis. An increase in apical membrane residency time of ENaC in the distal nephron leads to substantial sodium reabsorption and hypertension [13].

Dysfunction of ENaC may lead to hypotension as well as to hypertension. Many functional defects of the β and γ subunits that lead to ENaC hyperactivity (Liddle syndrome) are associated with monogenic forms of hypertension. Defects in regulation of the ENaC function underlie the majority of monogenic hypertension forms, including mineralocorticoid hypertension and glucocorticoid remediable aldosteronism. A point mutation of the mineralocorticoid receptor (MR) gene has been found to act so that progesterone comes to act as a MR agonist and Na^+ reabsorption through ENaC increases, which may lead to preeclampsia. Loss-of-function mutations of ENaC subunits may mimic hyposecretion of aldosterone, which results in lower channel activity and pseudohypoaldosteronism characterized by hypovolemia, hyperkaliemia, salt loss, and hypotension in some cases [2].

It is of interest that hypertension develops in mice knocked out in the sodium–bicarbonate electrogenic cotransporter (NBCe2) in the distal tubule. The physiological effect seems paradoxical at first glance, but is due to compensatory activation of other sodium transporters. Donghai Wen et al. [51] have shown that ENaC plays a main role in this hypertension. The role of ENaC in hypertension is evident from the fact that the mean blood pressure in NBCe2 knockout mice treated with the ENaC blocker amiloride does not significantly differ from that in wild-type mice. Moreover, the transepithelial potential is amiloride sensitive in NBCe2 knockout mice. Thus, ENaC is responsible for increased sodium reabsorption in the distal nephron in the case in question [51].

Experimental findings support the idea that ENaC interacts with CFTR (cystic fibrosis transmembrane conductance regulator, Cl^- channel). This indicates that ENaC may play a role in the pathogenesis of cystic fibrosis and other disorders associated with CFTR dysfunction. Recent studies have shown that the ENaC function in renal epithelial cells is distorted in animals and human patients with autosomal recessive polycystic kidney disease (ARPKD) [2].

NHE-3

This transporter belongs to the ion exchanger family including nine isoforms and is encoded by human *SLC9A3* according to the NCBI Gene database (https://www.ncbi.nlm.nih.gov/gene/6550). Only two isoforms are expressed in the kidney: NHE-3 on the apical membrane in the proximal tubule and NHE-1 on the basolateral membrane in the collecting duct. In contrast to NHE-3, NHE-1 is almost not involved in endosome traffic and resides mostly in the plasma membrane. As for NHE-3, its traffic plays a key physiological role in regulating sodium reabsorption in the proximal tubule [15]. Hence, only NHE-3 is considered below.

It is thought that NHE-3 accounts for approximately 50–60% of the filtered NaCl and 70–80% of the filtered HCO_3^- n the proximal tubule. To demonstrate the important role of NHE-3 in water–salt bal-

ance, mice knocked out in its gene (NHE-3–/–) have been obtained. The mice display a statistically significant decrease in basal blood pressure, salt loss, impaired intestinal absorption, increased renin expression in the kidney, and an approximately fivefold increase in circulating aldosterone. The findings indicate that the ATII influence increases as a result of salt loss and a decrease in total circulating blood volume [15].

A set of signaling molecules and intracellular regulators control the function of NHE-3, as is the case with the majority of sodium channels. Na^+–H^+ exchanger regulatory factor 1 (NHERF-1) is one of the regulators and is encoded by *SLC9A3R1* according to NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/9368). NHERF-1 is expressed and localized on the apical membrane in the proximal tubule and plays an important role in cAMP-mediated phosphorylation, which inhibits NHE-3 activity. Studies with NHERF-1 knockout mice have implicated EPAC (exchanger protein directly activated by cAMP) and PKA in mediating the regulatory effect of NHERF-1 on NHE-3 activity [15]. A regulation by NHERF-1 has additionally been observed for the sodium–phosphate symporter NPt2, which is another sodium transporter [52].

It is known that cAMP inhibits NHE-3 activity in the proximal tubule as a result of NHE-3 phosphorylation. An interesting biphasic effect is exerted on NHE-3 activity by ATII. Physiological ATII concentrations (10^{-12}–10^{-10} M) are known to stimulate NHE-3 in the proximal tubule by activating the AT1 receptor coupled with the G-protein, reducing the cAMP level, and increasing PKCβ activity. The effect plays a key role in maintaining extracellular fluid volume homeostasis and the blood pressure. However, NHE-3 activity is inhibited when the ATII concentration exceeds 10^{-7} M. Recent studies have shown that selective activation of the signaling pathway from the AT1 receptor associated with β-arrestin induces urine production and sodium excretion independent of G-protein-mediated signaling; i.e., NHE-3 activity is inhibited via this pathway. Microperfusion of opossum proximal tubules with 10^{-7} M synthetic peptide TRV120023 has shown that TRV120023 binds with the AT1 receptor, blocks the G-protein-mediated signaling pathway, and stimulates the β-arrestin pathway. As a result, NHE-3 expression on the surface of opossum proximal tubule cells decreases both in vivo and in vitro, and NHE-3 is additionally redistributed to the bases of microvilli in rat proximal tubules [53]. It is of interest that a biphasic effect of ATII is not observed for other transporters, such as SGLT1 and SGLT2. ATII inhibits both of the transporters regardless of its concentration, acting through PKC, MAPK, and phospholipase A2 (PLA2) [54].

Apart from ATII, glucagon is capable of exerting a biphasic effect. NHE-3 activity in opossum kidney P-cells has been reported to decrease upon acute (1 h) exposure to glucagon and to increase upon chronic (24 h) exposure (the pH restoration rate after challenging with acid has been measured using carboxyfluorescein). PKA inhibitors abolish the effects, implicating PKA in regulating NHE-3 activity [55].

Discrepant data are available for the effect of caffeine on NHE-3. Caffeine, which acts as a competitive antagonist of the A1 receptor, has been assumed to increase the cAMP level and thereby to suppress NHE-3 activity. Exposure to caffeine for 24 h has earlier been found to decrease expression of the NHE-3 protein in rats [56]. Fenton et al. [57] have compared the electrolyte and fluid excretion levels for NHE-3 knockout and control mice to check the hypothesis that caffeine affects NHE-3 to exert its natriuretic and diuretic effects. The study has not confirmed that the natriuretic effect of caffeine is due to changes in the localization, phosphorylation, or amount of NHE-3 on the basolateral membrane of proximal tubule cells [57].

NBC-1

The NBC-1 electrogenic sodium–bicarbonate cotransporter is expressed on the basolateral membrane in the proximal tubule and transports ions into the interstitial fluid and blood. NBC-1 plays an important role in regulating acid–alkaline balance in the kidney, maintaining pH in the blood and within cells, and regulating the sodium transport in the proximal tubule through NHE-3. NBC-1 activity is regulated by PKA/cAMP, PKC, Mg^{2+}, Ca^{2+}, ATP, carbonic anhydrases I and III, IRBIT (inositol-1,4,5-triphosphate (IP3) receptor binding protein released with IP3), and phosphatidylinositol 4,5-bisphosphate (PIP2) [58]. PKA-dependent phosphorylation of NBC-1 shifts the HCO^{3-}/Na^+ transport ratio from 3 : 1 to 2 : 1, leading to depolarization of the basolateral membrane. The direction of bicarbonate transport changes from outward to inward as a result. The mechanisms of the stimulating effect of PKC on NBC-1 are poorly understood. The function of NBC-1 depends to a great extent on Na^+/K^+-ATPase activity. However, bicarbonate secretion has been observed to decrease in response to prolactin in the fish intestine even when Na^+/K^+-ATPase activity has been inhibited with the cardiotonic steroid ouabain [59].

There are common points in the regulation of NHE-3 and NBC-1 because the functions of the two ion transporters are interrelated. For instance, there are data that chronic treatment with norepinephrine increases expression of the NHE-3 and NBC-1 proteins in the renal cortex in rats. The finding makes it possible to assume that the sympathetic nervous system of the kidney regulates its excretory system by affecting the transport systems in the nephron [60]. A

concerted function of the two transporters is additionally supported by the fact that administration of dexamethasone, which is a synthetic glucocorticoid analog, increases expression of the NBC-1 mRNA in rats and stimulates NBC-1 and NHE-3 activities (as has been inferred from the pH restoration rate after challenging with acid in the presence or absence of bicarbonate, respectively) [61].

SGLT2

The sodium–glucose exchanger SGLT2 belongs to a family of six cotransporters, has low affinity for sodium and glucose, and is expressed predominantly on the apical membrane in the proximal convolute tubule. SGLT2 is encoded by *SLC5A2* according to NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/6524) and transports sodium and glucose at a 1 : 1 ratio. It is known that 99.9% of the glucose filtered daily in renal glomeruli is reabsorbed in proximal tubules, and its reabsorption is due to the SGLT2 function. The other transporters of the family are also broadly expressed in the kidney and other tissues, but their physiological roles in transferring sodium and glucose is still poorly understood [15]. Expression of the SGLT transporters is sex independent in humans as opposed to rats, while expression of SGLT1 and SGLT2 in the kidney in female rats is higher than in male rats [62].

The transport of glucose and sodium through SGLT2 strongly depends on the sodium concentration. When sodium ions are replaced with other cations, such as lithium cations, cotransport stops. For instance, Burg and colleagues (cited from [15]) have perfused proximal convolute tubules with solutions containing glucose, lactate, alanine, and citrate. It has been observed that depletion of the luminal perfusate of all solutes decreases the sodium reabsorption rate by 45–75%, while addition of glucose or alanine stimulates a slight, but statistically significant increase in sodium reabsorption. On the other hand, the glucose transport inhibitor phlorizin decreases the transepithelial potential difference and the sodium and fluid reabsorption rates in the proximal tubule [15].

The role that SGLT2 plays in glucose metabolism has been studied in SGLT2 knockout mice (SGLT2−/−). The mice have been observed to develop glycosuria and polyuria with a substantial decrease in fractional glucose reabsorption on evidence of clearance and free flow micropuncture measurements. Wild-type and SGLT2−/− mice do not significantly differ in glomerular filtration rate (GFR) and sodium, potassium, and chloride fractional excretion. Free flow micropuncture measurements of the total and fractional reabsorption have made it possible to understand whether sodium reabsorption is distorted by the deletion of the SGLT2 gene in the knockout mice. However, SGLT2 inhibitors have recently come to be used to suppress glucose reabsorption in proximal tubules and thereby to decrease the blood glucose concentration in treating type diabetes mellitus [15].

A phosphoproteomics analysis has shown that SGLT2 occurs in a phosphorylated form in the renal cortex. In view of this, Ghezzi and Wright [63] have studied the protein kinases that are potentially capable of affecting SGLT2 activity. Studies with HEK-293T human embryonic kidney cells have shown that PKA and PKC stimulate SGLT2 activity via phosphorylation and that insulin also stimulates the SGLT2-mediated transport of sodium and glucose, although insulin receptors have not been found in the proximal tubule. It is possible that the insulin effects observed in vivo are mediated by the IGF-1 receptors, which are expressed in the respective segment of the kidney [63].

A maximum glucose transport in the kidney is observed in patients with type 1 diabetes mellitus, which is associated with defects in glucose transporter function. Rats with alloxan-induced diabetes display an increase in SGLT2 activity and and activity of the glucose transporter GLUT2, which occurs in the basolateral membrane of the proximal tubule. In humans, the mRNA and protein levels of SGLT2 and GLUT2 are significantly higher in patients with type 2 diabetes mellitus as compared with healthy volunteers. SGLT2 inhibitors are used in medicine to treat type 2 diabetes mellitus. The induction of glycosuria and osmotic diuresis is the main effect of these drugs [64].

As mentioned above, the set of signaling compounds that play an important role in sodium excretion includes ATII, vasopressin, aldosterone, NO, ET-1, ATP, etc. [1, 15, 34, 37, 44, 46, 56]. Some of the hormones exert a biphasic effect on the kidney, depending on their concentration. With certain hormones, the physiological effect differs depending on what signaling pathway is activated as a result of the hormone–receptor interaction. Dopamine as a signaling molecule is of particular interest to consider here because its role as a natriuretic factor is poorly understood. As is well known, dopamine acts as a mediator in the nervous system and is involved in regulating locomotion, cognitive functions, and neuroendocrine secretion. Dopamine circulates in the blood in considerable amounts, but the origin of circulating dopamine and its functions outside the brain need further investigation. The kidney possesses its own intrarenal dopaminergic system, which differs from that of the nervous system. Given that blood–brain barrier exists, it is possible to expect that dopamine synthesis and functions at the periphery are independent of the role that dopamine plays as a signaling compound in the brain [65].

Dopamine: Origin and Functions

There is a renal system of dopamine synthesis. Aromatic amino acid decarboxylase (AADC) is a limiting

enzyme of dopamine synthesis in the kidney [66] and is encoded by *DDC* according to NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/1644). The dopamine content in the serum is normally of a picomolar scale, while the renal dopamine level can reach nanomolar concentrations. Endogenous renal dopamine plays an important role in regulating electrolyte balance in vertebrates by inhibiting various sodium transporters in the kidney [66–69]. Studies with lower vertebrates have shown that, when a spotted scat is transferred from marine into fresh water, the serum dopamine concentration decreases dramatically and expression of the dopamine receptor D1 (*Sa*DRD1) is activated in the proximal tubule, thus stimulating the osmoregulatory signaling cascade [65]. As for mammals, acute treatment with the D1-like receptor agonist fenoldopam induces natriuresis and diuresis in humans, rats, and mice.

Based on the molecular structure and pharmacology, dopamine receptors are divided into two classes, D1-like (subtypes D1 and D5) and D2-like (subtypes D2, D3, and D4). The D1–D5 receptors mediate the dopamine effect, are encoded by *DRD1–DRD5*, and belong to the G-protein-coupled receptor family [66].

Cells of proximal tubules release dopamine in the kidney. The dopamine effect in the kidney is mediated mostly by the D1-like receptors [66]. It is thought that only the D1-like receptors play a role in maintaining sodium homeostasis and the renal blood pressure, which is regulated by dopamine [66]. The D5 receptor has higher affinity for dopamine than the D1 receptor [69]. It is thought that the intrarenal dopaminergic system controls approximately 50% of the excreted sodium and water, and its dysfunction may therefore cause severe alterations in the regulation of the systemic blood pressure [70].

The D1 receptor is expressed on the cell surface in proximal tubules of the kidney. In contrast, the D5 receptor is expressed exclusively on primary cilia, which are on proximal tubule cells and act as sensors of the fluid flow in the kidney. Dopamine and its agonist fenoldopam have been found to play a role in regulating the length of cilia and the calcium signaling, which is necessary for the normal function of cilia. Hence, the D5 receptor has been assumed to provide a good potential therapeutic target for treating various ciliopathies associated with a decreased length of primary cilia, such as polycystic kidney, nephronophthisis (Fanconi syndrome), and other disorders [71].

However, the D2-like receptors are also expressed in the kidney. The D2 receptor has been found in the proximal tubule and distal collecting duct; the D3 receptor, in the proximal tubule, the thick ascending limp of the loop of Henle, the macula densa, the distal convolute tubule, and the glomerule; and D4, in the distal convolute tubule and the cortical and medullar collecting ducts. The D2-like receptors contribute to the inhibition of ion transport in the kidney [70].

Defects in the function of dopamine receptors of any subtype cause hypertension in mice [69]. In humans, alterations of the renal dopamine system are involved in the pathogenesis of salt-induced increases in blood pressure in some individuals [66].

Dopamine Interactions with Other Hormones

As mentioned above, renal dopamine plays an important role in regulating salt balance. Many natriuretic factors, including vasopressin and NO, exert their effects through the renal dopamine system. For instance, the idea is supported by the fact that the ANP effect on the kidney is abolished when the D1 receptor is blocked or AADC inhibitors affect the proximal segments of renal tubules. The finding is possible to explain by assuming that ANP regulates the incorporation of the D1 receptor in the plasma membrane in renal tubules [72].

Ibarra et al. [66] have shown that prolactin and dopamine have common points in the signaling cascades that mediate inhibition of Na^+/K^+-ATPase. Inhibition of Na^+/K^+-ATPase in the proximal convolute tubule by prolactin and dopamine is mediated by similar signaling pathways, which include PKC- and PKA-dependent phosphorylation of Na^+/K^+-ATPase. Prolactin fails to affect activity of the sodium–potassium pump in the presence of specific inhibitors of PKC and PKA. Prolactin-induced coimmunoprecipitation of Na^+/K^+-ATPase and PI3K is mediated by the D1 receptor [66]. The following signaling cascade leads to endocytosis of the sodium–potassium pump according to the literature. PKC phosphorylates the α1 subunit of Na^+/K^+-ATPase at Ser18 (23). The protein 14-3-3 binds to the phosphorylated motif to facilitate the interaction of PI3K with the adjacent proline-rich domain of the α1 subunit. PI3K is thus activated. Activated PI3K facilitates the AP-2 binding to the α1 subunit, leading to endocytosis of Na^+/K^+-ATPase [3].

Dopamine is known to inhibit expression of prolactin, which is one of the most important osmoregulatory hormones in fish and facilitates fish acclimation in freshwater [66, 73]. In mammals, dopamine is secreted in the paraventricular and arcuate nuclei of the hypothalamus, reaches the adenohypophysis through its portal system, and interacts with the D2 receptor on lactotrophs to trigger the signaling cascades that inhibit transcription of the prolactin gene as well as prolactin synthesis and secretion [74]. It is of interest that prolactin regulates its own secretion via negative feedback by affecting the dopaminergic neurons in the hypothalamus. Hypothalamic prolactin receptors occur on the receptors that express tyrosine hydroxylase, which is a limiting enzyme in dopamine synthesis. Prolactin released in the pituitary reaches the arcuate nucleus via circulation, dopaminergic

neurons are activated, tyrosine hydroxylase synthesis is induced, and dopamine inhibits the synthesis and secretion of prolactin [75].

The D1-like receptor has been found to interact with the cholecystokinin B receptor (CCKBR) in the proximal tubule, thus stimulating sodium excretion and urine production. In HEK-293 cells coexpressing the D5 receptor and CCKBR, agonists of the two receptors induce a combined increase in their expression at the mRNA and protein levels [69].

Gastrin has also been reported to exert a natriuretic effect, which is associated with activity of the D1 receptor in the proximal tubule. Gastrin administration through the renal artery causes diuresis and natriuresis in Wistar-Kyoto rats. The gastrin effect is abolished in the presence of antagonists of the gastrin receptor, CCKBR, and the D1 receptor [76].

The interaction of dopamine with angiotensin II is of interest to consider. Fenoldopam administered through a microcatheter into the cortical interstitial space increases expression of both the D1 receptor and angiotensin II receptor (AT2R), and elevated D1-mediated natriuresis is accompanied by an increase in the incorporation of the two receptors in the plasma membrane of cells of the proximal tubule [77]. Interestingly, mutual inhibition occurs between the D1 dopamine receptor and AT1R, which is another angiotensin II receptor isoform and is also expressed in renal tubules. When sodium intake increases, dopamine causes the incorporation of additional D1 receptors in the plasma membrane close to domains with a high Na^+/K^+-ATPase content and simultaneously affects the AT1R molecules occurring in the same domain. AT1R is released from the membrane into the cytoplasm as a result. The effect of angiotensin II is thereby suppressed. When the extracellular angiotensin II concentration increases, AT1R is again incorporated in the domain, while the D1 receptor is released into the cytoplasm. Signaling from the dopamine receptor is thereby abolished [3].

Dopamine Effect on Sodium Transporter Activity

Dopamine affects transporters in various segments of the nephron. As mentioned above, dopamine inhibits Na^+/K^+-ATPase activity through various signaling cascades, which involve cAMP/PKA, PI3K, AP-2, and tyrosine phosphatases. This results in pump suppression and a natriuretic effect [3, 68]. Endocytosis of Na^+/K^+-ATPase via the clathrin-dependent pathway in the proximal tubule depends on activation of dopamine receptors, which regulate the Na^+/K^+-ATPase traffic in the kidney. The process is associated with the PI3K/PKCζ signaling cascade. A signal for Na^+/K^+-ATPase endocytosis is provided by phosphorylation of the Na^+/K^+-ATPase α1 subunit at Ser11 and Ser18 [68]. For instance, experiments with primary cultures of ray kidney cells have shown that a knockout of the dopamine receptor D1 (*Sa*DRD1) mRNA with a small interfering RNA significantly decreases Na^+/K^+-ATPase activity [66]. Activation of dopamine receptors in the mouse kidney has been reported to cause internalization of the sodium–phosphate symporter NPt2 in the proximal tubule [78]. Gildea et al. [79] have shown that activation of the D1 receptor primarily stimulates adenylate cyclase, while the D1/D5 heterodimer modulates the function of the D1 receptor through a signaling pathway that includes PLC, thus inhibiting both apical NHE-3 and Na^+/K^+-ATPase located in the basolateral membrane [79]. Like with the D1 receptor, activation of the D3 receptor similarly leads to NHE-3 inhibition in the proximal tubules. Mice knocked out in the D3 receptor demonstrate development of hypertension and have a lower capability of sodium excretion. The mechanisms underlying the regulation of NHE-3 via the D3 receptor are still unknown. The process possibly involves ubiquitin-specific proteases (USPs), which are a group of proteases that remove ubiquitin motifs from proteins and thereby suppress their internalization and degradation. USP48, which belongs to the group, binds to the D3 receptor in human cells. Dopamine treatment has been shown to increase the ubiquitinated NHE-3 content on the surface of opossum kidney cells. Thus, activation of the D3 receptor leads to inhibition of USP48 activity, preventing the elimination of the ubiquitin moiety from NHE-3 and leading to NHE-3 degradation [56].

Mice knocked out in the D5 receptor (D5R–/–) show an increase in expression of the NKCC2, NCC, and ENaC γ subunit proteins in the thick ascending limb of the loop of Henle when fed normal and high-salt diets. Expression of the NHE-3 protein is additionally increased on a high-salt diet. An increase in expression of these sodium transporters is possibly associated with the fact that the capability of maintaining normal sodium balance is distorted in D5R–/– mice [69, 80].

CONCLUSIONS

The key sodium transporters that are involved in maintaining water–salt balance in the kidney are considered in the review. It is rather difficult to isolate individual levels in the regulation of their function. The difficulty arises because many intracellular factors are involved in modulating the transporter function at several levels and may act as common regulators of several transporters. Moreover, some participants remain unknown in the signaling cascades that affect the sodium transporters, and this fact further complicates the understanding of the mechanisms involved in their regulation.

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