The renal paracrine peptide system – possible urologic implications of urodilatin

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Summary. Cardiodilatin/atrial natriuretic peptide (CDD/ANP) is a hormone system of great clinical importance. The prohormone CDD/ANP-1-126 is a peptide synthesized in the heart and cleaved during exocytosis into the circulating form CDD/ANP-99-126. Urodilatin (CDD/ANP-95-126) is a homologue natriuretic peptide that differs from CDD/ANP-99-126 by four amino acids. Whereas CDD/ANP-99-126 circulates in blood plasma and is not excreted into the urine, urodilatin is detected only in urine. Urodilatin exerts its renal effects in a paracrine fashion. After its secretion from cells in the distal tubule, it interacts with luminally located receptors in the collecting duct, resulting in increased diuresis and natriuresis. Results suggest that urodilatin plays an important role in the physiologic regulation of fluid balance and sodium homeostasis. Pharmacology studies reveal significant differences when urodilatin and CDD/ANP-99-126 are given intravenously, showing that stronger diuresis and natriuresis are induced by urodilatin as compared with those induced by CDD/ANP-99-126. Clinical studies indicate the prophylactic and therapeutic effect of urodilatin in patients suffering from acute renal failure following heart and liver transplantation. A significant reduction in requirements for hemodialysis/hemofiltration can be achieved using urodilatin. Postobstructive diuresis and natriuresis is probably due to a defective urinary concentrating mechanism and is usually resistant to treatment with antidiuretic hormone. The distal tubule and collecting duct have often been considered to be the site of altered sodium and water excretion following relief of obstruction. Since circulating CDD/ANP-99-126 levels are markedly elevated during obstruction and decrease upon relief of the obstruction, natriuretic peptides may play an important role in this clinical feature. On the basis of recent findings attributing an important role in sodium homeostasis to urodilatin in contrast to CDD/ANP-99-126, future studies have to clarify whether urodilatin, not CDD/ANP-99-126, might be responsible for the altered renal sodium excretion observed in postobstructive diuresis.

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In the past decade a considerable amount of research has led to the identification and characterization of hormones of the natriuretic peptide family [13]. These peptides are involved in the regulation of salt and water homeostasis. The prototype of the natriuretic hormones is cardiodilatin/atrial natriuretic peptide (CDD/ANP), or A-type natriuretic peptide. CDD/ANP is primarily produced in the heart [6]. It is synthesized as a precursor molecule, CDD/ANP-1-126, in specific granules in atrial myoendocrine cells [15]. The prohormone, upon appropriate stimuli for release, is cleaved into the C-terminus CDD/ANP-99-126 and excreted into the circulation via exocytosis [16]. Further members of the natriuretic peptide family are brain natriuretic peptide (BNP, or B-type natriuretic peptide) [45] and C-type natriuretic peptide (CNP) [46]. All the members of this family share many common features, including tissue distribution of gene expression, biosynthetic pathways, and pharmacologic effects in target organs [13, 26].

The main biologic effects of these hormones are natriuresis, diuresis, and vasodilation [5, 6, 14, 22], but these vary among the individual peptides. Natriuretic effects such as increased glomerular filtration, inhibition of aldosterone production, and secretion result from direct inhibition of sodium absorption in the collecting duct. Urodilatin (INN: Ularitide) is a member of the natriuretic peptide family, discovered in 1988 by Schulz-Knappe et al. [43]. This hormone is presumably synthesized in the kidney and exerts potential paracrine renal effects [17]. Results of clinical phase I–II trials suggest a potent therapeutic effect of urodilatin in the treatment of acute renal failure in patients following organ transplantation [4, 27, 33].

Isolation of urodilatin

Immunohistochemical staining of distal kidney tubule cells and the collecting duct with antibodies against the N-terminal and C-terminal epitopes of the prohormone [12, 15, 16] initially suggested synthesis or storage of a CDD/ANP peptide. Furthermore, CDD/ANP immunoreactivity (IR) was detected by radioimmunoassay (RIA)
against CDD/ANP in human urine. Chromatographic characterization revealed different elution patterns between the IR detected in urine and a synthetic CDD/ANP-99-126 standard. These observations, together with the lack of correlation between plasma and urine concentration, led to the isolation of urodilatin in 1988 [43]. Analysis of the primary structure showed that urodilatin was fully homologous with the C-terminal 32 amino acids found in the prohormone CDD/ANP-1-126. This suggests that the discovered urinary peptide urodilatin does not originate from the circulation but is probably synthesized in the kidney and excreted into the urine.

Receptors, second-messenger systems, and metabolism of natriuretic peptides

The biological activity of the natriuretic peptides is presumably mediated by intracellular generation of cyclic guanosine 3',5'-monophosphate (cGMP) following the activation of particulate guanylyl cyclase [34]. cDNA analysis and cloning revealed three types of natriuretic peptide receptors (NPRs): types A, B, and C [34]. NPR-A and NPR-B are coupled to the intracellular guanylyl cyclase catalytic domain, whereas the third member, NPR-C, is not associated with an intracellular guanylyl cyclase [31], indicating that this protein functions as a clearance receptor. Besides binding of circulating natriuretic peptides to NPR-C, enzymatic degradation in the lung, liver, and kidney takes place [10, 26, 38]. The main enzyme responsible for degradation is the metalloendoprotease E.C.3.4.24.11. One of the main location sites is the brush border of the proximal tubule and the tracheobronchial system in the lung. In contrast to CDD/ANP-99-126, results of several groups indicate a high level of resistance of urodilatin to enzymatic degradation. This finding may be due to its N-terminal extension by four amino acids [19]. The structural difference may induce conformational changes, thereby preventing the enzyme from attacking the cleavage site. Thus, exogenously applied urodilatin may reach the distal tubule and the collecting duct without being degraded and exert its renal effects at this location. Furthermore, its reduced rate of inactivation may enable a prolonged binding to biologically active NPR-A receptors in the lung inducing a more pronounced bronchodilation. The different profile of metabolization appears to be of great clinical importance in comparisons of the potential renal and bronchial effects of intravenous CDD/ANP-99-126 and urodilatin.

Renal effects of urodilatin: physiologic and pharmacologic investigations

Several observations suggest that urodilatin plays a key role in the physiologic regulation of renal function, especially in the control of renal sodium and water excretion. Our group [37] investigated the effect of a long-term sodium load in healthy volunteers. We found a close correlation between natriuresis and urodilatin excretion. A stepwise increase in sodium intake induced a concomitant increase in urodilatin excretion parallel to sodium excretion. Other groups demonstrated increased urodilatin and sodium excretion after the induction of an acute volume load by saline infusion [9] and following balloon dilatation of the left atrium [21]. Drummer and co-workers [7] demonstrated that the circadian rhythm of urinary sodium excretion paralleled urodilatin excretion. As compared with urodilatin, CDD/ANP-99-126 exerts only trivial effects on renal sodium excretion. Other groups demonstrated increased urodilatin and sodium excretion after the induction of an acute volume load by saline infusion [9] and following balloon dilatation of the left atrium [21]. Drummer and co-workers [7] demonstrated that the circadian rhythm of urinary sodium excretion paralleled urodilatin excretion. As compared with urodilatin, CDD/ANP-99-126 exerts only trivial effects on renal sodium excretion. Several experiments revealed a closer correlation of natriuresis with urodilatin excretion than with CDD/ANP-99-126 plasma levels [20]. These observations indicate that urodilatin may be the natriuretic factor primarily responsible for sodium and water regulation.

Immunohistochemistry results [12], the isolation of urodilatin from urine [43], the lack of urodilatin IR in plasma [8], and the above-mentioned physiologic findings support our working hypothesis that urodilatin is synthesized in distal tubule cells and secreted into the lumen. There urodilatin may interact with biologically active