

Does the Heart's Hormone, ANP, Help in Congestive Heart Failure?

Joseph Winaver, Aaron Hoffman, Zaid Abassi, and Aviad Haramati

In congestive heart failure, increased secretion of atrial natriuretic peptide (ANP) is an important compensatory mechanism that unloads the failing heart and promotes renal salt and water excretion. However, activation of opposing sodium-retaining factors, particularly the renin-angiotensin system, reduces renal responsiveness to ANP and shifts the cardiovascular system to a state of decompensation.

More than a decade has elapsed since the original description by de Bold and co-workers (6) of the potent natriuretic activity present in extracts of rat atria. Since then, major advancements have taken place in our understanding of the role of the heart's hormonal system, in both physiological and pathophysiological conditions (4). Atrial natriuretic peptide (ANP), the 28-amino acid residue peptide of cardiac origin, is the most familiar and thoroughly studied member of a family of natriuretic peptides containing at least two other members, brain natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), encoded by different, independent genes. The biological actions of the natriuretic peptides are mediated by binding of the peptide to specific membrane receptors (ANP_a and ANP_b) followed by activation of an intracellular signal transduction system using guanosine 3',5'-cyclic monophosphate (cGMP) as a second messenger. An additional class of receptor has been identified that is not coupled to guanylate cyclase and apparently serves to clear the hormone from the circulation (ANP_c receptor). Inactivation of the hormone is also achieved enzymatically by neutral endopepti-

dase 24.11 (NEP), a zinc metalloproteinase, located mainly in the kidney and lung.

Numerous studies have established the role of ANP in the regulation of extracellular fluid volume and the control of blood pressure. In addition to its powerful natriuretic activity, ANP also relaxes vascular smooth muscle, shifts fluids from intravascular to extravascular compartments, inhibits the activity of the renin-angiotensin-aldosterone system (RAAS) and other vasoconstrictor systems, and acts on the central nervous system to modulate vasomotor tone, thirst, and vasopressin release (4). ANP has also recently been shown to exert antiproliferative, growth-regulatory properties in cultured glomerular mesangial cells, vascular smooth muscle cells, and endothelial cells. Taken together, these multiple biological actions establish the importance of the ANP hormonal system in the regulation of body fluid and cardiovascular homeostasis.

ANP in congestive heart failure

Perturbations in the ANP system have been described in several pathophysiological conditions associated with abnormal regulation of body fluids and blood pressure control, particularly in edematous disorders (4). Congestive heart failure (CHF) is, perhaps, the most widely recognized pathological entity that involves aberrations in the ANP system. Although initially considered to be a state of "ANP deficiency," it soon became evident, based on direct measurements of plasma levels of the hormone, that circulating ANP levels were markedly elevated in CHF (5) (Fig. 1). In fact, the highest concen-

"The biological actions of the natriuretic peptides are mediated by . . . guanosine 3',5'-cyclic monophosphate (cGMP) . . ."

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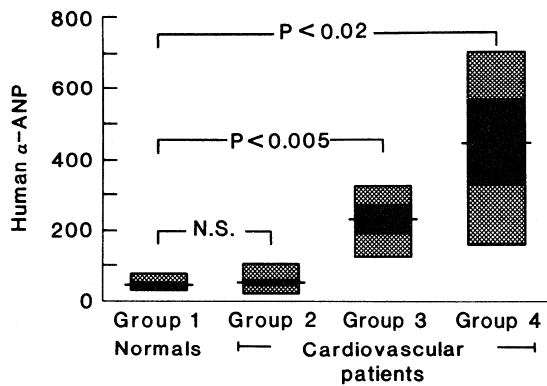


FIGURE 1. Circulating levels of atrial natriuretic peptide (ANP; pg/ml) in normal human subjects (*group 1*), in patients with cardiovascular disease but normal cardiac filling pressures (*group 2*), in patients with cardiovascular disease and elevated cardiac filling pressures but without congestive heart failure (*group 3*), and in patients with cardiovascular disease, markedly elevated cardiac filling pressures, and congestive heart failure (*group 4*). [Reprinted with permission from Burnett et al. (5). Copyright 1986 American Association for the Advancement of Science.]

trations of ANP in the circulation occur in CHF, above and beyond the levels found in any other edema-forming state. Moreover, plasma ANP levels in CHF were found to correlate with the severity of cardiac failure, as well as with the elevated atrial pressures and other parameters of left ventricular dysfunction. These high levels of ANP reflect enhanced synthesis and release of the hormone, not only by atria but also by recruitment of ventricular myocytes.

The elevated level of a potent natriuretic hormone appears to be at odds with the tendency of patients and experimental animals with CHF to retain salt and water. In fact, the observed rise in plasma ANP levels is viewed by some investigators as simply an epiphenomenon, secondary to a rise in intracardiac pressures. However, others consider the increase in circulating ANP as an important adaptive mechanism that helps unload the failing myocardium through systemic vasodilation, decreased venous return, and reduced vascular volume. In addition to these cardiovascular effects, ANP likely plays an important role in promoting salt and water excretion by the kidney in the face of myocardial failure. Indeed, studies in experimental models of CHF in which the biological activity of ANP was blocked by specific antibodies or, more recently, by the ANP receptor antagonist HS-142-1 (12), support this notion.

The question remains, however, Why does salt and water retention still occur in severe congestive heart failure, despite the high circulating levels of ANP? Several explanations have been put forth to resolve this apparent discrep-

TABLE 1. Proposed mechanisms for the attenuated activity of ANP in congestive heart failure

Mechanism
1. Decreased renal perfusion pressure
2. Increased activity of the renin-angiotensin-aldosterone system
3. Increased renal sympathetic activity
4. Downregulation of biologically active ANP receptors
5. Increased degradation of ANP or its second messenger cGMP
6. Release of less active forms of ANP (β -ANP, proANP)

ANP, atrial natriuretic peptide; cGMP, guanosine 3',5'-cyclic monophosphate.

ancy, such as the appearance of abnormal (less active) circulating forms of the peptide (β -ANP) and inadequate secretory reserves to the degree of heart failure (i.e., relative ANP deficiency). However, because circulating levels of the native biologically active form of ANP are clearly elevated in CHF, those factors cannot account for the avid salt and water retention. Rather, it appears that in CHF the kidney becomes less responsive to the natriuretic action of the endogenous hormone. Indeed, we believe that the development of renal hyporesponsiveness (and in severe cases refractoriness) to the renal effects of the hormone represents a critical turning point in the development of salt retention and edema formation in CHF.

Renal hyporesponsiveness to ANP in CHF

The blunted renal response to ANP is one example of a more generalized target organ hyporesponsiveness to the hormone in CHF. Thus there is also significant attenuation in ANP's systemic hemodynamic effects and the renin-suppressing activity of the hormone. Table 1 summarizes the potential mechanisms, suggested in the literature, that may contribute to the development of end-organ resistance to ANP in CHF.

In recent years, our group has studied the pathophysiological alterations of the ANP system in rats with aortocaval (A-V) fistula, an experimental model of CHF (1-3, 14). This model is characterized by renal and neurohumoral changes that closely mimic those found in patients with advanced cardiac failure. These include reduced renal blood flow and glomerular filtration rate, urinary salt and water retention, activation of the RAAS, and increased secretion of, but blunted response to, ANP.

“... in CHF the kidney becomes less responsive to the natriuretic action of the endogenous hormone.”

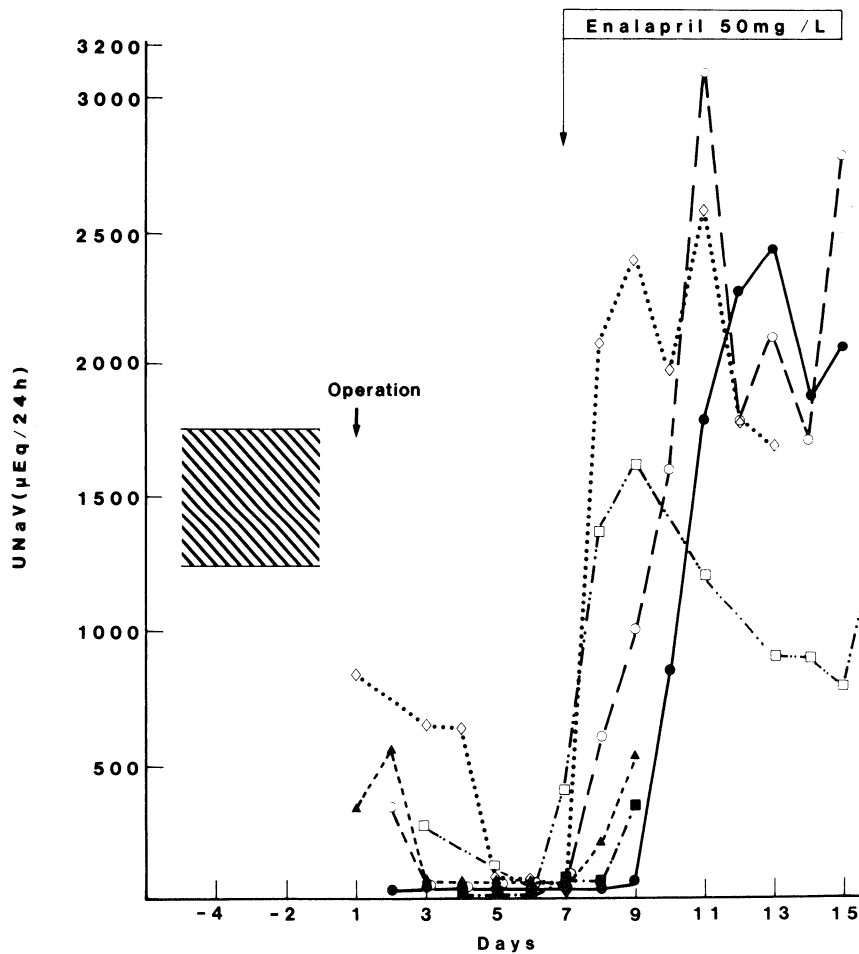


FIGURE 2. Effect of angiotensin-converting enzyme inhibitor enalapril on daily urinary sodium excretion (U_{NaV}) in decompensated rats with aorticaval fistula. Hatched area represents average daily sodium excretion \pm SE in control preoperative period. Oral administration of enalapril to sodium-retaining decompensated rats caused a dramatic increase in daily U_{NaV} within 24–48 h that in some animals exceeded basal rate of excretion. [From Winaver et al. (14).]

Moreover, based on their daily sodium excretion, the rats with A-V fistula could be further subdivided into two distinct groups: compensated CHF (which eventually returned to sodium balance) and decompensated CHF (which displayed progressive sodium retention and edema formation) (14). The initial studies demonstrated that the natriuretic response to exogenous ANP administration was attenuated in rats with A-V fistula compared with controls, although rats with compensated CHF responded more favorably than the decompensated group (2, 14). Interestingly, plasma ANP levels were similarly elevated in both subgroups, indicating that the difference in renal handling of sodium in the two subgroups was not related to alterations in the secretion of the peptide, but more likely to a change in renal sensitivity to ANP. Thus the findings suggested that, in animals with decompensated CHF, the presence of potent sodium-retaining factors may overwhelm the natriuretic effect of ANP.

We later demonstrated that the RAAS played

a major role as an antinatriuretic, volume-retaining force in rats with decompensated CHF. Removal of the influence of the RAAS, by pharmacological inhibition of the angiotensin converting enzyme (ACE), and more recently with specific angiotensin II (ANG II) receptor antagonists, significantly improved the natriuretic response to exogenous ANP (2, 3). Furthermore, ACE inhibition also restored daily sodium excretion to normal in rats with decompensated CHF, suggesting that the response to the high endogenous levels of the hormone was improved as well (Fig. 2). Numerous other studies provided evidence of the importance of the RAAS in the pathophysiology of CHF and the beneficial effects of pharmacological inhibition of this system in the treatment of patients with CHF. It is conceivable that the success of this treatment is related not only to improving cardiac performance by unloading the failing myocardium but also to restoring the natriuretic effects of ANP, the body's natural defense against volume overload.

“... the presence of potent sodium-retaining factors may overwhelm the natriuretic effect of ANP.”

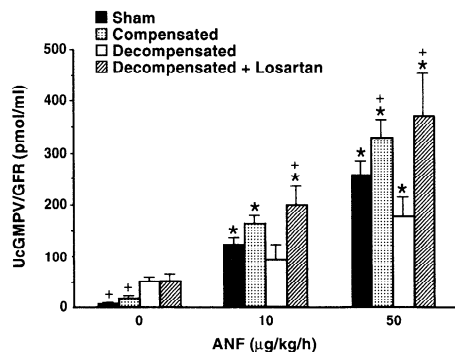


FIGURE 3. Effects of ANP on urinary guanosine 3',5'-cyclic monophosphate (cGMP) excretion (U_{cGMPV}) corrected for glomerular filtration rate (GFR) (U_{cGMPV}/GFR) in sham-operated rats and in rats with aortic fistula, either compensated, decompensated, or decompensated treated with losartan (ANG II receptor antagonist). ANG II receptor blockade restored urinary cGMP excretion in response to ANP in decompensated rats. * $P < 0.05$ vs. baseline value within each group. + $P < 0.05$ vs. decompensated rats not treated with losartan. [From Abassi et al. (3).]

Cellular mechanisms of ANP resistance in CHF

The mechanism(s) of the altered renal responsiveness to ANP in CHF has not been completely elucidated. The attenuated effects of ANP may be a consequence of altered renal hemodynamics, which include decreased renal perfusion pressure and changes in peritubular physical forces leading to enhanced tubular sodium reabsorption. This may be related, in part, to the effects of increased systemic and intrarenal ANG II concentrations, which occur in heart failure. At the cellular level, the interference with the biological activity of ANP may occur at any of the steps in the transduction of the hormonal signal. An interesting finding that deserves further investigation is the demonstration in cultured vascular smooth muscle cells and mesangial cells that ANG II, and perhaps other vasoconstrictor calcium-mobilizing agents, may increase cGMP degradation by activating a calcium-dependent phosphodiesterase (11). Indeed, we reported that the ANP-dependent increase in urinary cGMP excretion is also impaired in animals with CHF (1). Moreover, administration of losartan, a specific ANG II receptor antagonist, restored the ANP-mediated cGMP excretion in rats with decompensated congestive heart failure (Fig. 3). Other investigators have shown that administration of M&B-22948, a specific cGMP phosphodiesterase inhibitor, increased urinary sodium excretion and restored the natriuretic response to exogenous ANP in rats with A-V fistula, supporting the notion that enhanced cGMP degradation limits the effectiveness of ANP in severe CHF (13). Interestingly, the ability of isolated glomeruli to

generate cGMP, *in vitro*, in response to ANP did not differ between glomeruli derived from control and CHF rats (1).

These findings suggest that the intrinsic capacity to generate cGMP remains intact in rats with experimental CHF and that factors present *in vivo*, perhaps ANG II, may impede the action of ANP by increasing the degradation of the hormone's second messenger. The interference with the cellular action of ANP in experimental CHF is further complicated by the demonstration of decreased density of the biologically active ANP receptors in glomerular and medullary tissues of rats with severe decompensated CHF (15). It is possible that the decrease in ANP binding to its renal receptor, also reported by other investigators, may be due to homologous downregulation of the biologically active receptors, in response to the chronically elevated plasma ANP levels. Interestingly, high concentrations of ANG II have been shown to cause heterologous downregulation of the ANP receptors in cultured smooth muscle cells, although the effect is probably on the ANP_c receptor subtype. Thus both downregulation of ANP receptors and interference with cGMP contribute to the decrease in renal responsiveness to ANP in CHF.

Integrated regulation of sodium homeostasis in CHF

The data presented in this review suggest that urinary sodium excretion in this experimental model of CHF is largely determined by the balance between two antagonistic hormonal systems: RAAS and ANP. It is likely that other factors, circulating as well as locally produced, may contribute to this balance. For example, a similar antagonistic relationship has been reported to exist between ANP and the sympathetic nervous system, another vasoconstricting, antinatriuretic system activated in CHF. Indeed, renal denervation has been shown to improve the renal response to ANP in rats with CHF induced by coronary ligation (7). Moreover, it was recently suggested that the RAAS antagonizes the vasodilatory effect of the locally released, endothelium-derived nitric oxide, leading to a decrease in renal perfusion in rats with A-V fistula. Other vasoactive agents such as the vasodilatory prostaglandins and catecholamines, as well as vasoconstrictors like endothelin and vasopressin, may also contribute to this complex interaction and thereby modulate urinary sodium excretion in CHF.

Figure 4 illustrates the concept that it is the balance between the natriuretic and sodium-

“... downregulation of ANP receptors ... contribute to the decrease in renal responsiveness to ANP in CHF.”

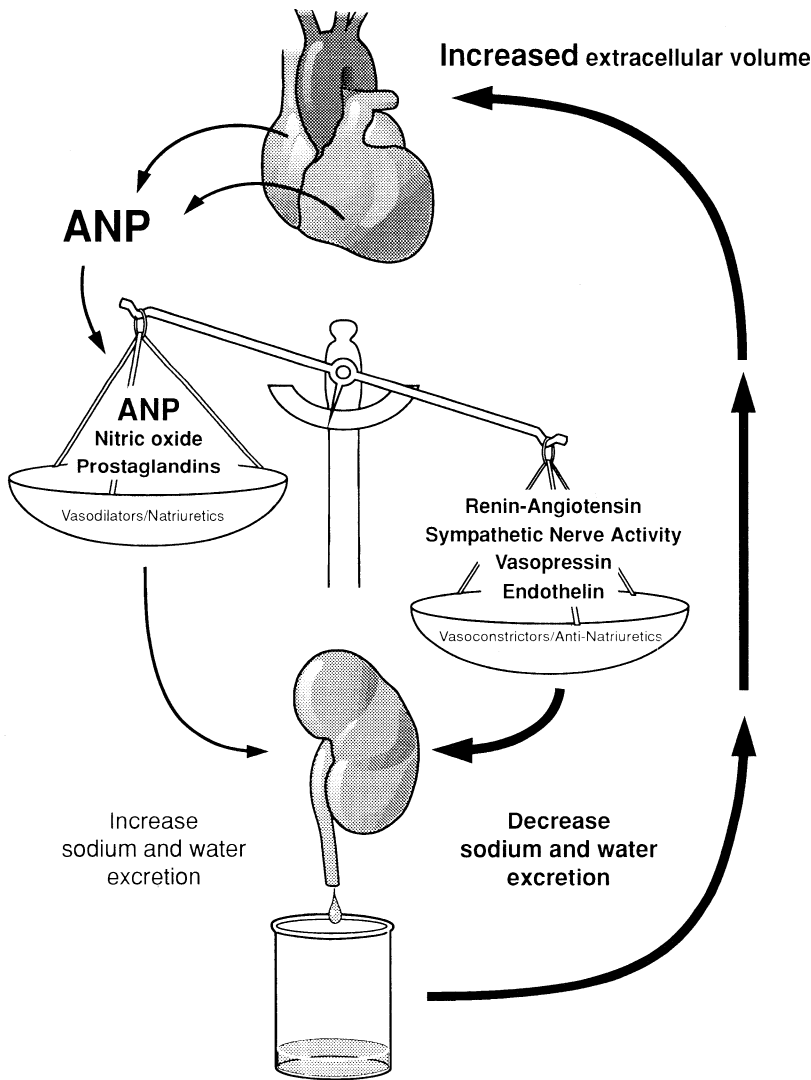


FIGURE 4. Volume homeostasis is determined by the balance between factors that reduce renal sodium/water excretion and promote increased extracellular volume (ECV) (*right*) and ANP (and perhaps other vasodilator/natriuretic factors), which increases urine output and reduces ECV (*left*). In uncompensated congestive heart failure, enhanced activities of sodium-retaining systems overwhelm effects of ANP (depicted by heavier right side of scale and bold lines), leading to a net reduction in sodium/water excretion and an increase in ECV. For compensation to occur, effects of ANP must prevail over those of the opposing systems and result in a rise in renal sodium/water excretion and a decrease in ECV.

retaining factors, rather than the action of a single system, that determines the final rate of urinary salt and water excretion in CHF. The kidney integrates the signals from several opposing as well as synergistic systems, through a variety of tubular and hemodynamic mechanisms, to yield the final excretion of sodium and water.

The notion of a dynamic equilibrium between natriuretic and sodium-retaining factors ultimately determining renal sodium excretion also provides a rationale for pharmacological intervention to correct the imbalance present in heart failure. Thus a shift in the balance in favor of natriuresis may be achieved by either increasing the activity of the natriuretic factors or reducing the influence of the antinatriuretic systems. In the interplay between the RAAS and ANP in CHF,

the approaches used in experimental and clinical medicine have included decreasing the activity of the RAAS by means of ACE inhibitors or ANG II receptor antagonists, or increasing the activity of ANP or its second messenger cGMP. With regard to ACE inhibitors, a large body of evidence attests to their beneficial effects on renal function in CHF. Also, more recent evidence suggests that the intrarenal RAAS may be activated in compensated CHF, when plasma renin activity and aldosterone levels may be normal, which may explain the unique sensitivity of the kidney to ACE inhibitors in CHF (10).

The potential efficacy of ANG II receptor antagonists in CHF is also now being intensively investigated. Initial results in experimental animal models of CHF have demonstrated that these compounds can maintain glomerular filtration

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“... ANP may exert a beneficial hemodynamic adaptive response by unloading the failing heart...”

rate, increase urinary sodium excretion, and improve the natriuretic response to exogenous ANP. However, the efficacy of ACE inhibitors and ANG II receptor antagonists as natriuretic agents is mitigated by their tendency to cause further reductions in arterial pressure and the limited ability of the failing myocardium to maintain adequate renal perfusion pressure.

Controlling the imbalance between the RAAS and ANP may also be achieved by enhancing the activity of ANP or its second messenger cGMP (13). This approach utilizes pharmacological agents that either inhibit the enzymatic degradation of ANP by NEP or block the clearance receptors of the hormone. The activity of cGMP can be enhanced by inhibition of the cGMP-related phosphodiesterase that degrades cGMP. Although experimental data suggest that each method may be beneficial in CHF, research in the past 3 years has focused mainly on the use of NEP blockers. Several differently structured compounds were reported to produce diuresis and natriuresis, an increase in urinary ANP and cGMP concentrations, an elevation of plasma ANP, and potentiation of the natriuretic action of the hormone, with no deleterious effects on glomerular filtration and renal hemodynamics. Further controlled studies will be required to establish the clinical usefulness of these drugs as a treatment modality in CHF.

On the basis of the balance concept, one can predict that a combination of RAAS blockade and NEP inhibition should be more effective than each treatment alone (9). This approach has been recently evaluated by several groups using a combination of either ACE inhibitor and a NEP blocker or ANG II receptor antagonist and a NEP blocker. Although some beneficial effects have been reported, confirmation of their added effectiveness has not yet been established. Finally, the synthesis of compounds that possess potent dual inhibitory properties of both ACE and NEP has been recently reported (8). It is expected that these highly potential compounds will be of increasing interest and intensive research efforts in the near future.

Extrarenal effects of ANP in CHF

Although the present review focuses on the renal natriuretic effects of ANP in CHF, it is important to underscore the potential role of ANP in extrarenal sites. As pointed out earlier, ANP may exert a beneficial hemodynamic adaptive response by unloading the failing heart through decreases in preload and afterload, as well as by diminishing intravascular volume. Indeed, it has been shown that infusion of

exogenous ANP might alleviate intracardiac pressures and improve cardiac index in patients with CHF. Similar to the kidney, the vascular effects of ANP may also be attenuated by increased activity of vasoconstrictor systems, and blocking the effects of the RAAS improved the systemic hemodynamic response to ANP in experimental CHF. It is also possible that ANP's antiproliferative growth-regulatory effects may serve to oppose the growth-promoting properties of ANG II in the cardiovascular system. Whether the high levels of ANP act to limit excessive cardiac hypertrophy in CHF remains to be established.

Conclusions

Nature has provided the organism with a potent defense mechanism against volume overload in the form of the cardiac peptide hormone ANP, which, on a molar basis, is 10,000 times more potent than any currently available diuretic agent. In CHF, increased secretion of ANP serves as an important compensatory mechanism, not only by unloading the failing heart but also by promoting renal excretion of salt and water. However, with the development of more severe cardiac failure, the natriuretic properties of ANP become markedly attenuated, despite a significant elevation in the endogenous levels of the peptide. The development of renal refractoriness to ANP represents a turning point at which the imbalance between the natriuretic and the volume-retaining forces shifts the cardiovascular system from a state of compensation to decompensation. Experimental evidence gathered in the last decade suggests that the renal hyporesponsiveness to ANP in CHF is related to activation of opposing sodium-retaining systems, particularly the RAAS. Pharmacological manipulation that will enhance the activity of ANP, either by blocking the antinatriuretic factors or by decreasing ANP degradation, may be a useful therapeutic intervention. Thus it is clear that the heart's hormone, ANP, plays an essential homeostatic role in preserving cardiovascular function and fluid balance in CHF.

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We regret that many relevant articles cannot be cited because editorial policy limits the number of references.

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Regulation of Na⁺-K⁺ Pump Activity: Pathways Between Receptors and Effectors

Alejandro M. Bertorello and Adrian I. Katz

Short-term regulation of membrane Na⁺-K⁺-ATPase activity is achieved by complex networks of receptor-mediated intracellular signals. Such regulatory pathways include activation of cyclic AMP-dependent protein kinase or protein kinase C and involve reversible phosphorylation of the catalytic (α) subunit of the enzyme directly, of additional mediators like eicosanoids and the actin cytoskeleton, or both.

As we approach 40 years since its discovery (15), Na⁺-K⁺-activated adenosinetriphosphatase (Na⁺-K⁺-ATPase or Na⁺-K⁺ pump), the

first transport system found to be enzymatic in nature, continues to captivate biologists from different disciplines. Ubiquitously expressed in virtually all cells (Fig. 1), the enzyme utilizes the energy derived from ATP hydrolysis to effect the active countertransport of Na⁺ and K⁺ across the plasma membrane. The electrochemical gradients generated by extrusion of Na⁺ from and uptake of K⁺ into the cell are essential for

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