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# ANP and Urodilatin: Who is who in the Kidney

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**Abstract**
Mounting evidence suggests that urodilatin, not atrial natriuretic peptide (ANP) is the responsible peptide in regulation of renal $Na^+$- and water homeostasis. Following the discovery of ANP this peptide was thought to be responsible for the induction of natriuresis and diuresis in the mammalian kidney. However, the isolation of urodilatin from human urine and substantial work contributed to a better understanding of the renal physiology of these two natriuretic peptides. Indeed, subsequent elucidation supported that urodilatin rather than ANP seems to be the natriuretic peptide responsible for the regulation of $Na^+$- and water homeostasis in the kidney. Urodilatin – synthesized and secreted from the distal tubules of the kidney - may act as a paracrine mediator when secreted into the lumen. In contrast, while the role of ANP as regulator of the cardiovascular system is established, its physiological regulatory role on transport processes in the nephron is questionable. This review attempts to analyze the roles of both ANP and urodilatin and to discuss new potential candidates which may also play a role in electrolyte and water handling in the kidney.

## ANP and Urodilatin: Discovery and Isolation

In 1969, Lockett and coworkers were the first to support an idea that was postulated earlier, namely that the heart is involved in the regulation of renal functions [61]. When the group of Sonnenberg applied atrial extracts into rats a strong diuresis and natriuresis was induced [17]. The relaxant effect of these atrial extracts on vascular smooth muscle was independently observed by Currie's as well as our group [29] [14]. With the establishment of the biological assay, namely smooth muscle relaxation, different groups isolated bioactive substances from cardiac atria of the rat [28], pig [29] and human [51].

Preliminary observations that ANP-immunoreactivity in blood and in urine did not correlate under physiological and pathophysiological conditions led to the idea that another natriuretic peptide is present in urine, however, cross-reacting with the ANP antibody. Based on this idea, ANP radioimmunoassay accompanied by a smooth muscle relaxation bioassay was used to isolate another putative natriuretic peptide. In fact, in 1988, out of 1,000 L of human urine our group discovered a natriuretic peptide which was named "urodilatin". This peptide is identical to the circulating form of ANP except for 4 extended amino acids at the N-terminus [77].

## ANP and Urodilatin: Structure and Receptors

The circulating form of ANP consists of 28 amino acids where 17 form a ring structure due to a disulfide bridge between two cysteine residues (see also Fig. 1). Urodilatin has an identical structure except for an extension of four additional amino acids at the N-terminus (threonine, alanine, proline, and arginine). Breaking of the disulfide bridge immediately leads to an inactivation of these peptides.

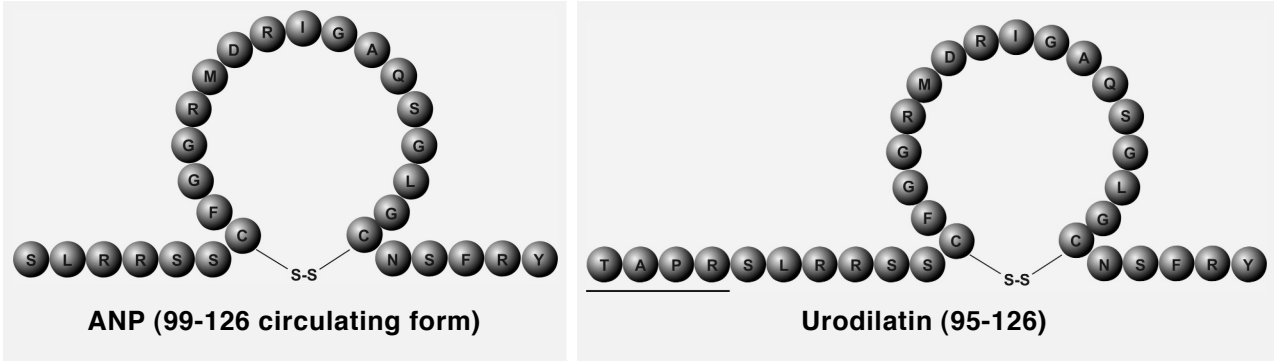


*Fig. 1.* Amino acid sequences of circulating ANP (99-126) and urodilatin (95-126). Urodilatin differs from ANP by an N-terminal extension of four amino acids (indicated by a black bar).

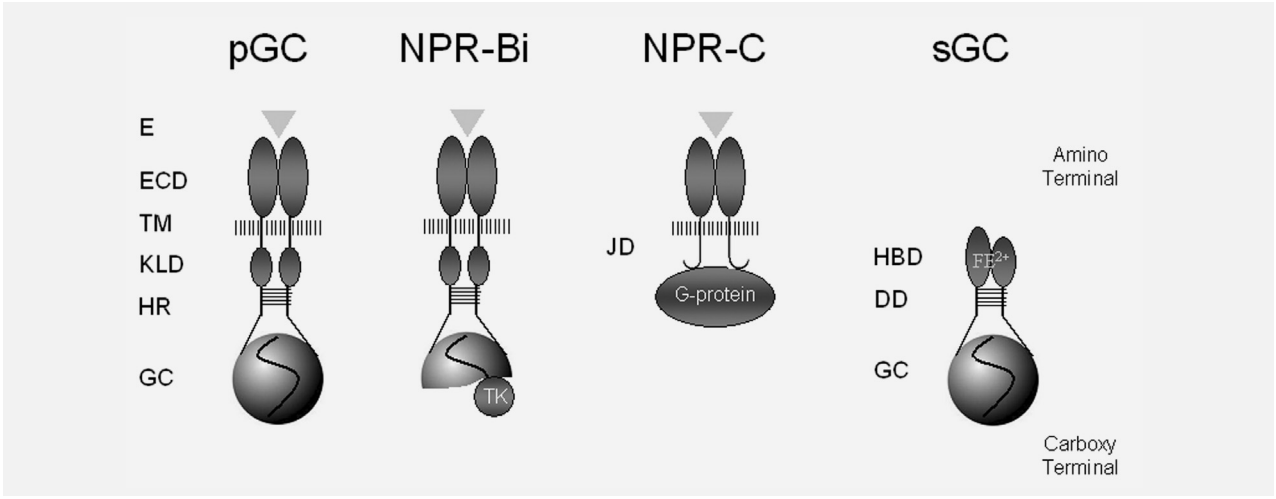


*Fig. 2*. Structural models of guanylate cyclases. Compared are structures of particulate (pGC) and soluble (sGC) guanylate cyclases as well as truncated receptors with no functional guanylate cyclase domain (NPR-Bi) or no GC-domain at all (NPR-C). The family of particulate guanylate cyclases (GC-A=NPR-A, GC-B=NPR-B, GC-C, GC-D, GC-E, GC-F, GC-G=GC-1) are homodimeric and possess a single ligand binding site. The effector (E) for GC-A are the natriuretic peptides ANP, BNP and urodilatin, for GC-B CNP and for GC-C guanylin, uroguanylin and the heat-stable enterotoxin STa from Escherichia coli. For the GC repeptors GC-D to GC-G (not shown in sketch) the ligand is unknown. They all share common motives: the effector binding site in the extracellular domain (ECD), the transmembrane domain (TM) followed by the kinase-like domain (KLD), the hinge region (HR) and the catalytic domain of the guanylyl cyclase (GC). The GC receptors GC-C to GC-F possess an additional carboxy-terminal tail which is missing in GC-A and GC-B and thus, not displayed in this sketch. The NPR-Bi receptor is a splice variant of the GC-B receptor which was cloned from human kidney cells but can also be found in various human tissues. It does not contain a functional catalytic guanylate cyclase domain. The signal transduction pathway of this receptor has not been identified yet but it may have a tyrosine kinase-like activity (TK). The NPR-C or clearance receptor is bound by all natriuretic peptides. It misses the kinase-like domain, the hinge region and the catalytic domain of the guanylate cyclase but is able to couple to a G-protein and a cAMP-mediated pathway has been described for this receptor. The soluble guanylate cyclases (sGC) form heterodimers where the amino-terminal a- and b-subunits form the heme-binding domain (HBD) with a ferrous ($Fe^{2+}$) core. Additionally the sGC possess dimerization domains (DD) and carboxy-terminal catalytic guanylate cyclase domains (GC).

Both peptides bind to transmembrane receptors containing an intracellular guanylate cyclase activity and generate intracellular cyclic guanosine monophosphate (cGMP) when activated [87]. Several guanylate receptors have been identified and cloned in mammalia so far [33, 42, 55, 62, 65]. ANP and urodilatin as well as BNP (brain natriuretic peptide) bind to the guanylate cyclase receptor type A also known as natriuretic peptide receptor type A (GC-A, NPR-A). Besides this recepetor there is also a type B receptor (GC-B, NPR-B) to which CNP binds (C-type natriuretic peptide) and a type C receptor (GC-C) which is bound by the related peptide hormones guanylin and uroguanylin as well as by the heat-stable enterotoxin of Escherichia coli (STa). This receptor can be found in the intestine and when bound by STa it causes severe diarrhea [76]. GC-D, GC-E, GC-F and GC-1 (=GC-G) are orphan receptors for which their respective activators are not known yet [32, 42, 92].

Besides the particulate guanylate cyclase receptors there is also a soluble form, GC-S, that is activated intracellularly via nitric oxide (NO) or NO-containing substances such as nitro-vasodilators [18, 49].

All known natriuretic peptides (ANP, BNP, CNP and urodilatin) have the ability to bind another important receptor which lacks guanylate cyclase activity (NPR-C) and was thought to be solely a clearance receptor for these peptides [13]. Lately, it was shown that this receptor has also the ability to couple its cytoplasmic domain to a pertussis toxin-sensitive G-protein [67] and can either inhibit [1] or activate adenylate cyclase activity [80] or endothelial nitric oxide synthetase (eNOS) in smooth muscle [68, 69].

The latest member of this receptor family is a splice variant of the NPR-B/GC-B receptor called NPR-Bi [44]. Due to an insertion of 71 bp, which represents intron sequences, a frameshift mutation is generated and alternative splicing leads to a functional receptor without guanylate cyclase activity [44]. Recently, this natriuretic peptide receptor was demonstrated to act most likely as a tyrosine kinase [46].

An overview of the different natriuretic peptide receptors is given in Figure 2.

## Physiological and Pharmacological Actions of ANP and Urodilatin in the Different Segments of the Kidney

Over the years the direct and indirect actions of ANP have been investigated to better understand the mechanism of natriuresis and diuresis regulation in the kidney. So far, a number of studies reported an increase in glomerular filtration rate (GFR) and filtration fraction after ANP application [9, 23, 52]. Furthermore, effects on the renal vasculature were reported [64] and changes of lumen diameter of arcuate arteries as well as afferent and efferent arterioles due to ANP could be visualized [30]. ANP may also be responsible for

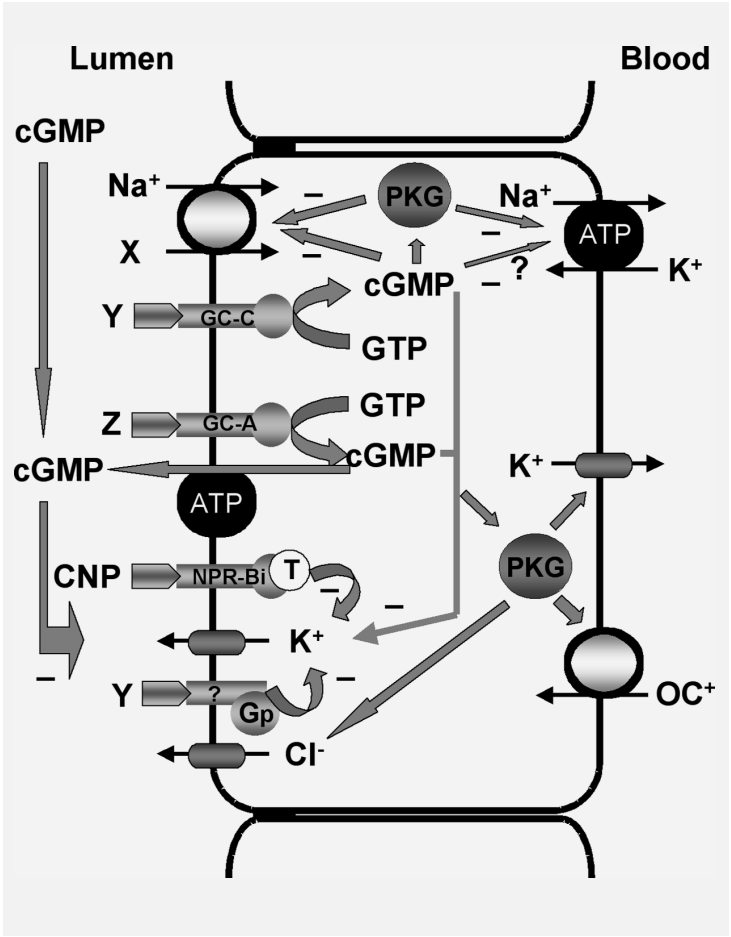


*Fig. 3*. Cell model of the proximal tubule. Shown are transport systems that are regulated by natriuretic peptides and their second messenger cGMP as well as novel pathways by newly identified natriuretic peptide receptors. In the luminal membrane $Na^+$-dependent transport proteins are located. X stands for protons, glucose, phosphate, and amino acids. Furthermore, a $K^+$-channel and a $Cl^-$-channel are found in this membrane. Important is also a specific cGMP-transporting pump. Four different receptors for natriuretic peptides have been described for this membrane so far: GC-C, which is bound by guanylin or uroguanilyn as well as STa (Y); GC-A, which is bound by ANP, BNP or urodilatin (Z), NPR-Bi, a novel receptor with a dysfunctional guanylate cyclase domain but tyrosine kinase activity is bound by CNP, and another receptor which lacks a guanylate cyclase domain but is coupled to a pertussis-sensitive G-protein and could be NPR-C. This receptor is also bound by guanylin and uroguanylin (Y). When any of these receptors is activated the $K^+$-channel is downregulated by all mechanisms. Furthermore, if intracellular cGMP is generated it can be pumped into the lumen where it can inhibit the channel from the outside. cGMP which is released from mesangial cells into the lumen can inhibit this channel from the outside as well. When intracellular cGMP activates a cGMP-dependent protein kinase (PKG) it can activate the basolateral $K^+$-channel, the basolateral organic cation transporter and the luminal $Cl^-$-channel. Furthermore, it can inhibit the basolateral $Na^+/K^+$-ATPase and some of the luminal $Na^+$-dependent transport systems. The inhibitory effects can be mimicked by cGMP alone.

the relaxation of mesangial cells due to an activation of a $K^+$-conductance leading to a hyperpolarization of these cells [11]. Mesangial cells possess the GC-A receptor and react to ANP exposure with strong elevations in intracellular cGMP [5]. A relaxation of mesangial cells will lead to an increase in ultrafiltration coefficient (Kf) and thus, to an increase in glomerular hydrostatic pressure, GFR, and filtration fraction [31].

## Proximal Tubule

In the search for an explanation of the mechanisms behind the ANP-induced natriuresis and diuresis researchers also focussed on the tubular system looking for direct effects of ANP on ion transport. Harris and coworkers were among the first to report an inhibitory effect of ANP on angiotensin II stimulated fluid reabsorption in the proximal tubule [38]. With the introduction of patch clamping and molecular biology more reports showed that ANP had direct effects on transport systems in various parts of the nephron. In the proximal tubule, ANP inhibits several $Na^+$-dependent transport systems, such as the $Na^+/H^+$-antiporter which is responsible for 50% of the $Na^+$-intake in this segment [90]. Furthermore, Murer and colleagues demonstrated that ANP had a stimulatory effect on the retrieval of membrane vesicles from the plasma membrane containing the NaPi-type IIa transporter, thus, decreasing $PO_4^{3-}$-uptake [3] quite similar to the mechanism reported for the $Na^+$-glucose transporter SGLT1 [43]. ANP in addition with endothelin-3 is capable to drastically reduce the activity of the high-capacity $Na^+$-glucose transporter SGLT2 [63] which accounts for 90% of the $Na^+$-coupled sugar uptake in the proximal tubule [91]. The $Na^+/K^+$-ATPase, responsible for essentially all secondary active processes, is also a regulatory target of ANP in the proximal tubule [2, 8]. But not only $Na^+$-dependent processes are regulated via ANP. Among the targeted transport proteins organic cation transporters, $Cl^-$- and $K^+$-channels can be found [15, 44, 48, 70]. For an overview of regulated processes in the proximal tubule see also Figure 3.

## Loop of Henle

Only little is known of the actions of ANP in the Loop of Henle. Among the reports that show clear effects is a decrease in $Cl^-$-reabsorption [4] and again an inhibition of the $Na^+/K^+$-ATPase [86]. The reason for the few reports might be the low response of the cells in this section to cGMP-stimulating agonists and thus, low cGMP formation [12, 54].

## Distal Tubule and Collecting Duct

Recently, it was shown in HEK-293 cells, which resemble distal tubule cells and are able to release urodilatin, that ANP was able to inhibit a $K^+$-conductance and this effect could be potentiated when genistein, a

tyrosine kinase blocker, activated a different $K^+$-conductance in these cells [45].

Since the collecting duct system is responsible for the fine regulation of $Na^+$-transport and the place for water reabsorption, this should be the nephron segment where ANP displays its fundamental actions. The water permeability is increased when vasopressin activates a cAMP-dependent protein kinase (PKA) and raises the intracellular cAMP levels, thus providing the signal for the incorporation of membrane vesicles that contain AQP-2 molecules [50]. It has been shown before that the vasopressin effect can be counterregulated by ANP [19]. Furthermore, it was demonstrated for several cell types that natriuretic peptides can decrease the intracellular cAMP levels by activation of the NPR-C receptor and its coupled G-protein [1] or by regular cGMP increase and activation of cyclic adenosine monophosphate (cAMP)-sensitive phosphodiesterases [7, 81]. For the cortical part of the collecting duct it was convincingly shown that ANP had neither any effect on $Na^+$-transport nor on electrogenic electrolyte transport in principal cells [75]. On the other hand, ANP does regulate the acid/base-household of intercalated cells via inhibition of the $Na^+/H^+$-exchanger [42]. In the inner medullary duct ANP inhibits transport-dependent oxygen consumption ($QO_2$) and blocks the $Na^+$-entry into these cells [93], most likely via inhibition of an apically located non-selective cation channel [60, 71].

## Renal Sodium Handling Through ANP and Urodilatin: Which Peptide is the Main Driving Force?

Shortly after the discovery of ANP, first data supported that ANP is the physiological natriuretic peptide. It was shown that ANP (a) is released into the blood stream and in greater quantities when atrial pressure increases [35] (b) that renal collecting duct cells contain high-affinity binding sites for ANP [16] (c) that ANP in pharmacological doses causes rapid development of an impressive natriuresis [82], and (d) that intravascular volume expansion with saline causes an increase in circulating ANP and a natriuresis [78]. However, first hints that ANP may not be the physiological regulator of $Na^+$-excretion came from a study in which left atrial pressure was elevated in two groups of dogs, one normal and the other cardiac denervated. The elevated atrial pressure increased circulating ANP by comparable amounts in each group of dogs, however, only the normal dogs developed a diuresis and natriuresis during these experiments [36] indicating that the renal response induced by atrial distension required intact cardiac nerves and not the release of ANP. A study investigating the circadian rhythm of plasma ANP demonstrated that there was no relationship between NaCl and circulating ANP levels [89].

After the isolation of the natriuretic peptide urodilatin from human urine and the establishment of a reliable assay system to detect this peptide, more and more data were generated supporting the view that in fact not ANP but urodilatin seems to be the responsible natriuretic peptide in renal $Na^+$-handling. In one of the first studies Drummer and coworkers investigated circadian body fluid regulation and the effects of an acute saline infusion on fluid and electrolyte metabolism [22]. Interestingly, they found that not ANP in plasma but urodilatin in urine closely correlated to the observed natriuretc responses. The same group demonstrated that the natriuresis following the ingestion of meals with different salt concentrations was accompanied by an increase in urodilatin excretion rather than an elevation of circulating ANP [21]. These data were consistent with reports showing that a stepwise increase in $Na^+$-diet induces a stepwise increase in natriuresis [66] and long term elevations of dietary $Na^+$ produce parallel increases in urinary urodilatin excretion rather than increases in plasma ANP concentrations [39]. Also a negative correlation between plasma ANP and renal $Na^+$-excretion was observed during left atrial distension in the cardiac-denervated dogs [34]. In total, this line of evidence suggests that urodilatin rather than ANP is the member of the natriuretic peptide family that is primarily involved in the physiological regulation of renal $Na^+$-excretion. In contrast, due to the rapid ANP secretion as response to certain cardiovascular stimuli and due to several effects on the cardiovascular system, it seems reasonable to postulate that ANP's primary target is the cardiovascular system and not the kidney.

## Regulation of Urodilatin Release from Distal Tubule Cells

Since urodilatin was isolated from human urine and has not been found in plasma [20] it is suggested that the peptide is synthesized, processed and secreted by the kidney. Studies have provided evidence that an ANP prohormone-like peptide is produced and secreted by primary cultures of neonatal and adult rat kidney cells [73]. With immunohistochemical and immunoassay techniques, it was shown that natriuretic peptides are synthesized in distal cortical tubular cells [27, 73] and that the synthesis is modulated in some pathophysiological situations in the rat [57]. In the human kidney, immunohistochemical analysis demonstrated that urodilatin is present in distal tubular cells [41]. There have also been reports claiming that the gene for ANP is expressed in rat kidney, although the mRNA of ANP is present only at a very low abundance in rat kidney tissue [37, 58]. Taken together, these data suggest that urodilatin is produced by distal cortical tubular cells and is secreted luminally into the urine to induce natriuresis by interaction with GCA (NPR-A), localized on inner medullary collecting duct cells [26].

However, the precise mechanisms regulating urodilatin production and excretion and its definite physiological role still remain to be defined. Our group investigated the effects of exogenously applied urodilatin in an isolated perfused rat kidney preparation [53]. We observed that the natriuretic and diuretic properties of urodilatin and ANP are coupled to the prevailing renal perfusion pressure, leading to an increased natriuretic response with higher pressures. Sehested and coworkers investigated patients after uncomplicated cardiac surgery. They observed that urine flow, urodilatin excretion, and diastolic blood pressure were positively correlated [79]. These findings may be

influenced by the confounding effects of surgery and cardiopulmonary bypass and, therefore, cannot prove that this interaction also applies to general physiology. But in conjunction with our data it can be suggested that urodilatin excretion may indeed be influenced by changes in arterial and renal perfusion pressure which was also supported by data of Heringlake and coworkers. They found in isolated perfused rat kidney that renal perfusion pressure and arterial blood pressure are determinants of urodilatin excretion [40].

Besides this, left atrial stretch was reported to cause urodilatin excretion [34]. In response to intravenous infusion of saline and left atrial distension, Goetz and coworkers found in conscious dogs that $Na^+$-excretion correlated better with urodilatin in urine than it did with ANP in blood. Interestingly, this effect was abolished in cardiac-denervated dogs suggesting a neuronal axis between heart and kidney. Also, using the split-infusion technique, infusion of hypertonic saline into the carotid artery of conscious dogs induced an increase in urodilatin and $Na^+$-excretion suggesting a neuronal link between cephalic $Na^+$-concentration receptors and urodilatin secretion in the kidney [24]. However, these effects on renal function were also detectable, if the kidneys were denervated [25], suggesting an additional humoral factor transmitting the increase of cerebral $Na^+$-concentration to the kidneys. Also, a neuronal influence was discussed explaining an increase of urodilatin and sodium excretion following water immersion in men. Here, renal sympathetic nervous system or dopaminergic nerves may have led to the release of urodilatin [72].

Furthermore, it was demonstrated that urinary $Na^+$ and urodilatin excretion follow a comparable circadian course and that urodilatin excretion is increased after an infusion of saline in healthy volunteers [22]. Urodilatin excretion is concomitantly increased with higher nutritional $Na^+$-load in humans, suggesting that urodilatin excretion is influenced by changes of $Na^+$-load and the plasma concentration of $Na^+$ [66]. The molecular mechanisms underlying the release of urodilatin were investigated by immunoreactivity using a human kidney cell line that displays characteristics of distal tubular cells. The authors found a rapid and regulated release of urodilatin in response to the osmotic effect of increased extracellular $Na^+Cl^-$ supporting the assumption of an interaction between urodilatin release and renal $Na^+$-handling [59].

Concluding, different mechanisms have been discussed being responsible for triggering urodilatin release in the kidney such as renal blood perfusion pressure as well as humoral or neuronal factors. However, the initial stimulus either direct or transmitted through nerves or hormones seems to be the extracellular $Na^+$-concentration.

## Further Candidates in Renal $Na^+$- and Water Handling?

Recently, two new candidates were introduced as regulators of natriuresis and diuresis to the kidney. Guanylin and uroguanylin, the intestinal natriuretic peptides, are known to inhibit $Na^+$-reabsorption and to induce $Cl^-$-, $HCO_{3-}$-, and water secretion in the intestine [6, 10]. They activate their specific guanylate cyclase receptor (GC-C), thus generating intracellular cGMP and inhibit the $Na^+/H^+$-exchanger and activate the cystic fibrosis transmembrane regulator (CFTR) $Cl^-$-channel [6, 56]. In the kidney these peptides produce natriuresis, kaliuresis, and diuresis [85]. In the proximal tubule guanylin and uroguanylin can bind to the GC-C receptor and inhibit via cGMP the $Na^+/H^+$-exchanger and a $K^+$-channel in the luminal membrane [83]. This $K^+$-channel has been discovered recently as the first mammalian directly cGMP-regulated $K^+$-channel [47]. Furthermore, cGMP is known to have an inhibitory effect on the $Na^+/K^+$-ATPase [2]. However, these effects were still seen in GC-C knock-out mice, which means the guanylin peptides use a different, cGMP-independent pathway [10]. Recently, it was shown that uroguanylin activates a pertussis toxin-sensitive G-protein-coupled receptor in human proximal tubule cells [83]. Through this receptor a luminal $K^+$-channel is activated. This receptor might even be the NPR-C receptor. Such a dual signaling pathway has also been established for ANP in human proximal tubule cells before. ANP binds to two different receptors, NPR-A, activating a cGMP-dependent pathway and to NPR-Bi, leading to tyrosine phosphorylation [44, 46]. An overview of regulatory processes in the proximal tubule is given in Figure 3.

In the cortical collecting duct (CCD) no guanylate cyclase receptor could be found, except GC-1 which is an orphan receptor [42]. Since GC-C was unlikely to be responsible for the guanylin and uroguanylin effects in the CCD, a further cGMP-independent pathway was detected in human and mice [84]. Guanylin and uroguanylin can activate a phospholipase $A_2$ ($PLA_2$) which downregulates ROMK, the luminal, secretory $K^+$-channel of the cortical collecting duct [84]. The regulation of ROMK by $PLA_2$ has been shown before in the thick ascending limb [88].

Experiments in isolated perfused rat kidneys demonstrated that ANP and urodilatin have synergistic effects with either uroguanylin or guanylin on natriuresis and kaliuresis when applied in physiological doses. An antagonism only occurred between ANP and urodilatin with uroguanylin applied at pharmacological doses [74]. Pretreatment with ANP clearly enhanced the natriuretic and kaliuretic activity of guanylin and uroguanylin leading to the assumption that ANP effects are most likely triggered by cGMP-dependent, while guanylin and uroguanylin effects are mediated through cGMP-independent mechanisms in the kidney. These data suggest that the interactions among the different peptides may play a contributory role in the regulation of kidney function in physiological but also in pathophysiological hypernatremic states where a saliuresis is needed.

Taken together, all these reports show that there is no major regulator of natriuresis and diuresis in the kidney but an elaborate interaction of various peptides executing their task on different regulatory pathways.

## Summary

There is a line of evidence supporting the hypothesis that urodilatin rather than ANP is the member of the

natriuretic peptide family primarily involved in the regulation of renal $Na^+$-excretion. Indeed, some studies suggest that ANP is only of trivial importance in the regulation of $Na^+$-excretion during normal living conditions. On the other hand, urodilatin which is produced in the kidney has properties very similar to ANP. However, even though a lot remains to be learned data suggest that urodilatin and ANP are not simply act-like peptides but rather serve appreciably different functions. ANP is likely to serve primarily as a regulator of the cardiovascular system with relatively little effect on various transport processes in the kidney under most circumstances. In contrast, urodilatin may be an important physiological paracrine peptide binding to the receptors in the inner medullary collecting duct and thereby participating in the intrarenal regulation of $Na^+$- and water transport. However, recent data suggest that guanylin and uroguanylin in concert with urodilatin may play a significant role in $Na^+$ and water handling in the kidney as well.

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