Urodilatin—Renal Natriuretic Peptide?

In 1981, the report by DeBold et al. (1) of potent natriuretic activity in extracts of cardiac atria ushered in the era of atrial natriuretic peptide (ANP). In just a few short years, the amino acid sequences of ANP and its prohormone were determined and its gene structure was elucidated, and the tissues in which it was synthesized were identified (for review, see references 2 and 3). At the same time, the biological actions of ANP were being recognized as potentially key to the integration of cardiovascular and renal function and the control of body fluid volumes; receptors were identified and characterized in target tissues, and the cellular actions of the peptide were related to activation of a membrane-bound guanylate cyclase with production of cGMP (2,3). Thus, a complete description of the biology of this peptide hormonal system, from gene structure and transcription, through translation, processing, and secretion, to receptor binding, activation of cellular signalling mechanisms, and final action in target tissues became available in a dazzlingly short time, reflecting the power and pace of contemporary scientific research.

Yet, despite this explosion of information, there has arrived no clear consensus of the role of ANP in volume homoeostasis. Despite several experimental settings suggesting a role for ANP in the body fluid economy (2–4), telling physiological studies in intact animals suggest that interruption of the circulating ANP system results in no discernible alteration in fluid regulation, save for an impairment in the natriuretic response to an acute volume challenge (5,6). Thus, it is possible that the functions of ANP may relate as much to tissue-specific expression and action as to circulating peptide levels, much as current research is suggesting to be the case for the renin–angiotensin system (7). The search for tissue ANP expression led to the discovery of brain natriuretic peptide, a peptide that has significant amino acid homology to ANP but that is the product of a separate gene (8). Brain natriuretic peptide is thought to function chiefly in the nervous system as a transmitter but is also expressed in the heart (9) and has renal actions mimicking ANP (8,10).

This quest received a new stimulus with the report in 1988 by Schulz-Knappe and associates of the isolation from human urine of a peptide structurally identical to human α-ANP but with an amino-terminal extension of four amino acids (Figure 1) (11). This 32-amino-acid peptide is identical with amino acids 95 through 126 of the precursor prohormone; it exhibits high-affinity binding to membranes from bovine adrenal medulla that matches that of ANP and stimulates particulate guanylate cyclase in these cells, also with equal potency to ANP (12). Because this new peptide possesses vasorelaxant properties when tested in an *in vitro* bioassay system (11), these authors termed it urodilatin, in parallel with the term cardiodilatin that they had earlier suggested for the name of the precursor peptide (13).

Little is known at this juncture of the site of synthesis and secretion and the mechanism of action of this newest member of the natriuretic peptide family. The absence of detectable urodilatin in the circulation (14) argues for a kidney-specific site of synthesis. Immunohistochemical studies and radioimmunoassay of renal extracts demonstrate α-ANP immunoreactivity in renal tissue, interpreted to show either *de novo* synthesis of the peptide or internalization of circulating α-ANP by the kidneys (15,16). Because the addition of four amino acids to the 28-amino-acid α-ANP taken up by renal cells from the circulation would be a truly novel form of peptide metabolism, the presumption is that urodilatin results from a processing pathway of the ANP gene product that is unique to the kidneys. Antisera to α-ANP show a great deal of cross-reactivity with urodilatin (17), and these earlier studies could well have detected the latter peptide rather than α-ANP; immunohistochemical studies with an antiserum recognizing the N-terminal region of urodilatin (with no cross-reactivity to α-ANP) localize the immunoreactivity to the same segments as shown when anti-α-ANP antiserum is used (13). Moreover, chromatographic analysis of renal extracts containing peptides of low molecular weight indicates that most ANP-like activity elutes with urodilatin rather than with α-ANP itself (13,18). Thus, evidence for a renal origin of urodilatin is strong, despite the failure to date to document expression of the ANP or urodilatin gene in kidney tissue (17).

Studies examining the physiological effects of urodilatin indicate with uniformity that it mimics the actions of α-ANP with respect to vasodilation, diuresis and natriuresis, urinary cGMP excretion, and hemoconcentration (10,17). These studies for the most part have involved bolus intravenous injections or infusions of the peptide and may therefore not be relevant to an understanding of its true physiological role, because circulating urodilatin has not yet been demonstrated. There is evidence to indicate that urodilatin is natriuretic in a lower dose than is α-ANP (17,19,20), suggesting that its physiological actions may be primarily referable to the kidneys. However, this conclusion is derived from studies comparing the effects of intravenous or intrarenal infusions of the peptides. Both peptides are filtered at the glomerulus, but α-ANP undergoes extensive degradation by a neutral metalloendopeptidase (EC 3.4.24.11) whereas urodilatin is resistant to such renal cortical peptidase activity (21). Consequently, a larger amount of fil-
peptides. Both peptides are filtered at the glomerulus, but α-ANP undergoes extensive degradation by a neutral metalloendopeptidase (EC 3.4.24.11) whereas urodilatin is resistant to such renal cortical peptidase activity (21). Consequently, a larger amount of filtered urodilatin could escape inactivation in proximal segments to exert a natriuretic effect by reaching more distal, sensitive sites, probably in the inner medullary collecting duct (10). This would result in greater potency because of resistance to degradation but would not necessarily reflect a greater sensitivity at the cellular level. Because urinary urodilatin cannot derive from peptide undergoing filtration from plasma, the importance of this resistance to peptidase degradation in contributing to the biological actions of urodilatin must be examined in future studies.

Another approach to the question of the physiological role of urodilatin has been taken by Goetz and colleagues (22) and Drummer and associates elsewhere in this issue of JASN (14). They have been able to demonstrate in both dog and man that urinary urodilatin excretion correlates closely with diurnal variations in sodium excretion and with the natriuresis after intravenous infusion of normal saline. In both species, these correlations were much stronger than the relatively weak correlations observed between sodium excretion and the concentration of α-ANP measured in plasma. Perhaps surprisingly, a strong correlation also existed between sodium and urodilatin excretion even when plasma ANP concentration was stimulated by left atrial stretch in the dog (22). These authors conclude that urodilatin may well be the member of the ANP family most closely linked to the effects of these peptides on sodium excretion.

Although such a possibility opens up an exciting new area of research in the physiological and pathophysiological regulation of salt balance, it should be recognized that data supporting such a role of urodilatin are based so far on circumstantial rather than direct evidence. Correlation of two biological events suggests but does not prove a causal relationship between them. Moreover, both sodium excretion and urodilatin excretion contain a term for urinary flow rate. If urodilatin concentration in urine was to be determined in some way as a passive consequence of flow rate, the correlation in excretion could simply reflect such an effect of flow rate itself. Although Goetz, Drummer, and their co-workers present arguments making such an interpretation less likely (14,22), studies designed specifically to address this issue are nevertheless needed to understand better the meaning of variations in urodilatin excretion.

A more fundamental reservation to the acceptance of a role of urodilatin in the regulation of sodium excretion relates to our ignorance regarding the mechanisms by which its secretion is regulated and its actions mediated. If urodilatin does indeed function as a participant in the regulation of salt balance, its secretion must in some way be linked to some derivative of salt balance, most likely extracellular fluid volume. We currently recognize sympathetic efferent nerves and hormonal factors such as ANP itself, angiotensin II, vasopressin, and possibly others to be the effector pathways adjusting the rate of sodium excretion in response to changes in extracellular fluid volume. If urodilatin is the final step in the pathway, then one or more of these, or other as yet unrecognized, signals must trigger its secretion. Is it secreted into the tubule lumen, as suggested by Feller and associates (13), or into the blood to reach receptor sites, as is apparently the case for circulating ANP (3)? Answers to questions such as these should allow us to develop quickly a clearer picture of the physiological role of urodilatin.

Although the nature of this picture is of course not yet known, it is enticing to speculate that this peptide may prove to have a major role in the intrarenal regulation of sodium excretion and may thereby help to resolve the ambiguity regarding the functions of α-ANP. Infusions of α-ANP produce profound effects on the systemic and renal circulations, the latter reflected by an increase in glomerular filtration rate, and the argument has been advanced that the natriuretic action of this peptide results from augmentation of glomerular filtration rate with a concomitant increase in filtered load not compensated for by glomerulotubular balance (2). Accordingly, the distal nephron is flooded with an increase in delivery that then becomes the major determinant of the natri-
natriuresis. Thus, the natriuretic action of α-ANP may be through vascular/hemodynamic actions rather than through a tubular mechanism. In support of this, transgenic mice constitutively expressing the ANP gene had concentrations of the peptide in plasma that were eightfold the level in normals but the only functional consequence detected was a lower blood pressure (23). It may therefore prove to be the case that tissue-specific actions of these natriuretic peptides may account for their specific effects, with α-ANP serving primarily to participate in the regulation of the circulation as a circulating hormone through actions on vascular smooth muscle, glomerular mesangium, and juxtaglomerular apparatus, whereas urodi Iatin functions in an intrarenal, paracrine manner to influence sodium excretion by an action on inner medullary collecting duct epithelium. Such target organ specificity would help to account for the difficulty in documenting an unequivocal role for α-ANP in sodium metabolism, yet would still maintain an important role of natriuretic peptide (urodilatin) in decreasing tubular sodium reabsorption to lead to natriuresis. If this should be supported by future experiments, then urodi Iatin may indeed emerge as the renal natriuretic peptide.

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ACKNOWLEDGMENTS

The author is pleased to acknowledge the helpful discussions with Jean-Pierre Valentin and the secretarial assistance of Annalisa Sipers. This work is supported in part by grant DK-31623 from the NIH.

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