A recent research group from Miyazaki, Japan, previously demonstrated that the nephrotic syndrome is associated with increased levels of uroguanylin (1). Kikuchi et al. return to the topic in this issue of JASN with a report that a model of nephrosis, which was induced in rats by treatment with puromycin, also causes marked perturbations in the levels of circulating and urinary uroguanylin. To most nephrologists, the primary questions that come to mind will be: What is uroguanylin and why do pathophysiological changes in a gut-derived peptide occur in nephrosis?

Human uroguanylin is a 16–amino-acid peptide that reaches its highest abundance in mucosae of the stomach and intestinal tract (reviewed in 2,3). The existence of uroguanylin and its cousin, guanylin, was foreshadowed by the discovery of an orphan receptor-guanylate cyclase (R-GC) in opossum kidney (4). These cell-surface R-GC signaling molecules are markedly activated by heat-stable enterotoxin (stable toxin, [ST]) peptides produced by strains of Escherichia coli, which cause a cholera-like form of secretory diarrhea (5). Pursuit of the endogenous peptide hormones that serve as natural agonists for this R-GC of kidney, intestine, and other epithelia led first to the isolation of guanylin from the jejunum of rats, followed closely by the purification of uroguanylin from opossum urine (6,7). The extraordinary abundance of both guanylin and uroguanylin in the intestinal epithelium combined with a remarkably high density of a cognate receptor-guanylate cyclase (R-GC-C) in cells comprising the intestinal mucosa was the most fascinating observation made in the early years following discovery of these signaling molecules. These findings, together with a body of older literature defining the biologic activities of E. coli ST peptides as diarrhea-inducing enterotoxin peptides, misled this field for quite a long time. Initially, it was considered that a physiologic role of guanylin and uroguanylin was to regulate the secretion of fluid and electrolytes by the intestinal epithelium. Some residual belief may remain for such an action of the guanylin peptides that influence cellular functions via the intracellular second messenger, cyclic GMP (cGMP). However, transgenic mice lacking R-GC-C, guanylin, or uroguanylin appear to have no abnormalities of intestinal fluid secretion (8–10). These findings suggest that other physiologic roles for guanylin and uroguanylin may exist, including the regulation of kidney function.

Evidence for renal actions of the guanylin peptides stems from the discovery of receptors for E. coli ST peptides located in the apical membranes of proximal tubules in opossum kidney (4). Since then, a number of studies have shown that guanylin, uroguanylin, and the guanylin-like peptide, E. coli ST, elicit increases in the urinary excretion of sodium, potassium, chloride, and water (11–13). Therefore, it was postulated that uroguanylin acts on the kidney through a novel endocrine axis linking the GI tract with the kidney via circulating levels of uroguanylin and/or guanylin (14). Because the kidney expresses mRNA transcripts for uroguanylin and guanylin, local effects of these peptides on the nephron could also play a role in the tubular actions of these cGMP-regulating peptides (3,4). Why then does nephrosis elicit increases in the plasma and urinary levels of uroguanylin and also stimulate the expression of uroguanylin mRNA in the kidney? While the answer to this question is still evolving, some bits of evidence now exist to form a reasonable hypothesis. Uroguanylin probably acts in the body as a natriuretic hormone when excess sodium chloride (NaCl) is consumed in the diet. Uroguanylin is one component of a complex physiologic mechanism that balances urinary sodium excretion to match the levels of NaCl absorbed into the body via the GI tract. Thus, uroguanylin may be thought of as a counter-regulatory hormone that opposes the sodium-retaining actions of hormones like aldosterone. Recent experiments with uroguanylin gene knock-out mice are consistent with this concept. Uroguanylin+/− animals had impaired saliuretic responses to an oral NaCl load and exhibited elevated BP (10).

The nephrotic syndrome may cause increases in uroguanylin levels secondary to the retention of NaCl by the kidney, which leads to an increase in total body sodium. Uroguanylin levels in the urine are also increased markedly in patients with sodium retention secondary to heart failure (15). Thus, physiological mechanisms exist, which regulate the production and/or secretion of uroguanylin when sodium retention occurs secondary to diseases of the kidney, heart, or other organs, as well as in times of excess NaCl consumption in the diet. From the report by Kikuchi et al. in this issue, it can now be accepted that sodium retention elicited by nephrosis leads to a stimulation of uroguanylin mRNA expression in the kidney. Prior studies in patients with congestive heart failure did not explore the sources of elevated uroguanylin found in urine (15). Therefore, it is possible that sodium retention per se leads to an increase in the
The production of uroguanylin by the kidney, which contributes to the increased urinary excretion of uroguanylin observed in both the nephrotic syndrome and congestive heart failure. Although uroguanylin expression in the intestine of nephrotic rats was not increased in the present study, it is likely that sodium-retaining diseases may enhance the expression of uroguanylin (and guanylin) in the GI tract as well as in the kidney. The report by Kikuchi et al. did not rigorously examine this possibility. Uroguanylin is expressed throughout the GI tract, whereas Kikuchi et al. only measured uroguanylin mRNAs by RT-PCR in the small intestine. Other parts of the GI tract, such as the gastric mucosa, could contribute to elevated levels of uroguanylin in the circulation of rats with puromycin-induced nephrosis.

In summary, Kikuchi et al. have advanced our understanding of the potential physiologic roles for uroguanylin as a natriuretic hormone that regulates the renal excretion of NaCl to help maintain sodium balance. The functional significance of uroguanylin clearly includes actions on the kidney to enhance urinary sodium excretion, both in times when excess NaCl is consumed in the diet and in diseases such as nephrosis and heart failure, when sodium retention leads to the pathophysiological accumulation of salt and water.

References

See related editorial, “Role of Uroguanylin, a Peptide with Natriuretic Activity, in Rats with Experimental Nephrotic Syndrome,” on pages 392–397.