Inhibitors of ANF Metabolism
Potential Therapeutic Agents in Cardiovascular Disease

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Atrial natriuretic factor (ANF), a 28–amino acid peptide hormone synthesized and secreted from atrial myocytes, has been suggested to play an important role in the regulation of extracellular fluid volume and arterial pressure. Physiological and pharmacological doses of this peptide have been shown to produce natriuresis and diuresis, vasorelaxation, and inhibition or antagonism or both of important hormonal regulatory systems, such as the renin-angiotensin-aldosterone system. Because of its multiple actions, ANF is thought by many investigators to play an important role in balancing or modulating the various sodium-retaining systems of the body. Obviously, the diverse actions of ANF have also led many investigators to speculate that ANF may be a potentially important therapeutic tool for the treatment of sodium-retaining diseases such as congestive heart failure and hypertension. The peptide structure of ANF, however, limits its therapeutic usefulness since peptides of this length can only be administered intravenously. This limitation has been overcome by the recent development of compounds which alter the metabolism of endogenously produced ANF. Inhibition of important degradative pathways of ANF in vivo could theoretically be a valuable therapeutic and physiological tool for regulating endogenous levels of ANF.

Once in the circulation, ANF has a half-life of 2–4 minutes. The specific metabolic pathway for ANF has not yet been fully elucidated. One pathway which has been suggested involves enzymatic degradation. Neutral endopeptidase (NEP) 24.11 is a protease that hydrolyzes peptide bonds on the amino-terminal side of hydrophobic proteins where that bond does not involve the N-terminal or C-terminal residue. The enzyme is distributed in various organs including the brain, lung, and kidney. ANF is cleaved by NEP at the Cys-105–Phe-106 and Ser-123–Phe-124 bonds.

Cleavage at these sites results in inactivation of ANF. In addition to endopeptidase-mediated inactivation of ANF, recent investigations have suggested that ANF levels may also be reduced by a receptor-mediated event whereby ANF binds to a high-capacity receptor that is not coupled to guanylate cyclase, the second messenger system for the biological receptor. Binding to the “clearance” receptor has been proposed to result in an uptake of the receptor ligand complex and removal of the peptide from the circulation. The quantitative importance of each of these pathways and other unknown pathways has not yet been determined. Inhibitors of the various metabolic pathways could theoretically provide a means of blocking ANF degradation and increasing circulating plasma levels of circulating ANF.

In this issue of Circulation, Cavero and colleagues provide one of the first published reports detailing the acute renal and cardiovascular actions of a specific neutral endopeptidase inhibitor (NEP-I) in experimental congestive heart failure. In dogs with severe congestive heart failure induced by 8 days of rapid ventricular pacing, NEP inhibition resulted in a slight increase in plasma levels of ANF. NEP inhibition also resulted in significant natriuresis and diuresis. Interestingly, infusion of exogenous ANF at a rate that increased plasma levels of ANF above those resulting from NEP inhibition had no significant effect on sodium excretion. These findings raise interesting questions related to the mechanisms whereby NEP-I increases sodium and water excretion. Are the effects of NEP-I mediated by ANF? Does NEP-I increase sodium excretion by mechanisms that are different than ANF?

The finding that the natriuresis produced by NEP-I occurred despite no significant changes in renal blood flow or glomerular filtration rate suggests a renal tubular action of NEP-I. Cavero and colleagues suggest that one mechanism whereby NEP-I might decrease renal tubular reabsorption of sodium is by inhibition of angiotensin II–stimulated proximal tubule sodium reabsorption. This suggestion is supported by the increased fractional excretion of lithium by animals in their study and by recent reports by Garvin and Harris et al illustrating, by use of isolated perfused tubule and microperfusion techniques, the reduction by ANF of angiotensin II–stimulated proximal tubule sodium reabsorption.
Although a proximal tubule effect of NEP-I is likely, other tubular mechanisms probably exist to explain why NEP-I produced a greater natriuresis than did exogenous ANF. Distal delivery of a higher concentration of intraluminal ANF is a possibility; however, there is no strong evidence that ANF can act on the luminal side of the renal tubules or that intraluminal ANF has access to receptors located on the basolateral membranes. It is possible that NEP-I inhibitor may be more effective in reducing intrarenal levels of sodium-retaining factors which are most likely responsible for the blunted natriuretic response to exogenous ANF in congestive heart failure.\textsuperscript{13} Whatever the mechanisms may be, it is clear from the study of Cavero et al\textsuperscript{10} that NEP inhibition is more effective in producing a natriuresis than is exogenous ANF in congestive heart failure.

ANF has also been shown to influence cardiac function in congestive heart failure via its systemic hemodynamic effects. Cody and colleagues\textsuperscript{14} previously reported that short-term intravenous infusion of ANF into patients with congestive heart failure improved cardiac output and decreased pulmonary capillary wedge pressure. Other studies in congestive heart failure patients and in animals with congestive heart failure have also demonstrated that short-term infusions of ANF result in an improvement in cardiac output.\textsuperscript{15–17} It is believed that this improvement in cardiac output is due to the ability of ANF to reduce cardiac afterload through its systemic vasodilatory action.\textsuperscript{18}

Although numerous studies have examined the short-term effects of exogenous ANF on cardiac function in congestive heart failure, there is very little, if any, published information regarding the cardiovascular effects of NEP inhibition in congestive heart failure. The paper by Cavero and colleagues\textsuperscript{10} describes the acute systemic hemodynamic response to NEP inhibition in dogs with severe congestive heart failure. They report that NEP inhibition had no significant effect on cardiac output or left atrial pressure. There was, however, a slight reduction in right atrial pressure during NEP-I administration. Systemic vascular resistance actually increased during NEP-I infusion. It is uncertain whether this increase in systemic vascular resistance is due to time-dependent factors, however, because time controls were not employed in their study. Interestingly, infusion of exogenous ANF had similar effects on systemic hemodynamics. The failure of exogenous ANF to improve cardiac output, as described in earlier studies, may be related to the severity of the congestive heart failure in their animal model. Further studies will be necessary to determine the effectiveness of NEP-Is in the improvement of cardiac function in varying degrees of congestive heart failure.

The renal excretory effects of NEP inhibition make NEP-Is potentially useful therapeutic tools for the treatment of sodium-retaining diseases such as congestive heart failure and hypertension. Their overall effectiveness as a class of drugs still remains to be determined. Many questions remain unanswered and many more experiments must be performed. Future studies should focus on the long-term actions of inhibitors of ANF metabolism. The full effectiveness of these drugs may only be realized after long-term administration (for a period of days rather than minutes). We have previously reported that the hypotensive effects of synthetic ANF are much more potent during long-term than during short-term administration in normal dogs.\textsuperscript{19} Similar findings have also been made in humans and in various hypertensive animals.\textsuperscript{20,21} Recent studies also suggest that the systemic hemodynamic mechanisms mediating the chronic hypotensive effect of ANF may be completely different than the mechanisms of its short-term administration.\textsuperscript{21} It would appear that studies on the long-term effects of ANF metabolic inhibitors are essential to determine their importance and effectiveness as therapeutic tools for the treatment of cardiovascular diseases such as congestive heart failure and hypertension. Indeed, in a recently published report by Sybertz et al,\textsuperscript{22} an orally active NEP-I was shown to reduce mean arterial pressure in spontaneously hypertensive rats by 30-40 mm Hg after 5 days of administration. In contrast, NEP-I had no effect on mean arterial pressure after the first 4 hours of administration.

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References


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