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ANP-induced signalling cascade and its implications in renal pathophysiology

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Abstract

The balance between vasoconstrictor/sodium retaining and vasodilator/natriuretic systems is essential for maintaining body fluid and electrolyte homeostasis. Natriuretic peptides, such as atrial natriuretic protein (ANP) belong to the vasodilator/natriuretic system. ANP is produced by the conversion of pro-ANP into ANP which is achieved by a proteolytical cleavage executed by corin. In the kidney, ANP binds to the natriuretic peptide receptor-A (NPR-A) and enhances its guanylyl cyclase activity, thereby increasing intracellular cyclic guanosine monophosphate production to promote natriuretic and renoprotective responses. In the glomerulus, ANP increases glomerular permeability and filtration rate and antagonizes the deleterious effects of the renin-angiotensin-aldosterone system activation. Along the nephron, natriuretic and diuretic actions of ANP are mediated by inhibiting the basolaterally expressed Na^+/K^+-ATPase, reducing apical sodium, potassium and protein organic cation transporter in the proximal tubule, and decreasing the Na^+-K^+-$2Cl^-$ co-transporter activity and the renal concentration efficiency in the thick ascending limb. In the medullary collecting duct, ANP reduces sodium reabsorption by inhibiting the cyclic nucleotide gated cation channels, the epithelial sodium channel, and the heteromeric channel transient receptor potential-vanilloid 4 and -polycystin 2 and diminishes vasopressin-induced water reabsorption. Long term ANP treatment may lead to NPR-A desensitization and ANP-resistance, resulting in augmented sodium and water reabsorption. In mice, corin deficiency impairs sodium excretion and causes salt-sensitive hypertension. Characteristics of ANP resistance and corin deficiency are also encountered in patients with edema-associated diseases, highlighting the importance of ANP-signalling in salt-water balance and renal pathophysiology.

1. Introduction

Maintaining body fluid and electrolyte homeostasis is a fundamental requirement in virtually all animals. The regulation is controlled by a variety of endocrine, autocrine and neuronal factors, which can be divided into two antagonizing systems: the vasoconstrictor/sodium retaining systems, such as the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system, endothelin-1 and antidiuretic hormones; and the vasodilator/natriuretic systems, such as the natriuretic peptides and nitric oxide (NO) (94).

The natriuretic peptides were evolved in the earliest vertebrates to serve as osmoregulatory hormones (105, 106). In mammals, the natriuretic peptide system is well preserved. Three similar peptides, *i.e*. atrial, brain or B-type and C-type natriuretic peptides (ANP, BNP and CNP, respectively) have been identified. Among them, ANP and BNP are more closely related, as indicated by high sequence similarities and a shared receptor, natriuretic peptide receptor-A (NPR-A), also called guanylyl cyclase-A. ANP is produced mainly in atrial and ventricular myocytes, and secreted in response to cardiac wall stretching and various stimuli such as endothelins and alpha-adrenergic factors (29). BNP is generated mostly in cardiac ventricles and released in response to volume or pressure overload (48). The function of CNP differs from that of ANP and BNP. CNP is widely expressed in the central nervous system, the vasculature, and the bones, where it acts in a paracrine fashion by binding to a separate receptor, the natriuretic peptide receptor-B (NPR-B) to regulate cell differentiation and organ function (31, 78, 84). All three natriuretic peptides indiscriminately bind to a third receptor, NPR-C, which serves as the clearance receptor for these peptides (37).

Like many peptide hormones, the natriuretic peptides are synthesized in precursors, *i.e*. pro-forms. Proteolytic cleavage to remove the pro-peptide is an essential step to activate the natriuretic peptides. In cardiomyocytes, where most ANP and BNP are produced, the membrane-bound serine protease corin has been identified as a critical enzyme for activating the natriuretic peptides (118). Corin, however, is not involved in pro-CNP processing. It has been shown that pro-CNP processing is mostly mediated by furin, an intracellular proprotein convertase (114).

2. Corin structure and function

Corin is a trypsin-like serine protease (116). The protein contains a single-span transmembrane domain at the N-terminus, which anchors corin on the cell surface. Among normal tissues, corin is most abundantly expressed in cardiomyocytes (117). Functional studies have shown that corin is critical for activating the natriuretic peptides and regulating

salt-water balance and blood pressure (6, 116). In mice, for example, lack of corin leads to salt-sensitive hypertension (20, 111), a phenotype similar to that in ANP knockout mice (59). To date, corin gene variations and mutations have been reported in patients with hypertension and heart disease, supporting the physiological importance of corin in maintaining normal blood pressure and cardiac function (35, 38, 93, 124). Most recent studies also indicate a local function of corin and ANP in the pregnant uterus to promote spiral artery remodelling and to prevent pregnancy-induced hypertension (26). Interestingly, corin mutations that impair the natriuretic peptide processing activity have been identified in patients with preeclampsia supporting a role for corin in preeclampsia–induced symptoms (26).

3. ANP receptors and downstream signalling

NPR-A/NPR-B and NPR-C are two major types of receptors for the natriuretic peptides. NPR-A and NPR-B are membrane guanylyl cyclase receptors, whereas NPR-C lacks the guanylyl cyclase activity (70). The binding of ANP to the receptor NPR-A leads to the conversion of guanosine triphosphate (GTP) to the intracellular second messenger cyclic guanosine monophosphate (cGMP) (55, 90). The active NPR-A receptor is a homodimer. Each NPR-A monomer contains an extracellular ANP-binding domain at its amino-terminus and an intracellular guanylyl cyclase domain at its carboxyl terminus (47). Synthetized cGMPs bind to target proteins, including the cGMP-dependent protein kinases (PKG) I and II, cyclic-nucleotide gated ion-channels, and the cyclic nucleotide phosphodiesterase (11).

Two different subtypes of NPR-C with molecular masses of 67 and 77 kDa, respectively, have been identified. These receptors may bind to a broad range of ligands, including ANP, BNP and CNP. $^{4\text{-}23}$C-ANP is a cleaved form of ANP, which also binds to NPR-C, but not NPR-A or NPR-B. The 77-kDa NPR-C primarily serves as a clearance receptor for ligand internalization, whereas the 67-kDa NPR-C also participates in adenylyl cyclase activity inhibition through inhibitory guanine nucleotide regulatory protein Gi and activation of phospholipase C to exert anti-hypertensive effects (70).

Recently, both NPR-A and NPR-C were shown to mediate the effects of ANP by enhancing the Ca^{2+}/calmodulin-dependent NO synthase (NOS) activity, another factor of the vasodilator/natriuretic system with similar renal effects as ANP. It appears that these receptors may act through different mechanisms; NPR-A-induced NO production was shown to be cGMP-dependent, whereas NPR-C-dependent NO release was partially mediated by Gi protein (41, 42).

4. Renal expression of ANP-signalling cascade components and its functional implications

Within the kidney, components of the ANP signalling cascade are widely expressed and antagonize the vasoconstrictor/sodium retaining system by affecting the activity and expression of various transporters, channels and other signalling components (Figure 1).

4.1. Glomerulus

Within the glomerulus, corin expression was undetectable (43), suggesting that glomerular ANP production and activation are negligible, if any. ANP from the circulation, however, may act on glomerular epithelial and mesangial cells (21, 66). The receptor NPR-A has been localized to the surface of podocytes and mesangial cells (82, 103). Attributed renal actions of ANP include the regulation of the glomerular filtration rate (GFR) and glomerular permeability. ANP-induced increases in GFR and filtration fractions have been reported in numerous studies [for review see (52)]. This function has been suggested to occur by raising the capillary glomerular pressure through relaxation of the afferent arteriole and contraction of the efferent arteriole (40). ANP was also shown to cause a rapid (within 5 min) increase in glomerular permeability (7). Analysis of the glomerular filtration barrier revealed that ANP directly and in a reversible manner increases the radius and the number of large glomerular pores without affecting the charge selectivity. As a result of the augmented glomerular permeability, ANP may induce microalbuminuria, which is associated with many diseases such as diabetes and congestive heart failure (CHF) (7, 125).

The ANP-induced cGMP production and its functional consequence are not fully understood. It may involve reorganization of F-actin filaments, thereby causing cellular relaxation (101). The possible function of podocytes in this process remains to be elucidated. Mesangial cells express NPR-A and respond to ANP with strong elevations in intracellular cGMP (10). ANP may also relax mesangial cells by increased hyperpolarisation, leading to an increase in ultrafiltration coefficient associated with augmented glomerular hydrostatic pressure, GFR and filtration fraction (52).

Additionally, the endogenous ANP/NPR-A/cGMP system may have pleiotropic and renoprotective properties (82) by antagonizing the RAAS. Ogawa et al. (82) demonstrated that an aldosterone-induced glomerular injury led to more severe proteinuria and fibrotic changes in NPR-A knockout mice than control wild-type mice. The authors proposed that ANP-induced NPR-A activation may inhibit local extracellular signal-regulated kinase and p38 mitogen-activated protein kinase signalling pathways as well as the formation of reactive oxygen species. Another possible mechanism underlying the aldosterone-antagonizing

effects of ANP was reported recently. In transfected human embryonic kidney cells, ANP attenuated the aldosterone-induced nuclear translocation of the mineralocorticoid receptor (MR) via NPR-A/cGMP-dependent PKGI, resulting in an association of NPR-A with the MR and thus preventing MR activation (75). Furthermore, the importance of the balance between the RAAS and the ANP systems is demonstrated by an Ang-(1-9)-induced ANP secretion from cardiomyocyte in an AT2-receptor-dependent manner involving phosphoinositide kinase 3, Akt, NO, and cGMP (19). Thus, the balance between the RAAS and the ANP-induced signalling cascade may be regulated through receptor interactions, hormone secretion and intracellular signalling pathways.

4.2. Proximal tubule

In the proximal tubule, corin was localized to the apical membrane of the endocytic apparatus and in the brush border membrane (BBM) of rodent kidneys (89) as well as in human kidneys (43). The particular corin expression pattern suggests the cleavage of filtered and locally produced pro-ANP into active ANP. In this nephron segment, local production of ANP mRNA was detected by in situ hybridization (67, 89). Natriuresis elicited by ANP has been attributed to the inhibition of sodium reabsorption at both proximal (122) and distal nephron segments including the collecting duct. ANP may promote natriuresis without altering GFR (96). Lithium clearance studies showed that ANP inhibited proximal tubular sodium reabsorption (17, 50), in part by counteracting angiotensin-stimulated sodium reabsorption (51). ANP also inhibits several Na^+-dependent transport systems, such as the Na^+/H^+-exchanger (112) and type IIa Na/Pi co-transporter (8). The Na^+/K^+-ATPase plays a pivotal role in sodium reabsorption in all tubular segments including the proximal tubule. It has been shown that the Na^+/K^+-ATPase is an ANP target (4, 15) and that the inhibition of the Na^+/K^+-ATPase by ANP is mediated, to a large extent, via renal dopamine 1-like receptors. Among other transports that may be regulated by ANP include protein organic cation transporter and Cl^- and K^+ channels (28, 53, 54, 76).

4.3. Distal tubule

Within the distal tubule, corin is highly expressed in vesicles near the apical plasma membrane of medullary thick ascending limb (89), where it is believed to cleave locally produced pro-ANP (67, 89). Cytochemical localization revealed a plasma membrane expression of NPR-A in the thick ascending limb upon ANP treatment (92). In this nephron segment, ANP was shown to inhibit Cl^--transport in a cGMP- and PKG-dependent manner (9, 80). Furthermore, increased intracellular cGMP levels were shown to directly inhibit Na^+-K^+-$2Cl^-$ co-transporter (NKCC2) activity (85, 86) by decreasing its apical surface expression through a mechanism mediated by cGMP-stimulated phosphodiesterase 2 (PDE2) (5).

Presumably, this effect may affect NKCC2 trafficking by PDE2-mediated reduction in cAMP and subsequently protein kinase A levels. Thus, ANP may inhibit NKCC2 and reduce urine concentrating capacity, thereby increasing urine excretion. It also has been shown that ANP may initiate Ca^{2+} transients in isolated cortical thick ascending limbs. This activity appeared to be mediated by NPR-C (27). ANP-dependent NPR-C activation is known to activate phospholipase C and release NO. The functional implication in ANP-mediated NO release remains to be determined.

4.4. Collecting duct

In the collecting duct system, corin was identified within the apical plasma membrane and apical vesicles (89). The signal intensity increased towards the medulla. Like in the nephron segments, local ANP mRNA and protein expression was detected. Moreover, all components of the ANP-induced signalling cascade could be identified within the inner medullary collecting duct (IMCD). Immunohistochemical studies localized NPR-A to the apical membranes of IMCD (45), and the cGMP-stimulated phosphodiesterase 5 (PDE5) and protein kinase G II (PKGII) in the cytosol (89, 104).

It is well established that the medullary collecting duct is the main site of ANP action in promoting sodium excretion (122). The current data indicate that ANP regulates Na^+ reabsorption at both the apical and basolateral sides in IMCD. As in the nephron segments, sodium reabsorption in principal cells of the IMCD consists of passive Na^+ entry through the apical membrane and active pumping into the peritubular space by the basolateral Na^+,K^+-ATPase. The epithelial sodium channel (ENaC) is the main sodium channel for sodium entry and is characterized by low conductance (4-5 pS) with high specificity for Na^+ over K^+ (>20 fold), which is inhibited by amiloride (18, 102).

Current data on cGMP/PKGII-induced ENaC activation are less conclusive. In single-patch clamp studies with Xenopus 2F3 cells, ANP and 8-pCPT-cGMP were shown to decrease the open probability of ENaC in an NPR-A-dependent manner (49). Long term ANP treatment, however, induced a translocation of ENaC into the apical membrane presumably to prevent sustained natriuresis after prolonged ANP exposure (110).

In addition to ENaC, another type of sodium channel exists in principal cells of the collecting duct, *i.e.* the cyclic nucleotide gated cation channels (CNG) (24, 71, 72). CNG channels have a higher conductance (28 pS), transport Na^+, K^+ and $NH4^+$ with similar affinities, and are inhibited by cGMP, amiloride and diltiazem (24, 71, 72). It has been shown that cGMP inhibits these channels by PKG-dependent channel phosphorylation and allosteric changes

(71). It is possible, therefore, that CNGs may serve as another ANP target in promoting sodium excretion (Figure 2).

At the basolateral site of IMCD, ANP is known to inhibit Na^+/K^+-ATPase activity through PKGII-induced phosphorylation and in a cGMP-dependent manner (Figure 2) (15, 44, 98). Moreover, ANP was shown to modulate transepithelial water transport in collecting duct cells. In isolated rat and rabbit CCD, short term ANP treatment reduces vasopressin-stimulated water permeability (33, 79). Furthermore, in vasopressin-pre-treated cells ANP markedly decreased the kinetics of cell swelling, which was mimicked by 8-bromo-cGMP and blunted by PKGII inhibition. ANP also reduced vasopressin-induced phosphorylation of aquaporin-2 (AQP2) at position S256 (64). However, in untreated collecting duct cells, long-term ANP treatment induced an AQP2 translocation into the apical membrane followed by increased phosphorylation, which may increase transepithelial water flux (14, 110). Thus, similarly as shown for ENaC, prolonged ANP actions favour volume retention.

Another mechanism of ANP-dependent natriuresis has been proposed recently and may involve the inhibition of flow-activated Ca^{2+} entry into collecting duct cells (Figure 2) (39). The transient receptor potential vanilloid 4 (TRPV4) and the transient receptor potential polycystin 2 (TRPP2) were shown to form a heteromeric channel complex in cilia, a crucial structure for flow sensation. It was found that ANP, cGMP and PKGII inhibited Ca^{2+} entry through their action on heteromeric TRPV4-P2 channels. PKGII was shown to phosphorylate the channel complex on $TRPP2^{T719A}$ and $TRPP2^{S827A}$, thereby inhibiting the channel complex formation and preventing the flow-induced Ca^{2+} entry in to CCD cells. These findings are intriguing. Further studies are needed to elucidate the influence of intracellular Ca^{2+} levels on sodium absorption.

5. Regulation of ANP-cascade components

ANP, corin and NPR-A expression pattern are mainly regulated by varying their transcription rate. The involved transcription factors as well as factors modulating their action have been identified in the past years.

GATA transcription factor family members, particularly GATA-4 and -6, and T box factor 5, have been shown to play an important role for ANP gene expression in cardiac myocytes. GATA-4 functionally synergizes with transcription factors GATA-6, MEF-2, dHAND, SRF, Nkx2.5 and YY1 (48). The phosphorylation of GATA-4 by p38 mitogen-activated protein kinase (MAPK) was shown to increase the binding affinity of GATA-4 to the ANP promoter, thereby promoting ANP gene expression (48). Other factors modulating ANP gene

expression include α-adrenergic agonists, endothelin, prostaglandin F2α, growth factors, vitamin D, retinoids, glucocorticoids, mechanical strain, and hypoxia (48).

In the corin gene promoter, similar conserved binding sites for Tbx5, GATA, Nkx2.5 and Krüppel-like transcription factors have been identified (34). GATA-4 appears to be the major transcription factor in the heart accounting for increased corin and ANP gene expression under hypertrophic conditions (115). Transcription factors controlling renal corin and ANP expression pattern as well as factors modulating the promoter activity in the kidney remain to be determined.

The NPR-A gene expression is regulated primarily by Sp1 possessing three binding sites in the promoter region, as determined by mutational analysis (48). A number of factors have been reported to regulate the NPR-A gene promoter activity, which includes vitamin D, angiotensin II, endothelin, osmotic stimuli, endothelial NOS, p38 MAPK (48) and serum and glucocorticoid inducible kinase 1 (23). Interestingly, ANP was demonstrated to negatively regulate NPR-A promoter activity and gene expression via a cGMP-dependent mechanism involving cGMP-response element-binding protein (CREBP) (74). CREBP is widely distributed in human tissues with high abundance in the heart and was found at low levels in the kidney.

Phosphorylation is another important mechanism in regulating NPR-A activity (99, 120). Binding of ANP to NPR-A induces a homologous desensitization of NPR-A which correlates with a complex phosphorylation pattern of the receptor. Under steady state conditions, NPR-A is highly phosphorylated at multiple sites on its intracellular domain including Ser473, Ser487, Ser497, Thr500, Thr502, Thr506, Ser510 and Thr513. ANP-provoked desensitization was accompanied with increased phosphorylation at Ser487, whereas at the other sites dephosphorylation occurred. Performing functional analysis of Ser487 using site-directed mutagenesis revealed that phosphorylation at this site blunts the NPR-A activation but also prevents further desensitization (99, 119). It is believed that ANP-mediated NPR-A-desensitization is one of the reasons for the receptor resistance in the presence of high circulating ANP levels.

6. Mechanisms in ANP Resistance

In many edematous disease states, ANP-induced signalling components may be improperly regulated and thereby prevent the natriuretic action of ANP. In fact, the ANP resistance is a hallmark of diseases such as CHF (22), liver cirrhosis (68, 77), and nephrotic syndrome (87, 107, 108), which are commonly associated with sodium retention. In these diseases,

cumulative sodium retention often leads to edema and ascites. As an underlying mechanism a maladaptive renal response to compensate edematous disorders has been identified and reduced ANP response and a dysregulated ANP-induced signaling was found (25, 65, 81, 91, 95).

In animal models of and patients with CHF, liver cirrhosis and proteinuric kidney disease, attenuated or reduced urine flow rate and decreased urinary sodium excretion are common (12, 22, 30, 32, 46, 57, 58, 61, 69, 73, 113). Increased circulating ANP levels often correlated with the severity of the disease (16, 68, 87, 100). Under these pathological conditions, the renal response to pharmacological ANP infusion was markedly attenuated (22, 83, 87, 88, 107). In fact, the lack of a proper renal response to ANP is a pathological feature, but the underlying mechanism remains controversially discussed. It has been suggested that the ANP resistance may be due to decreased ANP availability and/or NPR-A desensitization at the renal site.

To date, reduced uterine, cardiac and renal corin level and/or activity have been found in animal models of and patients with preeclampsia, heart failure and nephrotic syndrome (56, 89, 109). These findings suggest that corin deficiency may impair the ANP signaling pathway, contributing to the ANP resistance in these diseases. In addition, there is growing evidence that PDE5 up-regulation may also play a role in the ANP resistance. PDE5 is known to degrade cGMP. In chronic cardiovascular diseases, liver cirrhosis or nephrotic syndrome, increased PDE5 levels have been associated with decreased renal cGMP levels, which may contribute to ANP resistance and sodium retention in patients (1, 3, 87, 107).

The renal origin of volume retention has been located in the collecting duct, which involves increased activation of the Na^+/K^+-ATPase (2, 36, 73) and augmented expression and apical membrane targeting of ENaC subunits (60, 61, 123). In liver cirrhosis, this increase was shown to occur early in disease progression and was reduced subsequently, probably as a counter regulatory mechanism (62). It remains unclear whether $Na^+/K^+/2Cl^-$ and Na^+/Cl^- co-transporter contribute to volume retention under these disease conditions (60, 97, 121).

In rats, long-term ANP infusion induced AQP2 and ENaC trafficking into the apical membrane (110). Similarly, ANP- and cGMP-stimulated $mpkCCD_{cl14}$ cells led to increased membrane insertion of AQP2 (13). It is possible that in edematous conditions with high circulating ANP levels, the augmented membrane availability of ENaC and AQP2 may promote sodium and water retention and may therefore, at least partially, be accountable for the accompanied formation of edema and/or hypertension.

Corin is the rate limiting enzyme for ANP activation. Recently, reduced corin levels were found in kidneys of proteinuric rats (89) and patients with chronic kidney disease (43). So far, no data have been reported regarding the renal expression levels of the ANP-induced signaling components in patients with or animal models of CHF, liver cirrhosis and preeclampsia. Analysis of kidneys from corin knockout mice revealed a paradoxical increase of medullary PKGII, PDE5 and ENaC β-subunit, whereas ENaC α- and γ–subunits as well as Na^+/K^+-ATPase expression levels remained unchanged (89). Corin knockout mice developed salt-sensitive hypertension, which was caused by impaired sodium excretion and increased water retention (111). This phenotype was corrected by amiloride treatment; treatment with amlodipine, a Ca^{2+}-channel inhibitor or losartan, an AT1-receptor blocker had no such effect. These data suggest a potential role of ENaC in inducing a salt-sensitive hypertension in corin knockout mice. Similarly, kidneys of proteinuric rats had increased levels of PKGII and PDE5 in the medullary collecting duct (Figure 3). It remains unclear how corin reduction and/or the increase in PKGII and PDE5 lead to ENaC activation. Further studies are needed to elucidate the underlying molecular mechanism.

Summary and perspectives

Corin and ANP play an important role in regulating body fluid and electrolyte homeostasis. Components of the ANP signaling cascade are expressed in the glomerulus and along the nephron to exert natriuretic, diuretic and renoprotective effects. The main natriuretic and diuretic ANP actions occur in the medullary collecting duct via its receptor NPR-A. Dysregulation of the ANP-induced signaling cascade may impair sodium and water excretion. In this context, reduced corin activity, as the rate limiting enzyme for ANP production, and altered expression levels of ANP signaling components have been found in animal models and patients with ANP resistance and sodium and water retention. There are many open questions which need to be addressed in future. For example, what is the importance of the renal *vs*. the cardiac corin-ANP system on renal ANP-induced natriuresis and diuresis? What are the molecular mechanisms of long term ANP treatment leading to augmented ENaC and AQP2 membrane availability? How is the expression level of corin and ANP signaling components in CHF, liver cirrhosis or preeclampsia? How is the time course of expression level of corin and ANP-induced signaling components in edematous diseases? How may dysregulated ANP signaling cascade components contribute to the ANP resistance commonly observed in patients with edematous diseases? Further studies to answer these questions will help understanding the role of corin and ANP in sodium homeostasis and renal pathophysiology.

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Figure legend

Figure 1. Distribution of ANP production and corin expression along the nephron. In renal epithelia ANP mRNA was encountered together with corin expression in the proximal tubule, medullary thick ascending limb and medullary collecting duct (purple), suggesting an immediate activation of pro-ANP and subsequent paracrine signalling. Additional ANP mRNA without corin expression was found in podocytes, connecting tubule and cortical collecting duct (red) where a downstream activation of the secreted pro-ANP is necessary.

Figure 2. ANP-induced action in medullary collecting duct cells. Urinary ANP binds to its receptor NPR-A and thereby induces the conversion of GTP to cGMP. cGMP inhibits apically sodium entry through the cyclic nucleotide gated channels (CNG), heteromeric channel of transient receptor potential V4 (TRPV4) and -P2 (TRPP2) and basolaterally through the Na^+/K^+-ATPase (NKA) and thereby promoting natriuresis.

Figure 3. Effects of reduced renal corin expression in nephrotic syndrome. Reduced renal corin expression leads to increased pro-ANP and reduced ANP levels through diminished pro-ANP processing. The decreased ANP levels result in reduced conversion of guanosine triphosphate (GTP) into cyclic guanosine monophosphate (cGMP). The downstream impact on the signaling cascade involves increased phosphodiesterase 5 (PDE5) and phospho-PDE5, increased protein kinase G II (PKGII) and increased expression level of β-ENaC, which may lead to overall sodium and volume reabsorption/retention. This figure is adapted from an illustration in a commentary by J. Klein (63).