Ingestion of a salty meal induces secretion of guanylin (GN) and uroguanylin (UGN) into the intestinal lumen, where they inhibit Na⁺ absorption and induce Cl⁻, HCO₃⁻, and water secretion. Simultaneously, these hormones stimulate renal electrolyte excretion by inducing natriuresis, kaliuresis, and diuresis. GN and UGN therefore participate in the prevention of hypernatremia and hypervolemia after salty meals. The signaling pathway of GN and UGN in the intestine is well known. They activate enterocytes via guanylate cyclase C (GC-C), which leads to cGMP-dependent inhibition of Na⁺/H⁺ exchange and activation of the cystic fibrosis transmembrane regulator. In GC-C–deficient mice, GN and UGN still produce renal natriuresis, kaliuresis, and diuresis, suggesting different signaling pathways in the kidney compared with the intestine. Signaling pathways for GN and UGN in the kidney differ along the various nephron segments. In proximal tubule cells, a cGMP- and GC-C–dependent signaling was demonstrated for both peptides. In addition, UGN activates a pertussis toxin–sensitive G-protein–coupled receptor. A similar dual signaling pathway is also known for atrial natriuretic peptide. Recently, a cGMP-independent signaling pathway for GN and UGN was also shown in principal cells of the human and mouse cortical collecting duct. Because GN and UGN activate different signaling pathways in specific organs and even within the kidney, this review focuses on more recent findings on cellular effects and signaling mechanisms of these peptides and their pathophysiologic implications in the intestine and the kidney.

Guanylin peptides, guanylin (GN) and uroguanylin (UGN) are small, heat-stable peptides with 15 to 19 amino acids. Human GN consists of 15 amino acids and possesses two disulfide bonds between the cysteins in positions 4 to 12 and 7 to 15 (1). Human UGN consists of 16 amino acids and also has two disulfide bonds at the same positions (2). These disulfide bonds are essential for the activity of the peptides. The genes for guanylin peptides are located on the human chromosome 1 (p33 to p36) and the mouse chromosome 4 (3). Human GN and UGN are coded by different but similar genes that consist of three exons and two introns. Both peptides are synthesized as prepropeptide. Guanylin peptides are produced in the intestine after ingestion of a salty meal and secreted into the intestinal lumen (4). In the intestine, GN and UGN activate enterocytes via guanylate cyclase C (GC-C), with cGMP as second messenger (5,6). Activation of this pathway leads to the secretion of Cl⁻ and HCO₃⁻ and to the inhibition of Na⁺ absorption, which drives water secretion. In addition, these hormones induce an increased salt and water excretion in the kidney (7). The decrease of salt absorption in the intestine together with the increase of renal salt excretion prevents the development of hypernatremia after ingestion of high amounts of salt.

GC-C was first described as a receptor for the exogenous heat-stable enterotoxin of *Escherichia coli* (STa) (8). Unlike the endogenous peptides GN and UGN, STa contains three disulfide bonds. It is presumed that this is the reason for its stronger and uncontrolled activation of GC-C that leads to marked intestinal secretion of electrolytes and water and is manifested as secretory diarrhea (9). The identification of a receptor for the exogenous enterotoxin in the intestine and in other tissues (kidney, reproductive system, and lung) led to the search for endogenous ligands for GC-C and their physiologic function. In the early 1990s, GN was isolated from rat intestine (5) and UGN from opossum urine (6). Other recently discovered new members of this peptide family are renoguanylin (10) and lymphoguanylin (11). Like GN and UGN, renoguanylin has two disulfide bonds, whereas lymphoguanylin possesses only one. Lymphoguanylin is less potent than GN and UGN in the intestine (11). As guanylin peptides regulate electrolyte excretion by the intestine and the kidney, they complement other well-known hormonal systems that are involved in regulation of water and electrolyte homeostasis, such as the renin-angiotensin-aldosterone system, adiuretin (vasopressin) or atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C type natriuretic peptide (CNP).

A number of excellent reviews on various aspects of guanylin peptides exist (12,13); however, recent growing understanding of cellular signaling mechanisms also in humans is not covered in these reviews. Therefore, the aim of this review is to summarize the current knowledge on cellular effects of guanylin peptides and their signaling pathways and possible pathophysiologic implications in different organs, mainly the intestine and the kidney of different species including man.
Guanylate Cyclases

The big family of guanylate cyclases consists of one cytoplasmic (soluble) guanylate cyclase, which is the receptor for nitric oxide and carbonic monoxide, and six isoforms of membrane guanylate cyclases. GC-A, GC-B, and GC-C are receptors for natriuretic peptides that regulate electrolyte and water homeostasis and control BP (14). GC-A (or NPR-A) is the receptor for ANP and BNP; GC-B (or NPR-B) is the receptor for CNP. A third receptor that binds these three peptides, the so-called clearance receptor (or NPR-C), has no guanylate cyclase activity, and hormone binding to this receptor leads to endocytosis of the hormone-receptor complex and activation of a pertussis toxin-sensitive G-protein. The latter mediates an inhibition of adenylate cyclase (15,16). Guanylate cyclases D, E, and F (GC-D, GC-E, and GC-F) are expressed in sensory organs, and, until now, their agonists and functions are not known (17–20). GC-G is also an orphan receptor without known agonist, and it is present in skeletal muscles, lungs, and intestine. Hirsch et al. (21) showed for the first time the presence of GC-G also in the kidney and identified this guanylate cyclase as the only membrane-bound isoform present in principal cells of rat cortical collecting duct (CCD). Table 1 summarizes the tissue distribution and known agonists for the eight guanylate cyclases identified (22,23).

**GC-C**

GC-C is the main receptor for guanylin peptides in the intestine (Figure 1). GC-C forms dimers, trimers, or tetramers when inserted into the plasma membrane (24). mRNA for GC-C is present also in adrenal glands, brain, the embryonic or regenerating but not adult liver, placenta, testis, airways, spleen, thymus, and lymphatic nodes (25–27). Human and rat GC-C have 71% homology in the extracellular domain and 91% in the intracellular domain. The extracellular domain must be glycosylated for complete receptor activity (28,29), and dephosphorylation caused by binding of an agonist to the extracellular domain leads to loss of receptor sensitivity (30).

The most studied regulator of GC-C activity is protein kinase C (PKC). GC-C phosphorylation by PKC leads to an increase in cGMP accumulation. PKC-induced phosphorylation at the C-terminal tail increased STa-mediated cGMP generation by 70% when compared with the nonphosphorylated receptor (31,32).

The existence of additional receptors for guanylin peptides became evident when, for example, intestinal and renal effects of these peptides were examined in GC-C–deficient mice. These mice are resistant to intestinal secretion produced by STa (33–35), but approximately 10% of the intestinal binding sites for these peptides are still present when compared with wild-type mice. In the kidney, guanylin peptides still induce saluresis and diuresis in these GC-C–deficient mice (36), strongly suggesting an additional receptor and possibly signaling cascade for guanylin peptides at least in the kidney and to some extent also in the intestine. That renal effects of guanylin peptides are maintained when GC-C is absent also indicates that GC-C plays no or only a minor role for these peptides in the kidney.

![Figure 1. Guanylate cyclase C (GC-C) forming a dimer. The binding of guanylin (GN), uroguanylin (UGN), or heat-stable enterotoxin of *Escherichia coli* (STa) to the extracellular domain of GC-C leads to activation of the catalytic domain with the production of cGMP and the dephosphorylation of the kinase homology domain with receptor desensitization. For details, see text. L, ligand.](image)

<table>
<thead>
<tr>
<th>Cyclases</th>
<th>Tissue Distribution</th>
<th>Agonists</th>
</tr>
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<tbody>
<tr>
<td>Cytoplasmic</td>
<td>Skeletal muscle, platelets, lung, liver, kidney, heart, CNS</td>
<td>NO, CO</td>
</tr>
<tr>
<td>GC-A</td>
<td>Smooth muscle, kidney, adrenal gland, heart, CNS</td>
<td>ANP, BNP</td>
</tr>
<tr>
<td>GC-B</td>
<td>Fibroblasts, heart, CNS</td>
<td>CNP</td>
</tr>
<tr>
<td>GC-C</td>
<td>Intestine, adrenal gland, CNS, lung, reproductive glands, kidney</td>
<td>STa, GN, UGN</td>
</tr>
<tr>
<td>GC-D</td>
<td>Olfactory cells</td>
<td>Unknown</td>
</tr>
<tr>
<td>GC-E</td>
<td>Retina</td>
<td>Unknown</td>
</tr>
<tr>
<td>GC-F</td>
<td>Retina</td>
<td>Unknown</td>
</tr>
<tr>
<td>GC-G</td>
<td>Skeletal muscle, lung, intestine, kidney</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; CNS, central nervous system; CO, carbon monoxide; NO, nitric oxide; STa, heat-stable enterotoxin of *Escherichia coli*; GN, guanylin; UGN, uroguanylin.
Signaling Pathways of Guanylin Peptides in the Intestine

Guanylin peptides secreted into the intestinal lumen in response to high oral salt intake bind to GC-C localized in the luminal membrane of enterocytes and induce electrolyte and water excretion by a complex signaling cascade (Figure 2):

1. Increase of the intracellular concentration of cGMP (5,6,8)
2. Inhibition of Na\(^+/\)H\(^+\) exchange, which results in decreased Na\(^+\) reabsorption (37)
3. Activation of PKG II (38,39)
4. Activation of PKA directly (40,41) or indirectly via inhibition of phosphodiesterase III (PDE III), which leads to an increase of cellular cAMP and activation of PKA (39)
5. PKG II and PKA activate cystic fibrosis transmembrane regulator (CFTR) in the luminal membrane (42), leading to Cl\(^-\) secretion into the intestinal lumen
6. CFTR activates the Cl\(^-\)/HCO\(_3\)^- exchanger, which leads to bicarbonate secretion into the intestinal lumen (43)

GN and UGN are expressed along the intestinal tract (Figure 3) together with GC-C (44–46), which is the major intestinal receptor for GN and UGN. However, the expression pattern of these two hormones is differential, i.e., highest expression of UGN in the jejunum and highest expression of GN in ileum to proximal colon. The distal colon expresses only small amounts of both hormones.

As indicated above, a few studies show the existence of a signaling pathway at least for STa distinct of GC-C (33–35).

Furthermore, binding sites for guanylin peptides that are distinct from GC-C are also located on the basolateral membrane of colonocytes (47). STa also activates the Ca\(^2+\) signaling pathway with activation of PKC (48,49), which could be independent of GC-C activation.

The effects of GN and UGN on cellular cGMP via GC-C depend on extracellular pH. UGN is more potent at pH 5 compared with pH 8. Conversely, GN is more potent at pH 8 compared with pH 5 (Figure 4). As this pH dependence affects the ligand/receptor interaction, it was suggested that the N-terminal ends of the UGN and GN molecules are responsible for this pH dependence (50). The duodenum secretes bicarbonate to neutralize the acidic pH of the stomach contents that enter the duodenum. This acid-stimulated duodenal mucosal bicarbonate secretion is cGMP dependent. UGN regulates the luminal pH in the duodenum by activation of bicarbonate

**Figure 2.** Signaling pathway of guanylin peptides in the intestine. GN, UGN, and STa activate membrane-bound GC-C, which increases the intracellular concentration of cGMP. cGMP inhibits the Na\(^+/\)H\(^+\) exchanger (NHE) and activates protein kinase G type II (PKG II) and protein kinase A (PKA). Both protein kinases activate Cl\(^-\) and HCO\(_3\)^- secretion via activation of cystic fibrosis transmembrane regulator (CFTR) followed by an activation of the Cl\(^-\)/HCO\(_3\)^- exchanger. Depicted is a schematic drawing of an enterocyte including the major components necessary for electrolyte transport. PDE III, phosphodiesterase type III (inhibited by cGMP). Illustration by Josh Gramling—Gramling Medical Illustration.

**Figure 3.** Relative expression of GN (■) and UGN (□) mRNA along the intestinal tract. Adapted from reference (46).

**Figure 4.** GN and UGN increase the cellular concentration of cGMP pH-dependently. GN is more potent at pH 8.0, and UGN is more potent at pH 5.0. Adapted from reference (50).
secretion and inhibition of H⁺ secretion because unlike GN, UGN is localized predominantly in the proximal part of intestinal tract (Figure 3). This effect is enhanced as UGN has higher activity at acidic pH and leads to stronger HCO₃⁻ secretion into duodenal lumen.

**Signaling Mechanisms of Guanylin Peptides in the Kidney**

Guanylin peptides increase the secretion of Na⁺, K⁺, and water in the kidney without changes in GFR or renal blood flow (7,36). UGN is proposed to be an intestinal natriuretic peptide, as natriuresis produced by oral salt load is decreased in UGN-deficient mice (51). Thus, the action of UGN in the kidney can be endocrine (produced in the intestine with actions in the kidney), paracrine (produced by the kidney), or both. Kinoshita et al. (52) showed higher UGN concentration in blood and urine of individuals who were on a high-salt diet compared with those who were on a low-salt diet, which speaks in favor of an endocrine function of UGN. Recently, Fukae et al. (53) showed that rats that are fed a high-salt diet have higher UGN and cGMP concentrations in the urine but show no changes in the concentration of UGN in the plasma compared with control animals. UGN is expressed in the kidney, and its expression is higher in animals that are on a high-salt diet (53,54). It is still not clear whether the increase in the urinary concentrations of UGN and cGMP (52,53) are due to local production and secretion of UGN within the kidney or to filtration in the glomerulus.

Both GN and UGN circulate in the plasma and can be filtered in the glomerulus into the primary urine. UGN is excreted via the final urine, whereas hardly any GN can be found in the urine (6,55). A possible reason that GN is not present in the final urine is its sensitivity to chymotrypsin, which quickly degrades GN after glomerular filtration or secretion of GN into the tubular lumen (9,56). These differences in the degradation and expression pattern of GN and UGN suggest that GN probably acts strictly autocrine, whereas UGN has paracrine activity in the kidney. The concentration of UGN in the urine correlates with that of urinary cGMP, which again supports the hypothesis that cGMP and the GC-C signaling pathways are activated by UGN at least in the cells of the proximal tubule. However, another possible source of cGMP in the urine could be the activation of other members of the guanylyl cyclase family, such as the orphan receptor GC-G, which is present in the luminal membrane of principal cells of rat and mouse CCD (21,57). The source of guanylin peptides in the tubular lumen besides glomerular filtration from the circulation could also be tubular cells because mRNA for GN and UGN is also expressed in kidney epithelial cells (54,58,59). Similar to the difference in the axial expression along the intestine, GN and UGN are not expressed equally along the different nephron segments (Figure 5). UGN is present mostly in the proximal tubule, again comparable to the proximal intestine, and GN is more pronounced in the collecting duct, in analogy to GN expression in the colon.

Markedly different from the expression along the entire intestinal tract, GC-C, the first receptor for guanylin peptides identified, is not present in all nephron segments. Potthast et al. (54) localized GC-C in the mouse kidney only in glomeruli and proximal tubules. In the human kidney, we detected GC-C again only in the kidney cortex and specifically in proximal tubules (Figure 6) (60,61). In contrary to these findings in mouse and human, in rat kidney, Carrithers et al. (58) found mRNA for GC-C in all nephron segments, suggesting differences in tissue distribution of GC-C in different species. A few years ago, it became evident that proximal tubules are targets of guanylin peptides. Guanylin peptides increase the intracellular cGMP concentration in a proximal tubule cell line of opossum kidney (OK cells) via the opossum kidney GC-C (OK-GC), which is the analog to the human GC-C (62). Recently, we demonstrated an increase in the cellular cGMP concentration induced by guanylin peptides also in a human proximal tubule cell line (IHKE1) (61). In this cell line, GN and UGN also activated GC-C.

The intestinal pH dependence for the binding of GN and UGN to GC-C (see above) probably also is relevant in the
kidney. In the human proximal tubule cell line, UGN activated GC-C at pH 5 more pronounced than at pH 8 (Figure 4). At alkaline pH, when UGN effects on GC-C in these proximal tubular cells were lower, an additional signaling pathway via pertussis toxin–sensitive G-proteins was revealed (61). Therefore, tubular pH can play an important role in activating GN versus UGN signaling pathways and activating different signaling pathways for UGN (Figure 7). This might be even more relevant along the medullary collecting duct, where tubular pH can be significantly acidic. Data on effects of guanylin peptides along this nephron segment, however, are still completely missing.

Data from various proximal tubule cells in culture suggest that guanylin peptides inhibit Na\(^+/\)H\(^+\) reabsorption in this nephron segment. UGN decreases the expression of the Na\(^+\)/K\(^+\)-ATPase, which would lower the concentration gradient for Na\(^+\) and therefore reduce Na\(^+\)-coupled electrolyte and substrate reabsorption from the tubular lumen (63). According to our own observations in the human proximal tubule cell line, GN and UGN decrease the electrical driving force for Na\(^+\) reabsorption by inhibiting K\(^+\) channels via cGMP and depolarizing cells (61). Finally, the increase in cellular cGMP by GN and UGN should, like in the intestine (37), inhibit luminal Na\(^+\)/H\(^+\) exchange and thereby reduce Na\(^+\) and volume reabsorption. Indeed, in the human proximal tubule cell line, UGN inhibited Na\(^+\)/H\(^+\) exchange activity (Schlatter E., unpublished results). As mentioned above, guanylin peptides still cause natriuresis, kaliuresis, and diuresis in GC-C–deficient mice, suggesting a second receptor in the kidney for these peptides (36). In addition to this GC-C– and cGMP-dependent signaling pathway, UGN can activate a pertussis toxin–sensitive G-protein that leads to activation of a K\(^+\) conductance (61). Which signaling pathway will be activated by UGN could depend on luminal pH (Figure 7). Figure 8 shows a summary of actions of guanylin peptides on proximal tubular cells on ion and water transport. The molecular identity of this second receptor, the physiologic role of this cGMP-independent signaling pathway, and the relative contributions of these two signaling pathways remains to be elucidated.

The presence of two receptors for one peptide even at the same cell is known for other hormones that also act in the kidney. ANP activates two different types of receptors (64); one is GC-A, and, like GC-C, its activation leads to the production of cGMP (65). The other receptor is the natriuretic peptide receptor type C, or clearance receptor (NPR-C), which is a pertussis toxin–sensitive G-protein–coupled receptor (15,16). It remains to be clarified whether the G-protein–coupled receptors for UGN and ANP are the same or similar.

Fine regulation of renal electrolyte and water excretion takes place in the collecting duct. Principal cells of the CCD are responsible for K\(^+\) secretion (via K\(^+\) channels [ROMK]), Na\(^+\) reabsorption (via epithelial Na\(^+\) channels [ENaC]), and water reabsorption (via aquaporins 2, 3, and 4). In line with the observation that GC-C–deficient mice still exert natriuresis, kaliuresis, and diuresis upon infusion of guanylin peptides (36) is the absence of mRNA for GC-C in CCD of mouse and man (54,60). However, guanylin peptides induce changes in mem-

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**Figure 7.** pH dependence of effects of guanylin peptides on membrane voltages of human proximal tubule cells. At pH 5.5, UGN activated GC-C and depolarized cells; at pH 8.0, it activated a G-protein–coupled receptor and hyperpolarized the cells. GN and STa depolarize cells only via activation of the GC-C–dependent signaling pathway. Mean values \(\pm\) SEM, \(n\) given in brackets. Adapted from reference (61).

**Figure 8.** Signaling pathways of guanylin peptides in renal proximal tubule cells. Guanylin peptides activate two signaling pathways. One is GC-C and cGMP dependent. cGMP decreases Na\(^+\) reabsorption by inhibiting different proteins in the membrane: K\(^+\) channels, Na\(^+\)/H\(^+\) exchanger, and Na\(^+\)/K\(^+\)-ATPase. The other signaling pathway involves activation of a pertussis toxin–sensitive G-protein. AQP1, aquaporin 1; NBC, Na\(^+\)/HCO\(_3\) co-transporter; NHE3, Na\(^+\)/H\(^+\) exchanger; OK-GC, guanylate cyclase from opossum kidney. Illustration by Josh Gramling—Gramling Medical Illustration.
bran of principal cells and cell hyperpolarization. 

Figure 9 shows a model of a principal cell of the CCD indicating all mechanisms of actions of guanylin peptides identified so far. It is evident from this scheme that the guanylin peptides are the first peptides identified that act in this nephron segment primarily on K⁺ channels without directly affecting Na⁺ channels. In the human CCD, the depolarization of principal cells via inhibition of the secretory K⁺ channels results in natriuresis as the predominant effect observed in vivo with these peptides (7,36,67). Reduced Na⁺ reabsorption also decreases water reabsorption in this nephron segment and thus causes diuresis. GN was shown to decrease the cell volume and increase the luminal space in a concentration- and time-dependent manner, which suggests secretion of water and consequently diuresis (68). However, the kaliuresis also caused by guanylin peptides cannot be explained from the data obtained in the CCD and may be due to effects of these peptides in other parts of the nephron, e.g., the thick ascending limb or the medullary collecting duct. Again, the physiologic role of the second cGMP-dependent signaling pathway and the relative contributions of these two signaling pathways in the CCD of the mouse remains to be elucidated. This second pathway involves an activation of basolateral K⁺ channels and thereby should increase Na⁺ reabsorption without an increase in K⁺ secretion.

**Cellular Effects of Guanylin Peptides in Other Organs**

Patients with cystic fibrosis undergo changes in water and electrolyte secretion in the liver, the pancreas, the lung, and the intestine. Thus, it might be speculated whether guanylin peptides are also involved in the regulation of electrolyte and water secretion in those organs via CFTR. Guanylin peptides and parts of their signaling pathway are present in the pancreas. John et al. (69) showed that GN and STa increase intracellular cGMP via GC-C in a human pancreatic cell line. Kulaksiz et al. (70,71) detected mRNA for GC-C and UGN in cells of the exocrine part of the pancreas, and guanylin peptides increase cGMP, which leads to activation of CFTR in these cells.

Guanylin peptides and parts of the GC-C–dependent signaling pathway are also found in airways (26,27), sweat glands, the adrenal medulla, and the male reproductive system (72–74). According to this limited information on effects of guanylin peptides in various organs, the GC-C–dependent signaling pathway seems to be the predominant signaling pathway in most organs and only in the kidney does the signaling involve different receptors and signaling mechanisms.

**Guanylin Peptides in Pathophysiology**

Exiting observations are the involvement of guanylin peptides in the development and possible treatment of intestinal tumors. GN and UGN are less expressed or they are not present at all in colon adenocarcinoma, adenoma, and intestine polyps in human and mouse (75–77). The gene for GN is located at 1p34–35, which is a tumor-modifying region. One can presume that loss of GN activity leads to or is the result of tumor
development. Fitari et al. (78) hypothesized that the reason for the lower incidence of intestinal tumors in third-world countries is the higher incidence of intestinal infections that stimulate intestinal GC-C and lead to an increase in cGMP. Guanylin peptides and also STa in addition regulate proliferation and differentiation, prolonging the cell cycle, and induce apoptosis of T₄₅₄CaCO₃ cells, and mouse intestinal cells (78–81). Shailubahai et al. (77) showed that oral application of UGN leads to an increase in number and size of polyps in mice that develop intestinal polyposis, which allows us to speculate on the possible usage of UGN in the treatment of intestinal tumors.

The involvement of guanylin peptides was suggested also in different kidney diseases. More than 11 yr ago, Nakazato et al. (82) showed that human GN increases in patients who have chronic renal failure and undergo hemodialysis. The UGN concentration in plasma and/or in urine is increased in patients with chronic renal failure and glomerulonephritis and in patients on hemodialysis (52,83–85). In patients with nephrotic syndrome, UGN plasma concentration was higher and urinary concentration was lower compared with values in healthy volunteers (84). Possible explanations for these observations are kidney damages and reduced capability to metabolize and excrete guanylin peptides. Recently, Kikuchi et al. (86) suggested that UGN plays a role as a natriuretic factor in nephrotic syndrome. In experimental nephrotic syndrome, induced by intraperitoneal injection of puromycin aminonucleoside (PAN), changes in UGN concentrations in urine and plasma corresponded to changes in Na⁺ excretion. In the same animals, the expression of mRNA for UGN changed in the kidney but not in the intestine, and it was not seen in control animals.

In contrast to other natriuretic peptides, like ANP, the connection between guanylin peptides and hypertension is not well understood. UGN-deficient mice have increased mean arterial pressure, which is salt insensitive (51). However, GC-C–deficient mice show no difference in BP compared with wild-type mice (33,34), which rules out a significant involvement of GC-C in the regulation of BP. As shown in this review, guanylin peptides activate at least one cGMP-, GC-C–independent signaling pathway. Liberation of arachidonic acid in the renal collecting duct by guanylin peptides inhibits the secretory ROMK channels, which lowers the electrical driving force for Na⁺ reabsorption, resulting in natriuresis. In UGN-deficient mice, UGN cannot activate this signaling pathway, which will lead to higher reabsorption of Na⁺ and possibly induce hypertension (51).

Conclusions

GN and UGN regulate electrolyte and water transport in the intestine and cause kaliuresis, natriuresis, and diuresis in the kidney. The membrane-bound GC-C is the receptor for these peptides in the intestine. In the kidney, these peptides activate different signaling pathways along the nephron. Although GC-C is the predominant receptor mediating the effects of guanylin peptides in the intestine, it plays only a minor role in the kidney, probably restricted to the proximal tubule. Whereas in the intestine the signaling pathway of guanylin peptides is singular, in the kidney, at least three different receptors with different second messenger systems are activated and mediate complex effects on electrolyte and water excretion. The molecular identity of these renal receptors for guanylin peptides remains to be determined. First indications of an involvement of these peptides in various diseases indicate also a pathophysiologic role and possibly a therapeutic value of these peptides.

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