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REVIEW ARTICLE

ATRIAL NATRIURETIC PEPTIDE: PATHOPHYSIOLOGICAL CONSIDERATIONS

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Abstract : Atrial natriuretic peptide (ANP) is a cardiac hormone with potent diuretic and natriuretic properties. This hormone mediates a finely tuned control mechanism for the maintenance of blood pressure and volume. The altered pressure and volume in many important cardiovascular diseases suggest that understanding the functional role of ANP is integral to these conditions. ANP levels are increased in a wide variety of cardiac disorders such as hypertension, diabetes, congestive heart failure, myocardial infarction and valvular heart diseases. Several studies have indicated a positive correlation between the severity of cardiac disorders and plasma ANP levels highlighting its importance as a prognostic factor in cardiovascular diseases. Furthermore, its compensatory role in these situations has prompted a world-wide investigation on the use of ANP as a drug in cardiac diseases and it is not surprising that there has been a wealth of scientific papers on this subject. This review attempts to summarize the present knowledge concerning the physiology of ANP and evaluates some of the latest experimental findings and opinions on the involvement of ANP in cardiovascular diseases.

Key words: atrial natriuretic peptide guanylate cyclase cardiovascular diseases

INTRODUCTION

It was the classic work of DeBold et al. (1) who discovered that the heart is something more than a pump. Injection of the atrial extracts induced a profound diuresis and natriuresis in rats suggesting the presence of a putative natriuretic factor which they appropriately labelled as atrial natriuretic peptide (ANP). ANP has been shown to be central to the regulation of body fluid status encompassing a wide spectrum of actions including natriuresis, diuresis, vasodilatation increase in renal blood flow and glomerular filtration rate and decrease in aldosterone production, renin and catecholamine release, thirst and vasopressin secretion. Many cardiovascular diseases are associated with an over expression of the ANP in experimental models and in humans. This recruitment phenomenon might be considered as the appropriate response to maintain circulatory homeostasis. Measurements of the elevated plasma ANP and urinary cGMP levels have suggested a compensatory role for ANP in cardiovascular diseases. The present brief review will summarize the current understanding of ANP metabolism and its role in maintaining fluid volume. An effort will also be made to place ANP in perspective in volume-related disorders affecting the cardiovascular system.

PHYSIOLOGY OF ATRIAL NATRIURETIC PEPTIDE

Synthesis storage and degradation

The discovery by DeBold and co-workers of the potent diuretic and natriuretic properties of atrial extracts (1) led to the identification of a cardiac hormone, aptly termed as atrial natriuretic peptide (ANP). Elucidation of the molecular structure of circulating ANP and its precursors showed that it is synthesized as 151-amino acid molecule called prepro-ANP (2).

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The human sequence (3) shares strong homology with those in rat (4), dog (5), and rabbit (5). Cleavage of the hydrophobic-residues rich "signal" peptide yields pro-ANP (1-126), the principal storage form of the peptide (6). Bioactive peptides are derived from the carboxy-terminus, with the predominant circulating form being ANP (1-28) (7). Proteases (8) present in the atrial tissue and serum are responsible for this conversion to the active peptide. It must be pointed out however that human ANP is identical to that in rats except for the substitution of methionine for isoleucine at position 12 (9).

In addition to atrial myocytes, ANP has been shown to be synthesized and stored in a wide variety of tissues and their contribution in the overall body fluid homeostasis is still under investigation. Atrial natriuretic gene expression has been observed in fetal ventricles (10), aortic arch (11), lung (12), anterior pituitary (12), hypothalamus (12), brain (13), adrenals (14) and kidney (15). It is important to mention that in the fetus, the ANP content and mRNA levels are lower in the atria than in the ventricles, and these distributions reverse in early post-natal life (10). Similarly, in adults with normal cardiovascular hemodynamics, the ANP gene is expressed in both the ventricles and atria, but the concentration in the ventricles appears very low. However, a reinduction of the ANP gene occurs in ventricles "under stress" as in congestive heart failure (16).

ANP is a short-acting peptide with a half-life of 2 to 4 minutes in animals and humans, with maximal degradative potency being attributed to the kidney (17). The brush border of the proximal tubule in the kidney is very rich in degradative enzymes and plays a major role in degrading other peptides. Cleavage of the disulfide bond (Cys-Phe) at position 7-8 by a metalloendopeptidase variously termed enkephalinase or neutral endopeptidase (EC 24.11) disrupts the ring structure of ANP (18). This endopeptidase can be inhibited by phosphoramidon or thiorphan (19), UK69578 and UK79300 (20) with corresponding increases in plasma ANP, urinary cGMP (the second messenger of ANP) and urinary sodium. Thus inhibition of this endopeptidase leads to an augmentation of the hypotensive, natriuretic, and urinary cGMP responses to ANP, suggesting a therapeutic potential for selective inhibitors or EC 24.11. In addition to degradation by ectozymes, ANP is also removed from the circulation by binding to the so-called "clearance" receptor (discussed later). This plasma membrane protein is expressed in large abundance on vascular endothelial cells (21). It has a long extracellular ANP binding domain and a very short intracellular domain and thus serves to inactivate the circulating plasma ANP. These mechanisms represent the two primary ways of inactivating the circulating ANP.

ANP is secreted in response to a variety of mechanical and humoral stimuli. Cardiac stretch has been suggested as the principal mediator of ANP release (22). This belief arose from the fact that inflation of a balloon in the left atrium of dogs induced a marked increase in urine flow (23), whereas prevention of atrial stretch in volume-expanded animals abolished this renal response (24). Similarly Langendorff heart-lung preparations in rats release bioactive or immunoreactive ANP in response to atrial stretch induced by volume expansion (25). Ledsome et al. (26) observed increased plasma ANP levels in dogs subjected to mitral valve obstruction. Atrial distension which accompanies acute and chronic volume overloading in rats (27) and humans (28) is responsible for the raised plasma ANP levels. Similar increments in plasma ANP levels have been documented in pathological states associated with increased atrial pressures including rapid tachyarrhythmias, congestive heart failure and various disorders associated with expansion of extracellular fluid volume.

Apart from these mechanical stimuli, ANP is also released in response to humoral stimuli. Glucocorticoids and mineralocorticoids have been shown to have a priming effect for ANP release (29). Dexamethasone, a long acting steroid, can increase ANP gene transcription (30). Several other factors also influence ANP secretion. Acetyclcholine, epinephrine and and vasopressin all cause release of a natriuretic substance from rat atrial tissue *in vitro*, as detected by bioassay (31, 32). *In vivo*, intravenous administration of vasopressin, angiotensin II or phenylephrine raises plasma ANP levels in rats, possibly due to their systemic vascular effects since the rise in plasma ANP correlates closely with elevations in mean arterial blood pressure (33). Endothelin, a newly discovered potent

vasoconstrictor peptide elaborated from endothelial cells in response to increased shear stress and a variety of chemical agonists (e.g. thrombin, epinephrine, phorbol esters) has been shown to augment plasma ANP levels (34) as well as ANP release from isolated cardiac myocytes (35), from isolated contracting right atria (36) and from isolated heart preparations (34).

Biological effects

A prominent effect of ANP is the enhancement of renal sodium and water excretion (37,38). This natriuresis and diuresis is accompanied by similarly marked increases in phosphate, calcium, magnesium, chloride, and cGMP excretion (39-41). Studies utilizing inhibitors of ANP degradation (42) as well as specific anti-ANP antisera (43,44) have shown that elevation of circulating ANP levels are accompained by increased salt and water excretion.

The observed solute and water excretion could be explained as a response to increased renal blood flow. However, in studies showing augmented renal blood flow, the increase was transient, lasting less than a minute (45). It is perhaps true that changes in sympathetic nervous tone and the circulating levels of vasconstrictors can modify overall vascular responsiveness to ANP. Therefore changes in renal blood flow *per se* are not the major factors responsible for enhanced renal solute excretion (46).

Many studies have demonstracted that ANP increases GFR and filtration fraction (47). ANP dilates preglomerular (afferent) artierioles and constricts postglomerular (efferent) arterioles effectively increasing hydraulic pressure within glomerular capillaries (48) while offsetting effects on glomerular blood flow. Using quantitative video microscopy, Marin-Grez et al. (49) observed dose-dependent dilatation of arcuate, interlobular, and proximal afferent vessels and constriction of efferent arterioles in response to ANP infustion. Fried et al. (50) examining isolated perfused dog glomeruli, reported significant increases in glomerular hydraulic pressure and efferent resistance. In addition, ANP may act to relax glomerular mesangial cells (51). This effect may alter GFR in two ways. First, relaxation of the mesangial cells results in expansion of capillary surface area available for filtration (52) and thereby opening regions of the capillary tuft for perfusion and filtration. Second, these cells increase the K_f i.e. the glomerular capillary ultrafiltration coefficient. It must be stressed that though it is attractive to postulate that the increase in GFR is responsible for the observed natriuresis and diuresis, this is not always the case. Many studies have detected no changes in GFR on low-dose ANP infusion while natriuresis and diuresis occurred (53); at higher doses, the increase in GFR is more marked (54). Several investigators also believe that ANP also directly alters tubular Na^+ and water reabsorption and thereby causes the observed effects (55). Moreover, experimental studies have shown that high doses of the peptide, injected into man, increase urine volume and electrolyte excretion, lower arterial pressure, and renin and aldosterone concentrations, while raising heart rate, hematocrit and plasma noradrenaline (56). These data along with a host of information from animal experiments (41, 42, 47) have suggested to many observers that atrial peptides serve as protectors against fluid overload, and as a counterbalance to the renin-angiotensin system and perhaps and sympathetic system. But there is uncertainity as to whether or not ANP plays a pathophysiologically important role in man. If indeed atrial peptides are important to the maintenance of fluid volume and arterial pressure in normal man and in patients with disorders of fluid balance, then a couple of predictions might be made. First ANP levels should respond predictably to volume-loading or pressor stimuli. It is well-known that manoeuvers which increase the volume of the central circulation stimulate ANP release (56) and also a dose-response relationship has been demonstrated (57). Second, a physiological and pathophysiological role would be supported by evidence that minor increases in plasma ANP, to levels seen in clinical disorders and preferably within the range seen in healthy volunteers induced clear-cut biological effects. Cuneo et al. (58) demonstrated that low-dose infusion of ANP inhibits the normal aldosterone response to angiotensin II in sodium-restricted subjects, while also suppressing renin levels. Similarly Morice et al. (59) reported an increase in urinary sodium excretion with low-dose of ANP. There is therefore a general consensus that plasma ANP levels are increased in response to control hypervolemia.

Mechanism of action

ANP binds to stereospecific cell surface receptors and thereby evokes physiological responses in target cells. This hormone-receptor interaction induces the plasma membrance associated guanylate cyclase which converts MgGTP to cGMP. The cGMP activates cGMP-dependent protein kinases, which in turn are capable of phosphorylating a large number of intracellular proteins, thereby expressing the physiological actions induced by ANP.

a) *ANP Receptors*

Autoradiography has identified specific ANP binding sites in various target tissues, most notably of which are the kidney, adernal and the vasculature. Receptors have also been identified in the cetral nervous system, pigmented epithelium and ciliary process of the eye, hepatocytes, gall bladder, colonic smooth muscle and lung parenchyma (60-62). In the kidney, binding sites are shown to be concentrated in large renal vessels, glomeruli and renal medulla (63). Besides binding sites have also been identified in a number of cell types including adrenal glomerulosa cells, renal inner medullary collecting duct cells, renal glomerular mesangial and endothelial cells, arterial smooth muscle and endothelial cells and the pig kidney epithelial cell line LLC-PK1 (64-65).

Radioreceptor assay systems and affinity cross-linking experiments have suggested the presence of several distinct cell surface ANP binding sites in most cells and tissues (66,67). However, there still exists considerable debate over the nature, function and even in fact existence of these receptors amongst the investigations. A consensus of different opinions agrees on the existence of at least three different receptors viz. ANP-receptor 1 (ANP-R1), ANP-R2 and ANP-R3.

ANP-R1 also is a membrane-associated protein with an apparent molecular mass of 130 kDA (68,69). It has a selective affinity for ANP (1-28) (64). The binding of ANP at R1 activates particulate guanylate cyclase (70). Studies have confirmed the ANP binding site and guanylate cyclase activity on the same transmembrane protein (71). It must be mentioned that another 180-kDa membrane protein with guanylate cyclase activity was also purified to homogeneity from rat adrenocortical cells (72). The 1:1 ANP-receptor stoichiometry suggests that this receptor too is a bifunctional protein (72). However, further investigation including the sequencing of the gene that encodes this 180-kDa ANP binding site is required to decide whether it is a distinct receptor or currently known ANP receptors associated with other membrane-bound proteins.

ANP-R2, also referred to as the clearance receptor or C-receptor, is a plasma-membrane associated protein that binds ANP with high affinity. SDS-PAGE analysis has shown it to be a 120-130 kDa molecular mass under non-reducing conditions (65-70 kDa under reducing conditions) (68, 69, 73). This receptor is devoid of guanylate cyclase activity, the second messenger for expression of the biological activites of ANP. In fact, there is no evidence whatsoever to suggest that binding of ANP to this receptor is capable of eliciting specific cellular responses. Moreover, this receptor not only binds ANP (1-28) or the bioactive ANP but also ANP fragments and internally ring-deleted ANP analogues with equal affinity (74). The ANP-R3 is also a distinct receptor for ANP sharing over 70% homology in the guanylate cyclase and kinase domains. It has been identified in human placenta and rat brain (75, 76). However, no specific function has yet been ascribed to it.

b) *Guanylate cyclase*

Guanylate cyclase belongs to a family of proteins involved in cell signalling mechanisms. It has been shown to exist in various cellular compartments, and its different forms are yet to be resolved (77). Different forms have been recognized based on their presence in the plasma membrane, cytosol or a detergent-insoluble cytoskeletal fraction (78,79). Thus, studies have shown that Ca^{2+} via an intermediary binding protein regulates guanylate cyclase (80) which in this case probably resides in the plasma membrane or cytoskeleton. Ca^{2+} has been shown to be capable of modulating the activity of guanylate cyclase, In several species it has been conclusively proved that addition of Ca^{2+} stimulates the plasma membrane associated guanylate cyclase (80). A role for calmodulin has been suggested in mediating this response though the exact nature of the intermediary binding protein is under dispute (81).

The plasma membrane-associated forms of guanylate cyclase, known to be transmembrane proteins (82) can be regulated by various peptides. These on SDS-PAGE analysis have a molecular weight ranging from 120,000 to 180,000 Da. They can be distinguished from the soluble form of guanylate cyclase in that while the soluble form exhibits linear kinetics as a function of the substrate (77,78), the particulate or plasma membrane form characteristically displays positive cooperative behaviour as a function of the substrate (77,78).

The physiological effects of ANP involve interactions at the target cell surface resulting in the activation of particulate guanylate cyclase and the elevation of intracellular levels of cGMP. The binding of a ligand to an extracellualr domain of the guanylate cyclase transmits a signal to an intracellular catalytic site. Indeed, ANP stimulates particulate guanylate cyclase in a concentration-dependent manner in responsive tissues where it exclusively stimulates the maximum enzyme activity (V_{max}) without altering the Michaelis constant (K_m) of the enzyme (83). ANP binding to the receptor domain of guanylate cyclase induces conformational changes in an adjacent catalytic domain, thereby increasing the rate of cGMP formation. Cyclic GPM then acts as the "second messenger" coupling ANP-membrane interactioris to the ultimate physiological response.

In vascular smooth muscle, cGMP activates cGMP-dependent protein kinase and phosphorylates a number of intracellular proteins (84). cGMP also dephosphorylates myosin light chains thereby inducing relaxation of vascular muscle. In the kidney phosphorylation by cGMP-dependent protein kinase inhibits a amiloride-sensitive cation Na^+ channel (85), thereby inducing natriuresis. In other cell types, phosphorylation by cGMP dependent protein kinases appear to mediate the actions of ANP, but by mechanisms that are poorly understood (86).

In keeping with its role in mediating smooth muscle relaxation, ANP acting via cGMP has been postulated to alter the intracellular Mg^{2+} concentration (87). The fact that cGMP may play a role in the exit of Ca^{2+} from the cell is suggested by the finding that cytosolic Ca^{2+} stores, normally depleted with repeated agonist stimulation are depleted more rapidly in the presence of agents that elevate cytosolic cGMP (88). Studies have shown that ANP reduces cytosolic Ca^{2+} concentrations in rat and aortic smooth muscle cells (52) and rat glomerular mesangial cells (89). The mechanism by which ANP alters Ca^{2+} mobilization could invlove regulation at the level of Ca^{2+} release from intracellular stores, reuptake of Ca^{2+} into these stores, or Ca^{2+} influx or efflux across plasma membranes. The available evidence thus favors the view that ANP has a role in mediating cytosolic Ca^{2+} concentrations thereby maintaining an optimal intracellular Ca^{2+} concentration.

PATHOPHYSIOLOGICAL CONSIDERATIONS

Hypertension

The potential role of ANP in mediating natriuresis and diuresis have suggested its possibl involvement in the chronic regulation of blood pressure. Injection of ANP to normotensive rats reduces blood pressure, counteracting the effects of angiotensin II, antidiuretic hormone, and aldosterone (90). This antagonistic effect of ANP for angiotensin II-mediated vasocostriction has been demonstrated not only in vascular smooth muscle preconstricted with angiotensin II but also on simultaneous infusion in experimental *in vivo* studies (91). This effect holds greater significance in hypertensive studies where the ability of ANP to reduce the blood pressure is greater. A plausible mechanism forwarded is that normotensives exhibit a decrease in their vascular resistance as their basis for lowering BP (92), while in hypertensive it is suggested that possibly a reduction in cardiac output could be the plausible explanation (93). This response to ANP infusion may result in a more marked renal loss of salt and water and more marked inhibition of plasma renin activity and aldosterone than seen in normotensives. Contrary evidence also exists in the literature. Korn et al. (94) have shown that there is a diminoshed natriuretic and diuretic response on ANP infusion, in hypertensive subjects. At any rate, the effectiveness of ANP as an antihypertensive agent is limited by the unavailability of an orally effective preparation. Intranasal sprays and inhibitors of the ANP degradative enzyme may provide a solution to this effect though further research is warranted.

Hypertension-prone rats atria have a higher ANP

content (85). Similarly SHR rats also reveal increased levels of ANP in the atria (19). However, *in vitro* studies show that in hypertension-prone rats, the renal papillary collecting tubular cells generate less cGMP in response to ANP (95). There is also a blunted response to ANP induced cGMP generation in SHR as compared to their WKY controls (74).

Several studies report higher levels of ANP in hypertensive patients than in their normotensive controls, though there is a considerable degree of overlap. In experimental settings such as the one-kidney one-clip and DOCA salt models, the increases in atrial pressures induced by the attendant volume expansion are associated with elevated ANP levels in plasma. The transcription rates of the prepro-ANP showed a linear increase with the volume overload, preceding a natriuresis that finally reduced the volume overload experienced by these animals (96). These findings lend further credence to the role of ANP as a safety mechanism.

However, borderline and mild essential hypertensives fail to show an increase in plasma ANP levels. A good deal of confusion awaits clarification, and the available evidence suggests that ANP is primarily a short-term or acute regulator. In acute studies, ANP has been shown to have a narrow therapeutic index, with lower doses having little effect and slightly higher doses inducing intolerable hypotension. Probably, its use singularly as an antihypertensive agent may not be spectacular, but in combination with other drugs may be effective.

Congestive heart failure

In pathophysiological states such as congestive heart failure (CHF), plasma ANP levels are 5 to 10 fold higher as compared to controls (97,98). Normal individuals and patients with heart disease who do not suffer from CHF exhibit plasma ANP levels ranging from 10 to 50 pmol/L, whereas patients with CHF typically exhibit levels in excess of 100 pmol/L, with wide individual variation (99, 101). The plasma level of ANP correlates closely with indices of the severity of the CHF, varying directly with right atrial and pulmonary capillary wedge pressures and inversely with cardiac index, stroke volume, blood pressure and New York Heart Association class (102-104). Animal models of CHF show that high plasma ANP levels also correlated inversely with atrial tissue concentrations, denoting prompt secretion and little tissue storage despite high ANP mRNA levels (105). It is noteworthy that effective therapy for CHF leads to reductions in plasma ANP levels usually in proportion to improvement in clinical status and cardiac performance (101).

There are several reports which indicate that sensitivity to ANP in the kidney is reduced in heart failure. One explanation for the reduction in renal sensitivity may be down-regulation of ANP receptors in the kidney. Down-regulation of peptide receptors in response to elevated plasma levels is a well documented phenomenon noted with other peptide hormones. Although, whether or not down-regulation of ANP receptors contribute to the development of congestive heart failure remains an interesting issue (106). It may be pointed out that some attempts were also made to maintain plasma ANP levels by using neural endopeptidase inhibitors, necessary to prevent fluid accumulation and vasoconstriction in congestive heart failure (107).

Diabetes mellitus

Functional changes in the diabetic kidney have been documented by various studies. Micropuncture studies in diabetic rats have shown increased GFR, renal plasma flow (RPF), single-nephron GFR, and intraglomerular capillary pressure (108,109). The increased GFR that occurs is probably caused by greater reduction in afferent than efferent arteriolar resistances and increased glomerular transcapillary hydraulic pressure gradient. Several mechanisms have been implicated to explain the elevated GFR in diabetes. e.g. hyperglycemia, growth hormone and glucagon (110). One of the mechanisms to explain this hyperfiltration implicates a cardiac hormone, ANP with potent natriuretic and diuretic properties (111). It is possible that hyperglycemia, with its attendant chronic plasma volume expansion, stimulates atrial ANP release and that elevated plasma ANP levels may contribute to the hyperfiltration observed in diabetes. A recent report suggests (112) down-regulation of ANP receptors in diabetic kidney. Experiments from this laboratory have shown that the ANP receptor-postreceptor mechanism may have a key role to play

in modulating the response to diabetes (113-115). An uncoupling of the receptor-post receptor system may be the cause of diabetes-induced heart failure (106).

Myocardial ischemia

Myocardial ischemia with its attendant defects in cardiac pumping ability has been shown to be associated with increasing plasma ANP levels (116). Though levels varied in the different experimental observations possibly due to differences in time sampling after the induction of infarct as well as infarct size, plasma ANP showed a linear correlation with the severity of clinical manifestations. Severe left ventricular dysfunction concomitant with a decreased ejection fraction showed the highest levels of plasma ANP (117). The atria correspondingly in these rats were low in tissue ANP content (116). The ejection fraction is decreased in these animals in spite of compensatory ventricular hypertrophy. These results probably imply a compensatory recruitment of the ventricles with an increased rate of secretion in response to ventricular dysfunction. The fluid imbalance as a consequence of the ineffective pumping action of the heart seems to be the same proximate signal (i.e. atrial stretch) mediating increase in plasma ANP levels. Moreover, these animals reveal a blunted ability to excrete a saline load. Though the mechanism of action still remains to be explained, their measurements could be a sensitive indicator of the degree of left ventricular dysfunction.

Other cardiac disorders

Numerous studies have documented an increase in plasma ANP pari passu with arrhythmias (118, 119). This would suggest that frequency (heart rate) may also be playing a role in the secretion of ANP. Studies have shown that patients with atrial fibrillation had greater levels of plasma ANP than those with sinus rhythm even in the same New York Heart Association heart failure class. Plasma ANP levels are markedly elevated in patients with a VVI mode pacemaker accompanied by AV dissociation or atrial fibrillation whereas they are normal in patients with an AV-sequential pacemaker (120). Once again, this would suggest that abnormal atrial contraction may also be causative factor in altering ANP release. It has also been observed that patients with ventricular tachycardia had higher levels of plasma ANP than those with atrial fibrillation or supraventricular tachycardia, as did subjects with acute versus chronic tachycardia. However, it is suggested that ventricular rate *per se* seems less likely to be important except insofar as it modifies atrial stretch.

Valvular heart disorders are also associated with alterations in plasma ANP levels. Pathological states such as mitral stenosis, mitral valve prolapse, etc. are associated with elevated plasma ANP levels (121). A probable mechanism for these increased levels could be explained by increased plasma volume consequent a defective pumping ability. The relevance in these situations probably exists in trying to correct for the impaired pumping ability by decreasing afterload. Decreasing ANP levels after valvular replacement could serve as humoral markers and represent an improved hemodynamic situation. Future, investigation is however warranted to delineate clearly the role of ANP in these conditions.

CONCLUSIONS

The pathophysiology of hemodynamic abnormalities in cardiovascular diseases remains largely unknown. Alterations in ANP levels and target-organ responsiveness have been implicated in these conditions. From the foregoing review, it can be appreciated that ANP has considerable prognostic and therapeutic implications, and future research is warranted.

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