invited review

Natriuretic peptides and acute renal failure

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Vesely, David L. Natriuretic peptides and acute renal failure. Am J Physiol Renal Physiol 285: F167–F177, 2003;10.1152/ajprenal.00259.2002.—Atrial natriuretic peptides (ANPs) are a family of peptide hormones, e.g., ANP, long-acting natriuretic peptide, vessel dilator, and kaliuretic peptide synthesized by the ANP gene. Brain natriuretic peptide (BNP) and C-type natriuretic peptide are also members of this family but are synthesized by separate genes. Within the kidney, the ANP prohormone’s posttranslational processing is different from that of other tissues, resulting in an additional four amino acids added to the NH₂ terminus of ANP (e.g., urodilatin). Each of these natriuretic and diuretic peptides increases within the circulation with acute renal failure (ARF). Renal transplantation but not hemodialysis returns their circulating concentrations to those of healthy individuals. BNP and adrenomedullin, a 52-amino acid natriuretic peptide, have beneficial effects on glomerular hypertrophy and glomerular injury but do not improve tubular injury (i.e., acute tubular necrosis). Vessel dilator ameliorates acute tubular necrosis with regeneration of the brush borders of proximal tubules. Vessel dilator decreases mortality in ARF from 88 to 14% at day 6 of ARF, even when given 2 days after renal failure has been established.

adrenomedullin; atrial natriuretic peptide prohormone; acute tubular necrosis; transplantation; hemodialysis

ACUTE RENAL FAILURE (ARF) develops in 2–5% of all patients sent to tertiary-care hospitals (125). In 60% of patients, the underlying cause is a renal insult [i.e., acute tubular necrosis (ATN)] (39, 125). In the mid-1940s, when dialysis was introduced, the mortality from severe ARF was ~50% (39). This poor prognosis has not improved, and mortality now remains in the 40–80% range in oliguric ARF patients (4, 9, 22, 38, 39, 90, 125). The occurrence of ARF in the hospital increases the relative risk of dying by 6.2-fold and the length of hospitalization by 10 days (77). Thus ARF not only occurs with a high frequency but is also associated with high morbidity and mortality.

The present review will concentrate on the atrial natriuretic peptides (ANPs), adrenomedullin (ADM), and urodilatin, their pathophysiological changes with ARF, and their potential for the treatment of ARF. There are several excellent reviews on the biochemistry and molecular biology (28, 32, 56, 69, 73, 83, 106) and the physiology (7, 10, 36, 43, 54, 84, 86, 105, 119) of these natriuretic peptides so these aspects will not be reviewed in detail in the present review.

ANPs

ANPs consist of a family of peptides that are synthesized by three different genes (28, 32, 56, 73, 83) and then stored as three different prohormones [i.e., 126-amino acid (aa) ANP, 108-aa brain natriuretic peptide (BNP), and 126-aa C-type natriuretic peptide (CNP) prohormones] (56, 104). In healthy adults, the ANP prohormone’s main site of synthesis is the atrial myocyte, but it is also synthesized in a variety of other tissues, including the kidney (31, 116). The sites of synthesis of the ANPs in the approximate order in which they contribute to the synthesis are listed in Table 1.

Peptide Hormones Originating From the ANP Prohormone

Within the 126-aa ANP prohormone are four peptide hormones (Fig. 1), with blood pressure-lowering, natriuretic, diuretic, and/or kaliuretic (i.e., potassium-excreting) properties in both animals (8, 25, 26, 35, 37, 61, 113, 118, 127) and humans (109–112). These peptide hormones, numbered by their aa sequences beginning at the NH₂-terminal end of the ANP prohormone, consist of the first 30 aa of the prohormone [i.e., proANP-(1–30); long-acting natriuretic peptide (LANP)], aa 31–67 [i.e., proANP-(31–67); vessel dilator], aa 79–98 [proANP-(79–98); kaliuretic peptide], and aa 99–126 (ANP) (Fig. 1). Each of these four
peptide hormones circulates in healthy humans, with LANP and vessel dilator concentrations in plasma being 15- to 20-fold higher than ANP and 100-fold higher than BNP (24, 29, 30, 41, 114, 123). More than one peptide hormone originating from the same prohormone is common with respect to the synthesis of hormones (104). ACTH, for example, is derived from a prohormone that contains four known peptide hormones (104). The BNP and CNP genes, on the other hand, appear to each synthesize only one peptide hormone within their respective prohormones, i.e., BNP and CNP (7, 28, 32, 54, 55, 73). The natriuretic effects of LANP, kaliuretic peptide, and vessel dilator have different mechanism(s) of action from ANP, in that they inhibit renal Na\(^{+}\)/H\(^{+}\)-ATPase secondarily to their ability to enhance the synthesis of prostaglandin E\(_2\), which ANP does not do (18, 35). The effects of ANP, BNP, and CNP in the kidney are thought to be mediated by cGMP (10, 36, 84, 104).

ANP has been found to be a potent in vivo and in vitro inhibitor of aldosterone secretion via a direct effect on the adrenal (5, 14, 17, 23, 33, 51, 59) and indirectly through inhibition of renin release from the kidney (14, 53, 59, 103). Kaliuretic peptide and long-acting natriuretic peptide are also potent inhibitors of the circulating concentrations of aldosterone in healthy humans (108). Kaliuretic peptide and LANP effects on decreasing plasma aldosterone levels last for at least 3 h after their infusions have stopped, whereas ANP no longer has any effect on plasma aldosterone concentrations within 30 min of cessation of its infusion (108). Vessel dilator does not appear to have direct effects on aldosterone synthesis but is a potent inhibitor (66%) of plasma renin activity (117). The site of synthesis, molecular weight, and hemodynamic effects of each of the natriuretic peptides in humans is summarized in Table 1. ANP, LANP, and vessel dilator cause a significant diuresis and natriuresis in healthy humans (112). Kaliuretic peptide does not cause a significant natriuresis in healthy humans, but when infused in humans with congestive heart failure it causes a significant natriuresis (70).

**Urodilatin.** ANP prohormone posttranslational processing is different within the kidney from that which occurs in the heart, resulting in an additional four amino acids added to the NH\(_2\) terminus of ANP (i.e., proANP:95—126; urodilatin) (56, 69, 93) (Fig. 2). The rest of the amino acids in urodilatin are identical and in the same sequence as those in ANP (Fig. 2). Urodilatin and ANP have identical ring structures formed.

<table>
<thead>
<tr>
<th>Molecular Wt</th>
<th>Site of Synthesis</th>
<th>MAP</th>
<th>Diuresis</th>
<th>Natriuresis</th>
</tr>
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<tr>
<td>LANP 3,508</td>
<td>Atria, ventricle, GI, lung, kidney, brain, adrenal</td>
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<td>↑</td>
<td>↑</td>
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<tr>
<td>Vessel dilator 3,878</td>
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<td>↓</td>
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<tr>
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<td>↑</td>
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<tr>
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<td>Adrenal, kidney</td>
<td>↓</td>
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</table>

LANP, long-acting atrial natriuretic peptide; ANP, atrial natriuretic peptide; MAP, mean arterial pressure; BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide; CNS, central nervous system; DNP, *Dendroaspis* natriuretic peptide; GI, gastrointestinal tract; ↓, decrease; ↑, increase; −, no significant effect. The sites of synthesis are listed in approximate order in which they contribute to synthesis.
with cysteine-to-cysteine bonding (Fig. 2). Urodilatin is not formed in the heart or in other tissues except the kidney. This peptide hormone is synthesized by the same gene that synthesizes ANP, but in the kidney, as opposed to all other tissues that have been investigated, the ANP prohormone is processed differently, resulting in the formation of urodilatin rather than ANP (56, 69, 93). Urodilatin circulates in very low concentrations (i.e., 9–12 pg/ml) (115). Infusion of ANP increases the circulating concentration of urodilatin, suggesting that some of ANP’s effects may be mediated by urodilatin (115). Infusion of LANP, vessel dilator, and kaliuretic peptide, on the other hand, do not affect the circulating concentration of urodilatin in healthy humans (115).

**BNP and CNP**

**BNP.** BNP has similar diuretic and natriuretic effects and a short half-life as ANP (98). BNP’s half-life is 100-fold shorter than the half-lives of vessel dilator and LANP (1, 54, 98, 99, 104). BNP has remarkable sequence homology to ANP, with only four amino acids being different in the 17-aa ring structure common to both peptides (Fig. 2) (54, 55, 73, 83, 84, 98). Although BNP was named (98) for where it was first isolated (i.e., porcine brain), the main source of its synthesis and secretion is the heart (Table 1) (36, 54, 56, 84, 101). As with ANP, the highest levels of BNP are found in the atria of the heart (36, 101). BNP levels in the atria, however, are <1% of ANP levels (101). The immuno-reactive level of BNP within the ventricles is only 1% of BNP’s concentration within the atria (101). BNP, however, has been termed a “ventricular” peptide based on ventricular BNP mRNA levels being similar to those in the atria, and the ventricles are much larger than the atria (69).

The 108-aa BNP prohormone is processed within the heart to yield a biologically functioning BNP consisting of aa 77–108 of the BNP prohormone and the NH₂ terminus of the BNP prohormone (aa 1–76 of prohormone), both of which circulate (54). The circulating concentration of BNP is <20% that of ANP (36). The sequence homology of BNP differs appreciably across species (both in size and amino acid sequence) (28, 54, 68, 73, 101). BNP’s marked sequence variability explains, in part, the variations in its biological activity in different species. The peptide hormones from the ANP prohormone, on the other hand, have remarkable homology across different species (28, 32, 73, 104).

Mice overexpressing the BNP gene, where the circulating concentration of BNP is 10- to 100-fold higher than in healthy mice, have less glomerular hypertrophy and mesangial expansion with intraglomerular cells than healthy mice 16 wk after both received renal ablation (45). This mouse model of subtotal renal ablation, however, also has significantly increased ANP concentrations (74, 102, 128), which may also have contributed to the effects attributed to BNP in the BNP gene-overexpressing mice (45).

**CNP.** CNP has remarkable similarity to ANP in its amino acid sequence but lacks the COOH-terminal tail of ANP (Fig. 2) (6, 7, 99). CNP is present within the human kidney (62, 100) and has been found to have little effect on renal vasoconstriction (126). Although CNP has been reported to have natriuretic effects in some animals, when infused in humans at physiological concentrations and in concentrations that reached 4- to 10-fold above those observed in disease states, CNP did not affect renal function (6). Thus in healthy humans CNP had no effect on renal hemodynamics, systemic hemodynamics, intrarenal sodium handling, sodium excretion, or plasma levels of renin and aldo-

**Fig. 2.** Amino acid sequences of the natriuretic peptides. Each of the sequences are the human sequences except for **Dendroaspis** natriuretic peptide (DNP), whose sequence is only known in the snake. The brackets illustrate the location of cystine bridges that help to form a ring structure in a number of these peptides. BNP, brain natriuretic peptide; CNP, C-type natriuretic peptide.
terone (6). In another study of infusion of CNP in healthy humans, CNP increased 60-fold in plasma and there were no significant hemodynamic or natriuretic effects (40). The authors of this study concluded that it is unlikely that CNP has any endocrine role in circulatory physiology (40). There is one study in humans where infusion of CNP to increase CNP plasma levels 550-fold caused a 1.5-fold increase in urinary volume and sodium excretion (42). With this very high plasma concentration of CNP, both ANP and BNP also increased 2.4-fold (42), which may have been the cause of the natriuresis and diuresis observed. Each of these studies suggests that CNP does not contribute physiologically to any natriuresis or diuresis in humans (6, 40, 42).

**ADM**

ADM, a 52-aa peptide originally isolated from an extract of a pheochromocytoma (48), also has biological properties nearly identical to those of the ANPs (Table 1) (43, 48, 86). Infusion of ADM lowers blood pressure and produces a diuresis and natriuresis (43, 48, 86). ANP but not LANP, vessel dilator, or kaliuretic hormone increases the circulating concentration of ADM three- to fourfold, suggesting that some of the reported effects of ANP may be mediated via ADM (107). However, the natriuresis and diuresis secondary to ANP in the above investigation were much larger than has ever been observed with ADM (107), suggesting that ADM does not mediate all of the natriuretic and diuretic effects of ANP. ADM is not produced in the atrium of the heart and therefore is not one of the ANPs per se as these peptides were so named because they are synthesized in the atrium of the heart (Table 1). ADM is a larger peptide than any of the ANPs, with its main site of synthesis being in the adrenal, but isolated renal cells also have the ability to synthesize ADM secondarily to stimulation by vasopressin via V₂ receptors (Table 1) (88). Because vasopressin [antidiuretic hormone (ADH)] inhibits a diuresis, these findings are opposed to findings that ADM causes a diuresis (43, 48, 86).

*Dendroaspis Natriuretic Peptide*

*Dendroaspis* natriuretic peptide (DNP) is the newest of the natriuretic peptides. This peptide was isolated from the venom of the green mamba, *Dendroaspis angusticeps* (94). The venom also contains several polypeptide toxins that block cholinergic receptors to cause paralysis (94). DNP-like peptide has been reported to be present in human plasma and in heart atria (91). In plasma, DNP’s concentration is very low, i.e., 6 pg/ml, which is one-half of 1% of the circulating ANPs (91). This peptide has a 17-aa disulfide ring structure similar to ANP, BNP, and CNP (Fig. 2) and causes a natriuresis and diuresis in dogs (58). Infusion of DNP does not cause any significant change in the circulating levels of ANP, BNP, or CNP (58).

Richards et al. (81) have questioned whether DNP actually exists in humans and mammals because it has not been characterized by HPLC linked to immunoassay, followed by purification and analysis to establish the human amino acid sequence as has been done with the above natriuretic peptides. The gene for DNP has not been cloned in the snake or in any mammal as has been done for each of the other natriuretic peptides (81). Richards et al. suggest that DNP may be “snake BNP” because BNP varies markedly in amino acid sequence among species (and the BNP sequence in this snake is unknown). The peptides from the ANP prohormone are markedly conserved among species (36, 104), and one would not suspect that DNP is one of these peptides as their amino acid sequences are markedly different from DNP. Further experimentation with the above studies suggested by Richards et al. (81) should give us more insight with respect to this interesting peptide.

**IMMUNOCYTOCHEMICAL LOCALIZATION AT ANPs IN THE KIDNEY**

The kidney is a prime target organ (along with vasculature) of the physiological effects of ANPs (10, 56, 104). Immunohistochemical studies have localized ANP, vessel dilator, and LANP to the sub-brush border of the pars convoluta and pars recta of the proximal tubules of animal (79) and human (85) kidneys (Fig. 3). Immunofluorescent studies reveal that each of these peptides has a strong inclination for the perinuclear region in both the proximal and distal tubules (79, 85). Immunohistochemical studies localize urodilatin to the distal tubule, with no evidence of urodilatin in the proximal tubule (85). ANP mRNA studies have confirmed that ANP prohormone is synthesized in the kidney (34, 76, 97, 102). The amount of ANP prohormone present in the kidney, however, is only one one-ninetieth of that produced in the atria of the heart (104). These studies taken together suggest that because urodilatin (93) is found mainly in the distal nephron (82, 85) and because it is part of the ANP prohormone (104), synthesis of the ANP prohormone may take place in the distal nephron (82, 85). The ANP prohormone gene is present and can be expressed in the kidney (34, 76, 97, 102). The gene is upregulated within the kidney in early renal failure in diabetic animals (34) and in the remnant kidney of rats with % reduced renal mass (102).

**INFLUENCE OF ARF ON THE CIRCULATING CONCENTRATION OF ANPs**

Each of the ANPs from the ANP prohormone (30, 41, 50, 70, 114, 123, 124), BNP (13, 16, 21, 54, 55), and CNP (7, 40, 42) increases in the circulation in salt- and water-retaining states such as congestive heart failure and renal failure compared with their concentrations in healthy individuals. Thus in salt- and water-retaining states there is no decrease in production of these natriuretic and diuretic peptides, but rather there is increased production (mainly from the ventricle of the heart) (32, 76) in an apparent attempt to overcome the salt and water retention via their natriuretic and di-
uretic properties (123). The disease state associated with the highest circulating concentrations of ANPs is renal failure (29, 30, 89, 122, 124). One would suspect that ANPs are higher in renal failure vs. class IV congestive heart failure patients because of the added pathophysiology of decreased degradation of these peptides with the decreased functioning of renal parenchyma (124). However, Franz et al. (30) have shown that there is an increased excretion of ANPs in renal failure and that the increase in vessel dilator excretion occurs even before serum creatinine levels begin to rise. The circulating concentrations of ANPs in chronic renal failure (CRF) appear to reflect volume status (50, 66, 80, 124). Despite increased circulating ANPs in sodium-retaining disease states, the kidney retains sodium and is hyporesponsive to ANP, LANP, and BNP (11, 54, 77, 109). The mechanism for the attenuated renal response to these natriuretic peptides is multifactorial and includes renal hypoperfusion and activation of the renin-angiotensin-aldosterone and sympathetic nervous systems (10, 36, 65).

Hemodialysis

ANPs. These peptides have been suggested as possible indicators of when to perform dialysis in persons with CRF (50, 66, 80, 89, 124). However, other data suggest that ANPs are not useful in predicting when hemodialysis is necessary (29). Hemodialysis lowers the circulating concentration of ANP by 34–42%, with the amount of decrease appearing to be related to the volume status of the patients (50, 121, 124). Hemodialysis does not decrease the circulating concentrations of vessel dilator and LANP (124). Part of the reason for the difference in the effects of hemodialysis on ANPs is that <1.5% of vessel dilator and LANP crosses the dialysis membrane compared with 15–25% of ANP crossing hemodialysis membranes (124). Hemodialysis using cellulose-triacetate dialyzers reduces plasma levels of these peptides in ARF more than hemodialysis therapy with polysulfone dialyzers (29).

BNP. Hemodialysis has been reported to both lower (55) and have no effect on circulating BNP levels (49). Before dialysis in persons with CRF, plasma BNP levels have no relationship to serum creatinine or mean blood pressure (55). In those CRF patients in whom plasma BNP levels decrease with dialysis, this decrease correlates with the degree of postural blood pressure drop, but there is no correlation with the fall in serum creatinine (55). In none of the studies of BNP and dialysis (13, 21, 49, 55) has BNP ever returned to its circulating concentration in healthy individuals. With volume repletion after hemodialysis, there is an exaggerated release of ANP, but changes in BNP are small and without any correlation with either atrial or ventricular volume (21).

Renal Transplantation

Successful transplantation of functioning kidneys decreases the markedly elevated circulating levels of ANPs in persons with ARF to those in healthy individuals (75, 78). Nonfunctioning renal allografts continue to have elevated circulating concentrations of ANPs (78). Postrenal transplantation, it takes 7 days for ANP and 10 days for vessel dilator to return to normal (75). This suggests that the allograft kidney does not fully function immediately with respect to clearing these peptides. The half-life of ANP in healthy persons is only 2.5–3.5 min (1, 104). If the transplanted kidneys began to function immediately, one would have expected the circulating concentration of ANP to have decreased to the normal range within 24 h (i.e., 360 half-lives). Vessel dilator has a 20-fold longer half-life compared with that of ANP (1, 104), which may explain why it takes 3 more days for this peptide hormone to
normalize in the circulation after successful renal transplantation. If one gives ANP (via infusion) at the time of renal transplantation, this does not appear to have any beneficial effect on the outcome of the renal allograft (87).

**PROTECTIVE AND THERAPEUTIC EFFECTS OF ANPs IN ARF**

**ANP and Urodilatin**

Several of the atrial peptides have been investigated as possible treatment(s) of ARF. ANP had encouraging results in early studies of ARF in animals (20, 57). The infusion of ANP (20, 57, 60, 66, 68, 71, 74, 77, 90, 95) or urodilatin (63, 92, 96) in rat models of ischemic ARF attenuated renal tissue damage and preserved glomerular filtration rate (GFR). Nakamoto et al. (68) and Shaw et al. (95) were able to shorten the course of renal artery cross-clamping-induced ARF in rats with ANP. Conger et al. (20) found a marked improvement in GFR in a rat renal artery clamp model when ANP-III (0.2 μg·kg⁻¹·min⁻¹) was given intravenously immediately after clamp release in combination with dopamine sufficient to maintain mean arterial pressure above 100 mmHg. In the rat, ANP had no effect on GFR when given intravenously (56) but did have an effect on GFR when given directly into the renal artery for 4 h (95). The inability of ANP to increase GFR when given intravenously could be restored if dopamine were given simultaneously (20). In the dog, the improvement in renal perfusion only lasted for a short period after a 180-min infusion of ANP (71). When ANP was given by intra-aortic bolus on days 1 and 2 after the above-mentioned infusion, there was not any significant improvement in renal perfusion on those days (71). Thus in animals the improvement in renal failure with ANP was only of short duration and depended on whether ANP was given intravenously or directly into the artery (20, 56, 71).

The administration of 0.2 μg of ANP·kg body wt⁻¹·min⁻¹ for 24 h to humans with ARF revealed that ANP did not cause significant improvement and did not reduce the need for dialysis or reduce mortality (3). ANP infusions were associated with decreased survival in the nonoliguric ARF subjects, who represented 75% of the subjects (3). The usefulness of ANP for treatment is hampered by its short half-life of 2.5 min (1, 104) and by its very short duration of action (20, 57, 59, 61, 77, 112). Of 504 ARF patients treated with ANP, 46% developed hypotension, which would further limit its usefulness in ARF (3). Use of several of the ANPs investigated to treat ARF has each resulted in severe hypotension and bradycardia (3, 47). In addition to ANP resulting in 46% of renal failure patients becoming hypotensive (3), urodilatin has also been associated with severe hypotension and bradycardia, when given as a potential treatment of congestive heart failure (47). ANP is now considered more harmful than helpful with respect to the treatment of ARF (11). ANP has also been investigated in humans with CRF to determine whether it could prevent radiocontrast-induced nephropathy, one cause of hospital-acquired ARF (52). When ANP was given before and during a radiocontrast study in 247 patients, no beneficial effect was found (52). Urodilatin has been suggested as a possible treatment of renal failure (63, 92, 96), but in double-blind trials in ARF patients urodilatin was found to have no beneficial effect (63).

**Vessel Dilator**

Vessel dilator appears to be one of the ANPs with promising therapeutic potential in the treatment of ARF. Vessel dilator (0.3 μg·kg⁻¹·min⁻¹ via ip pump) decreases blood urea nitrogen and serum creatinine from 162 ± 4 and 8.17 ± 0.5 mg/dl, respectively, to 53 ± 17 and 0.98 ± 0.12 mg/dl in ARF animals in which ARF was established for 2 days (after vascular clamping) before vessel dilator was given (19). At day 6 of ARF, mortality decreased to 14% with vessel dilator from 88% without vessel dilator (19). The ARF animals that did not receive vessel dilator had moderate (i.e., 25–75% of all tubules involved) to severe (i.e., >75% of all tubules necrotic) ATN by day 8 after the ischemic event (Fig. 4B). The brush borders of the proximal and distal tubules, with the proximal tubules being more severely affected (Fig. 4B). The glomeruli of the ARF animals was spared compared with the renal tubules, with the glomeruli appearing to be normal in the ARF animals (Fig. 4, A and B). The addition of vessel dilator after renal failure had been present for 2 days resulted in a marked improvement in renal histology, with scores ranging from 0 (i.e., no tubular necrosis) to 1 (i.e., <5% of the tubules involved) (19). When the kidneys were examined at day 8 of renal failure, the brush borders of the proximal tubules in the ARF animals treated with vessel dilator were present (Fig. 4C), which was similar with respect to the proximal tubules in healthy animals (Fig. 4A). In the ARF animals not treated with vessel dilator, the brush borders of the tubules were destroyed (Fig. 4B). The glomeruli of vessel dilator-treated ARF animals also appeared normal (Fig. 4C). It should be pointed out that the animals treated with vessel dilator did have severe renal failure before vessel dilator was begun on the second day of renal failure (19). It is also important to note that the animals treated with vessel dilator that had a significant increase in survival had nonoliguric renal failure (19). As noted above, nonoliguric renal failure subjects treated with ANP had a decreased survival rate, and it was nonoliguric renal failure subjects who did not respond to ANP (3). Vessel dilator, LANP, and kaliuretic peptide, as opposed to ANP, BNP, and urodilatin, have never caused a hypertensive episode when given to either healthy animals or humans (61, 111, 112) or when given to humans with sodium and water retention (70, 109, 110).

The ability of vessel dilator to reverse ischemic ARF is consistent with the important concept, based on experiments at the cellular level and in humans with...
ATN, that the pathophysiology of ischemic ARF is due to a sublethal and reversible injury to renal tubular cells (9, 64). This reversible injury is now thought to contribute more predominately to renal tubular dysfunction than permanent tubular cell necrosis (9, 64). Pathological similarities between humans and rats with ischemic ATN are that the injury is to the proximal tubular brush border, with a predilection for the most severe injury to occur in the proximal straight (S3 segments) tubules (64). As outlined above, it was the proximal tubule brush borders that were mainly regenerated by vessel dilator even when given 2 days after ischemic ATN (19). Part of the improvement by using vessel dilator may be due to its ability to cause intra-renal vasodilation because it is a strong vasodilator (113). The reason vessel dilator has greater beneficial effects than ANP, BNP, CNP, and urodilatin in ARF appears due, at least in part, to its ability to cause the endogenous synthesis of renoprotective PGE2, which ANP, BNP, CNP, and urodilatin do not have (18, 35).

Prostaglandins have renoprotective effects in ARF (2, 46, 121). An indication that PGE2 is renoprotective (by maintaining glomerular hemodynamics) is the observation that cyclooxygenase inhibitors in congestive heart failure and volume depletion states augment the reduction in renal blood flow and GFR (27, 120). With respect to the mechanism of the protective effects of prostaglandins in ARF, after ischemic injury there is a dramatic decrease in perfusion in the outer medulla (44), a region of renal tissue that normally operates “on the verge of ischemia” (12). Prostaglandins have a favorable effect on blood flow distribution to this region (67). In addition, prostaglandins have distinct cytoprotective effects and improve microvascular permeability in ischemic ARF (15, 46). Prostaglandins are not stored in the kidney but rather have to be synthesized acutely secondarily to a stimulating agent such as vessel dilator (18, 35) for prostaglandins to have a positive beneficial effect in renal failure.

ADM

There is evidence that ADM is renoprotective in Dahl salt-sensitive rats in that when they were perfused for 7 days, their glomerular injury score was 54% less ($P < 0.05$) than in untreated Dahl salt-sensitive rats (72). The ADM-treated salt-sensitive rats, however, had considerably more ($P < 0.01$) glomerular sclerosis and anterolateral sclerosis and atrophic tubules after treatment than the control Dahl salt-resistant rats (72).

CNP

CNP increases in the circulation in ARF (42), but its effects in ARF are unknown. As above, CNP has no natriuretic effects in healthy humans (6, 40, 42).

DNP

DNP has been evaluated in persons with end-stage renal disease on dialysis and was found not to correlate ($P = 0.62$) with the echocardiographic left ventricular mass index, whereas ANP and BNP did correlate with the left ventricular mass index of these end-stage renal patients (16). DNP has not been investigated with respect to its possible therapeutic effects in renal failure.

SUMMARY AND FUTURE DIRECTIONS

ANPs are both synthesized (34, 76, 102), and have some of their most potent biological effects, e.g., natriuresis and diuresis, within the kidney (8, 25, 26, 35, 37, 61, 118, 127). Vessel dilator, via its ability to ameliorate ARF and enhance tubule regeneration in ATN (19), may prove useful in the future in the treatment of ARF. BNP and ADM, with their effects in glomerular hypertrophy (45) and glomerular injury (72), respectively, may be useful in the treatment of renal glomerular diseases. Because BNP, ANP, and ADM do not appear to help tubular diseases such as ATN, the major cause of ARF (39, 125), their therapeutic potential in
ATN appears limited. Future studies with these peptide hormones in humans with ARF and/or glomerular diseases are necessary to determine whether the findings in animal models of ARF are applicable to the treatment of humans with ARF.

The author thanks Charlene Pennington for secretarial assistance and the numerous coinvestigators without whom all of the investigations reported herein could not have been completed.

DISCLOSURES

This work was supported in part by grants from the National Institutes of Health, a Merit Award from the U.S. Department of Veteran Affairs, and a Grant-in-Aid from the American Heart Association, Florida-Puerto Rico Affiliate.

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