Review

The role of natriuretic peptides in cardioprotection

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Abstract

Atrial natriuretic peptide (ANP) and brain (B-type) natriuretic peptide (BNP) are circulating hormones of cardiac origin that play an important role in the regulation of intravascular blood volume and vascular tone. The plasma concentrations of ANP and BNP are elevated in heart failure, and they are considered to compensate for heart failure because of their diuretic, natriuretic, and vasodilating actions and inhibitory effects on renin and aldosterone secretion. Evidence is also accumulating from recent work that ANP and BNP exert their cardioprotective functions not only as circulating hormones but also as local autocrine and/or paracrine factors. In studies using cultured neonatal myocytes and fibroblasts, exogenous administration of both ANP and ANP antagonists demonstrated that ANP has antihypertrophic and antifibrotic functions. Corroborating these in vitro results, mice lacking natriuretic receptor-A (NPR-A), the receptor for ANP and BNP, develop cardiac hypertrophy and fibrosis independent of their blood pressure. Recent studies also suggest that the intracardiac natriuretic peptides/cGMP system plays a counter-regulatory role against the intracardiac renin–angiotensin–aldosterone system and TGF-beta mediated pathway. In a clinical setting, human recombinant ANP and BNP may be used for a therapy of heart failure; however, further evaluation is required in the future.

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1. Role of natriuretic peptide in cardiovascular homeostasis

Atrial natriuretic peptide (ANP) was first isolated from cardiac tissues [1,2]. Other natriuretic peptides, brain or B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP), were isolated from porcine brain tissues by the same Japanese investigators [3,4]. Later studies found that ANP and BNP are mainly synthesized in cardiac tissue: ANP in the atrium and BNP in the ventricle. CNP is mainly expressed in the central nervous system, although recent studies indicate that expression of CNP in the endothelium [5], macrophages [6], and cardiac fibroblasts [7] are higher than that in the brain. Subsequently, three major natriuretic peptide receptors were cloned [8–10]. Natriuretic peptide receptor-A (NPR-A) and natriuretic peptide receptor-B (NPR-B) are guanylyl cyclase-linked, and they utilize cyclic guanosine monophosphate (cGMP) as the intracellular messenger. Both ANP and BNP bind preferentially to NPR-A, whereas CNP preferentially binds to NPR-B. All three natriuretic peptides bind to the third receptor, known as natriuretic peptide receptor-C (NPR-C). NPR-C is not linked to guanylyl cyclase, but appears to act to clear the natriuretic peptides from the circulation (Fig. 1).

Thus, the natriuretic peptide system consists of three ligands and three receptors. These peptides cause effects such as diuresis, natriuresis, vasodilation, and inhibition of aldosterone synthesis and renin secretion as a circulating hormone, and thereby play an important role in regulating
blood pressure and blood volume (Table 1). The intensity of actions differs among the three peptides. ANP and BNP are each produced within the heart and secreted in response to stretching of muscles that typifies an increase in blood volume. The release of ANP and BNP from the heart has the most immediate biologic effect of increasing electrolyte and water excretion in the kidney by functionally antagonizing the “salt-sparing” role of the renin–angiotensin–aldosterone system. However, ANP and BNP also regulate the permeability of the systemic vasculature, cellular growth, cellular proliferation, and, as shown more recently, cardiac hypertrophy. Accumulating evidence suggests that the three natriuretic peptides act not only as circulating hormones, but also as autocrine and/or paracrine factors. In this review, we focus on the recent advances in our understanding of the natriuretic peptides as a cardioprotective peptide.

2. Natriuretic peptides in the modulation of cardiac hypertrophy

Apart from acting as circulating hormones, ANP and BNP act locally at the sites of their synthesis. This has been suggested by the observation that in addition to being produced in the heart, these peptides are produced by many other tissues but in amounts far too low to induce endocrine effects [11]. However, whether the heart itself represents a site of action for natriuretic peptides was controversial. Early experiments using isolated heart preparations failed to demonstrate direct effects of ANP on cardiac performance [12,13]. Moreover, ANP had no direct effect on cardiac performance in patients with heart failure or hypertension using simultaneous left ventricular micromanometer pressure and radionuclide volume measurement techniques [14,15]. These findings appear to be in accordance with autoradiographic data suggesting that binding of natriuretic peptides in the heart is confined to the endocardium and absent in cardiac myocytes [16–18]. Subsequently, however, several experiments showed that administration of ANP altered the physiological functions of isolated myocytes, supporting the view that natriuretic peptides exist on heart muscle cells [19,20]. Furthermore, Lin et al. [21] showed the presence of transcripts for NPR-A as well as NPR-B and

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ACTH: adrenocorticotropic hormone.
NPR-C directly by using the RT-PCR technique after single cell collections. cGMP generation in purified myocytes was stimulated only by ANP and BNP, which specifically bind to NPR-A, whereas CNP (an NPR-B agonist) was ineffective, suggesting that rat ventricular myocytes produce predominantly NPR-A.

The role of NPR-A in the myocyte has also been addressed using the recent advances of gene technology. Thus NPR-A deficiency in mice leads to marked cardiac hypertrophy [22], suggesting that the endogenous ANP-NPR-A system may have an inhibitory role in the regulation of cardiac cell growth. Calderone et al. [23] investigated the effect of exogenously administered ANP on the cardiac cell hypertrophy induced by norepinephrine. ANP, as well as nitric oxide (NO) donor and 8-bromo-cGMP, decreased the hypertrophy induced by norepinephrine. ANP, as well as endogenous ANP, attenuates the effects of norepinephrine on the growth of cardiac myocytes via a cGMP-mediated inhibition of norepinephrine-stimulated Ca$^{2+}$ influx, and raise the possibility that endogenous ANP suppressively regulates the development of cardiac myocyte hypertrophy.

To test the hypothesis that endogenous ANP inhibits the cardiac myocyte hypertrophy, we investigated the effects of a specific antagonist of natriuretic peptide receptors, HS-142-1, on the expression of fetal-type contractile protein genes as well as the protein synthesis in cultured cardiac myocytes [24]. HS-142-1 increases the basal and phenylephrine-stimulated incorporation of [3H] leucine in ventricular myocytes. They also showed that ANP inhibited an increase by the Ca$^{2+}$ channel agonist BAY K8644 of norepinephrine-stimulated incorporation of [3H] leucine in myocytes. These findings indicate that ANP and NO can attenuate the effects of norepinephrine on the growth of cardiac myocytes via a cGMP-mediated inhibition of norepinephrine-stimulated Ca$^{2+}$ influx, and raise the possibility that endogenous ANP suppressively regulates the development of cardiac myocyte hypertrophy.

To test the hypothesis that endogenous ANP inhibits the cardiac myocyte hypertrophy, we investigated the effects of a specific antagonist of natriuretic peptide receptors, HS-142-1, on the expression of fetal-type contractile protein genes as well as the protein synthesis in cultured cardiac myocytes [24]. HS-142-1 increases the basal and phenylephrine-stimulated protein syntheses in a concentration-dependent manner. This antagonist also induced a significant increase in the size of myocytes. In addition, the expression levels of the genes coding for skeletal-actin, beta-myosin heavy chain, and ANP, markers of hypertrophy were partially elevated by treatment with HS-142-1 under nonstimulated or phenylephrine-stimulated conditions. Zaprinast, a cGMP analogue and an inhibitor for a cGMP-specific phosphodiesterase, suppressed the basal and PE-stimulated protein syntheses. These observations indicate that endogenous ANP inhibits cardiac myocyte hypertrophy under basal as well as phenylephrine-stimulated conditions, probably through a cGMP-dependent process. Thus, ANP may play a role as an autocrine factor in the regulation of cardiac myocyte growth. Consistent with these observations, chronic treatment with either enalapril, furosemide, hydralazine, or losartan were all effective in reducing and maintaining BP at normal levels without affecting heart weight/body weight in NPR-A knockout mice [25]. In addition, transverse aortic constriction (TAC) resulted in a 15-fold increase in ANP expression, a 55% increase in left ventricular weight/body weight (LV/BW), dilatation of the LV, and a significant decline in cardiac function in NPR-A knockout mice. In contrast, banded wild-type mice showed only a three-fold increase in ANP expression, an 11% increase in LV/BW, a 0.2 mm decrease in LV end diastolic dimension, and no change in fractional shortening. These results suggest that the NPR-A system has direct antihypertrophic actions in the heart, independent of its role in BP control. Thus, the NPR-A system modulates the cardiac response to hypertrophic stimuli, such as TAC.

To examine the effect of overproduction of NPR-A in the cardiac myocytes, Kishimoto et al. [26] produced transgenic mice that specifically express NPR-A in the heart with myosin heavy chain promoter. They crossed NPR-A null mice and wild-type mice with the NPR-A transgenic mice. Cardiac myocyte size was larger (approximately 20%) in NPR-A null mice than in wild-type mice at baseline. However, overexpression of the NPR-A gene in the heart reduced cardiac myocyte size in both wild type and null mice. Coincident with the reduction in myocyte size, ANP was reduced significantly at both mRNA and peptide levels by the overexpression of NPR-A. This reduction was independent of the genotype of animals. Thus, cardiac overexpression of NPR-A reduced cardiomyocyte size and ventricular ANP expression in either wild-type or NPR-A null background, suggesting again a role of NPR-A in cGMP signaling pathway in the regulation of cardiac myocyte hypertrophy and ANP mRNA expression. These findings were further confirmed by the studies in cardiomyocyte-restricted NPR-A deletion in mice [27]. In these mice, the NPR-A gene was selectively deleted in cardiomyocytes by homologous loxP/Cre-mediated recombination. The mice exhibited mild cardiac hypertrophy, marked increase in mRNA expression of cardiac hypertrophy markers such as ANP (5-fold), skeletal-actin (1.7-fold), and alpha-myosin heavy chain (2-fold), and increase in circulating ANP levels. Their blood pressure was 7–10 mm Hg below normal, probably because of the elevated systemic levels and endocrine actions of ANP. Furthermore, cardiac hypertrophic responses to aortic constriction were enhanced and accompanied by marked deterioration of cardiac function. The phenotype of these mice provides definitive evidence that an antihypertrophic regulatory circuit within cardiac myocytes directly antagonizes the hypertrophic growth response. Thus, ANP, BNP/NPR-A/cGMP system plays an important role in modulating the molecular program of cardiac hypertrophy as an antihypertrophic factor (Fig. 2).

Multiple signaling pathways agonize and antagonize hypertrophic growth of cardiac myocytes. In the NPR-A deficient mice, a previous study showed that ligand induced cGMP elevation, and the following activation of cGMP-dependent protein kinase type I (PKG I) negatively regulates cardiac myocyte hypertrophy via inhibition of the calcineurin-nuclear factor of activated T cells (NFAT) signaling pathway [28]. Consistent with this finding, a recent study suggests that local ANP/NPR-A/cyclic GMP signaling counter-regulates the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)- and calcineurin/NFAT-dependent pathways of cardiac myocyte growth in hypertensive eNOS (−/−) mice [29]. The action
of ANP and BNP, through the NPR-A, stimulates the production of cGMP and PKG, which in turn function to antagonize hypertrophic growth within the cardiac myocyte itself. A recent study by Tokudome et al. also showed the interaction of natriuretic peptide with hypertrophic signaling, such as endothelin-1 [30], by demonstrating that increased cGMP production by CNP inhibits endothelin-1-mediated Ca\(^{2+}\) influx, calmodulin-dependent protein kinase II activation, ERK phosphorylation, and the activation of transcription factors of GATA-4 and myocyte enhancer factor-2 in cultured cardiac myocytes. CNP also inhibits endothelin-1 secretion from cardiac nonmyocytes. The same group of investigators very recently demonstrated that calcineurin activity, nuclear translocation of NFAT and modulatory calcineurin-interacting protein 1 gene expressions were increased in the hearts of NPR-A knock out mice compared with wild-type mice [31]. Blockade of calcineurin activation by FK506 significantly decreased the increased heart weight, cardiomyocyte size, collagen volume fraction, and mRNA levels of ANP, BNP, collagen, and fibronectin in NPR-A knock out mice. Electrophoretic mobility shift assays showed that GATA4 DNA-binding activity was increased in NPR-A knock out mice, and this increase was inhibited by calcineurin blockade. These results suggest that the natriuretic peptides/cGMP system protects the heart from excessive cardiac remodeling by inhibiting the calcineurin-NFAT pathway [31].

Thus, natriuretic peptide/GC-A/cGMP signaling negatively regulates cardiac hypertrophy by inhibiting the variety of hypertrophic cellular signaling.
3. Natriuretic peptides in the modulation of fibroblasts

There was a long-standing controversy regarding whether or not the heart muscle cells themselves are the targets for natriuretic peptides. Recently, however, Lin et al. [21] demonstrated that not only cardiac myocytes but also cardiac fibroblasts express natriuretic receptor mRNA. Interestingly, myocytes express predominantly NPR-A, but fibroblasts express both NPR-A and NPR-B. Indeed, ANP and BNP, but not CNP, increase the intracellular cGMP levels in cardiac myocytes, whereas ANP, BNP, and CNP similarly increase the intracellular cGMP levels in cardiac fibroblasts. Both ANP and BNP increase the cGMP levels in cardiac fibroblasts and inhibit preproendothelin-1 mRNA expression induced by angiotensin II [32]. In addition, both ANP and BNP inhibit DNA synthesis stimulated by angiotensin II or endothelin-1 in cardiac fibroblasts. Other study also demonstrated the presence of mRNA for NPR-A, NPR-B, and NPR-C in cardiac fibroblasts and that the ANP, BNP, and CNP increase the intracellular cGMP levels and inhibit DNA synthesis induced by angiotensin II, endothelin-1, acidic fibroblast growth factor, insulin-like growth factor I, and basic fibroblast growth factor. These results suggest an important paracrine role of the natriuretic peptides in regulating fibroblast growth under certain pathologic conditions [33]. In accordance with these observations, myocyte-conditioned medium, as well as exogenous ANP, inhibits the collagen synthesis in cardiac fibroblasts and that this effect was suppressed by HS-142-1, a natriuretic peptide receptor antagonist [34], suggesting again that endogenous ANP released from cardiomyocytes inhibits collagen synthesis. Thus ANP and BNP secreted by myocytes inhibit the proliferation of cardiac fibroblasts as a paracrine factor. Indeed, NPR-A KO mice have hearts exhibiting marked hypertrophy with interstitial fibrosis resembling that seen in human hypertensive heart disease [22], whereas ANP KO mice show salt-dependent hypertension but have no obvious cardiac hypertrophy at baseline [35]. Nevertheless, the production of aortic banding in ANP KO mice causes robust interstitial and perivascular fibrosis with collagen deposition compared with wild-type mice [36]. Aorto-caval fistula, volume-overload also increases interstitial and perivascular fibrosis with collagen deposition in the ANP KO mice compared with wild type mice, suggesting that the ANP/NPR-A/cGMP system acts as a paracrine antifibrotic factor when the heart receives hypertrophic stimuli such as pressure- and volume-overload [37]. It is interesting to note that mice lacking BNP, in contrast, have multifocal fibrotic lesions in the ventricles, although they do not have either hypertension or cardiac hypertrophy [38]. Moreover, ventricular pressure overload caused by abdominal aortic banding induces an increase of multifocal fibrotic lesions in the ventricles in mice lacking BNP, but not in wild-type mice, despite the increase of ventricular weights is similar between the two genotypes [39]. Taken together, these results indicate that ANP and BNP exert antifibrotic effects in vivo and play a role as a local regulator of ventricular remodeling (Fig. 2). The differences in phenotype between ANP knockout and BNP knockout mice at baseline may reflect the predominance of BNP in ventricle.

Earlier reports failed to detect CNP in cardiac tissue [39]. However, recent studies showed that CNP levels are elevated in the hearts of patients with congestive heart failure [40], and that rat cardiac fibroblasts secret immunoreactive CNP [7]. Transforming growth factor (TGF)-beta1, basic fibroblast growth factor, and endothelin-1 significantly stimulated CNP secretion, and Northern blot analysis detected significant expression of the mRNAs of both CNP and its specific receptor, NPR-B, in cultured cardiac fibroblasts [7]. CNP stimulated intracellular cGMP production in fibroblasts more intensely than ANP and BNP, and CNP inhibited both DNA and collagen syntheses of cardiac fibroblasts. Interestingly, these inhibitory effects of CNP were stronger than those of ANP and BNP in cardiac fibroblasts. Collectively, these findings suggest that CNP is synthesized and secreted from cardiac fibroblasts and that CNP has a suppressive effect on fibroblast proliferation and extracellular matrix production via cGMP/NPR-B mediated mechanisms. Thus, in addition to ANP and BNP, CNP is produced by cardiac fibroblasts and plays a role as an autocrine regulator against excessive cardiac fibrosis (Fig. 2).

A recent study by Tokudome et al. described above also reported that CNP inhibits the endogenous ET-1-induced paracrine hypertrophic effect by inhibiting ET-1 secretion from cardiac fibroblasts [30]. Moreover, CNP inhibits ET-1-induced cardiac myocyte hypertrophy via a cGMP-dependent mechanism, and conversely, ET-1 inhibits CNP signaling by a protein kinase C- and Ca2+ mechanism, suggesting mutual interference between the CNP and ET-1 signaling pathways. These observations suggest that CNP may be a third member of the cardiac natriuretic peptide family and that it acts as an antihypertrophic and antifibrotic factor in the heart. Thus, in addition to ANP and BNP, CNP may be included as “cardiac natriuretic peptides.”

4. Natriuretic peptide in myocardial ischemia/ reperfusion and infarction

It is well known that plasma levels of ANP and BNP are markedly increased in patients with acute myocardial infarction as well as in those with congestive heart failure [41,42]. However, the roles of ANP and BNP in the pathophysiology of acute myocardial infarction are not clearly understood. Myocardial ischemia/reperfusion causes coronary vascular injury as well as myocardial injury [43,44]. Endothelial injury caused by the activated neutrophils has been shown to play an important role in the process of coronary vascular damage by myocardial ischemia/reperfusion [45,46]. Incubation of human neutro-
phil with ANP and BNP modulates the neutrophil functions and exerts protective effects against the neutrophils-induced endothelial cytotoxicity such as adhesiveness to human endothelial cells [47]. In addition, low-dose administration of the natriuretic peptide, urodilatin, at the time of coronary reperfusion can limit myocardial cell death secondary to transient coronary occlusion [48], suggesting that the increased cGMP in myocytes induced by ANP may limit necrosis after reperfusion. The effects of ANP on susceptibility to ischemia reperfusion injury were also investigated in isolated rat hearts, which were subjected to Langendorff perfusion [49]. ANP reduced infarct size compared to that in the control hearts and the effect was reversed by N(omega)-nitro-L-arginine methyl ester, chelerythrine, a PKC inhibitor, and sodium 5-hydroxydecanoate, an antagonist of mitochondrial ATP-sensitive K+ channel, but not methylene blue. These results suggest that preischemic infusion of ANP exerts cardioprotective effects, possibly through the nitric oxide-protein kinase C dependent pathway, followed by mitochondrial KATP channel activation. The cardioprotective effects of ANP against ischemia-reperfusion injury on cardiac function were also studied in isolated rat hearts [50]. ANP was added to the perfusate and the postsischemic recovery of cardiac output, coronary flow, and cGMP release was measured. In the ANP-added group, the recovery of cardiac output was significantly better than that in the control group, and a similar trend was seen for recovery of coronary flow. The improved cardiac function was closely related to a significant increase in postsischemic cGMP release, suggesting that administration of ANP at the time of reperfusion protects the myocardium from ischemia-reperfusion injury without negative inotropic effects.

One possible mechanism for the inhibition of reperfusion injury by ANP is to limit the polymorphonuclear neutrophil activation. A recent study showed that ANP alone and its potentiation by the neutral endopeptidase (NEP) inhibitor significantly inhibited superoxide, lysozyme, and matrix metalloproteinase (MMP)-9 release by stimulated polymorphonuclear neutrophils [51]. Hypoxia significantly increased the adhesion of polymorphonuclear neutrophils to endothelial cells and their subsequent MMP-9 release. ANP and its potentiation by NEP inhibitor limited adhesion of polymorphonuclear cells to hypoxic endothelial cells and thus decreased their MMP-9 release. Smooth muscle cells incubated with conditioned medium of stimulated polymorphonuclear neutrophils exhibited morphological and biochemical changes characteristic of apoptosis. However, ANP and its potentiation by NEP inhibition were able to limit these changes in smooth muscle cells. Thus, ANP can limit polymorphonuclear neutrophil activation, and the consequences on vascular cells may be one of the possible mechanisms of coronary reperfusion injury. Collectively, endogenous and exogenous natriuretic peptides increase intracellular cGMP levels in myocardial cells, endothelial cells, and neutrophils in acute coronary syndrome and exert cardioprotective effects against myocardial reperfusion injury in acute coronary syndrome.

A caution, however, has been raised by the experiments by Kawakami et al. [52] who recently reported that BNP-transgenic mice tended to die of cardiac rupture more frequently than non-transgenic mice after acute myocardial infarction. Although at 6 weeks after ligation, LV dilatation and hypertrophy of the noninfarcted zone are attenuated in BNP-transgenic mice compared to non-transgenic mice, the numbers of neutrophils infiltrating the infarct area were significantly higher in BNP-transgenic mice 3 days after acute myocardial infarction. In addition, both the gene expression and zymographic activity of MMP-9 was significantly higher in BNP-transgenic mice than non-transgenic mice. The transient MMP-9 expression induced by the elevation in BNP during the earliest phase after myocardial infarction is a cardioprotective mechanism affecting the later LV remodeling. Nevertheless, an excessive administration of BNP may be harmful because marked increasing activity of MMP-9 may increase the risk of cardiac rupture.

5. Natriuretic peptides in heart failure

As we described above, ANP, BNP, and CNP have actions of diuresis, natriuresis, vasodilatation, inhibition of aldosterone synthesis and renin secretion as circulating hormones, and play an important role in regulating blood pressure and blood volume (Table 1), although there are different intensity for their actions among the three peptides. Since ANP and BNP predominantly bind to NPR-A, whereas CNP predominantly binds to NPR-B, the physiological effects of ANP and BNP on the vasculature and kidney are stronger than those of CNP. In heart failure, it is well known that plasma levels of ANP and BNP are increased and considered to compensate heart failure [53,54]. In fact, a natriuretic peptide receptor antagonist, HS-142-1, significantly decreases urinary sodium excretion in an animal model of heart failure without changing hemodynamics, suggesting that the natriuretic peptide system exclusively compensates for heart failure through its natriuretic and diuretic action [55,56]. Furthermore, HS-142-1 increases plasma renin and aldosterone levels in an animal model of severe pacing-induced heart failure, suggesting an inhibitory role of the NPR-A system in renin and aldosterone secretion in severe heart failure [56].

Recently, we have investigated the contribution of the NPR-A/cGMP system in the development of heart failure using mice lacking NPR-A [57]. Volume-overload heart failure was produced by aortocaval fistula in mice that were wild-type (+/+), heterozygous (+/-), and homozygous null (-/-) for the NPR-A gene. NPR-A (-/-) mice with aortocaval fistula had higher left ventricular end-diastolic pressure, left and right ventricular weights, lung weight, and left ventricular dimension, as well as lower fractional...
shortening and urinary sodium and cGMP excretion than did (+/+)) mice with aortocaval fistula. In addition, ventricular mRNA expression of natriuretic peptides and β-myosin heavy chain was increased markedly only in (−/−) mice. Increase in the plasma levels of ANP, renin, and aldosterone was greater in (−/−) mice than in (+/+)) mice. But the levels of cGMP in response to aortocaval fistula were the same in two groups. These results provide genetic evidence that NPR-A signaling protects against heart failure induced by volume overload in mice.

6. Metabolic effects of natriuretic peptides

Several studies have shown that natriuretic peptides also have important metabolic effects. Adipose tissues express significant amounts of NPR-A and NPR-C, suggesting that natriuretic peptides may have a functional role in the adipose tissue [58]. Indeed, Framingham Heart Study showed that obese individuals had higher odds of having low plasma BNP and low plasma N-terminal proANP levels compared with lean individuals. The authors speculated that obese individuals have low circulating natriuretic peptide levels, which may contribute to their susceptibility to hypertension and hypertension-related disorders [59].

ANP activates hormone-sensitive lipase in human fat cells in vitro via phosphorylation of the enzyme through an cGMP-mediated mechanism [60]. Hormone-sensitive lipase then breaks down triglycerides into non-esterified fatty acids (NEFAs) and glycerol. Hydrolysis of triglycerides into NEFA and glycerol is commonly termed lipolysis. Application of high ANP concentrations through a microdialysis probe increased lipolysis in healthy young men [61]. Furthermore, systemic ANP infusion increased lipolysis [62]. Recently, Birkenfeld et al. [63] reported that systemic ANP infusion stimulates lipid mobilization and oxidation at plasma concentrations that are encountered in conditions such as heart failure. These results caution that lipid mobilization induced by natriuretic-peptide might contribute to cardiac cachexia in patients with heart failure, and that drugs which interfere with the natriuretic peptide system should be evaluated for potential metabolic side effects. These findings may also have implications in other conditions under which natriuretic peptide secretion is altered such as in subjects with left ventricular dysfunction, congestive heart failure and obesity. Further studies are necessarily to elucidate the exact pathophysiological role of metabolic effect of natriuretic peptides.

7. Clinical applications of natriuretic peptides in patients with heart failure and acute myocardial infarction

Saito et al. [64] first examined the effects of synthetic ANP on hemodynamics, renal excretory function, and hormone levels in patients with severe heart failure. The infusion of ANP at a rate of 0.1 µg/kg/min significantly decreased pulmonary capillary wedge pressure and increased stroke volume index in patients with heart failure. The ANP infusion also significantly increased the urine volume, excretion of sodium, and endogenous creatinine clearance, and decreased the aldosterone concentrations. The effects of intravenous infusion of BNP on hemodynamics, renal excretory function, and hormone levels were also examined in patients with heart failure [65]. BNP infusion at a rate of 0.1 µg/kg/min decreased pulmonary capillary wedge pressure and systemic vascular resistance and increased stroke volume index. BNP infusion also increased the urine volume, excretion of sodium, and excretion of chloride, and decreased the plasma aldosterone concentrations. These results indicated the possibility that BNP as well as ANP could be used as a therapeutic drug in patients with heart failure. To determine whether BNP could be used as a therapeutic drug for heart failure, prospective and randomized trial has been carried out. In the Nesiritide (human BNP) Trial, patients hospitalized because of symptomatic congestive heart failure were enrolled in either an efficacy trial or a comparative trial [66]. In the efficacy trial, 127 patients with heart failure were randomly assigned to double-blinded treatment with placebo or nesiritide for 6 h. Nesiritide infusion decreased pulmonary-capillary wedge pressure, resulted in improvements in global clinical status, reduced dyspnea, and reduced fatigue. In the comparative trial, 305 patients were randomly assigned to open-label therapy with standard agents or nesiritide for up to 7 days. In this trial, the global clinical status, dyspnea, and fatigue were improved with the nesiritide therapy for up to 7 days and the improvements were similar to those observed with standard intravenous therapy for heart failure. These results suggest that nesiritide is useful for the treatment of decompensated congestive heart failure by improving hemodynamic function and clinical status. A subsequent randomized study also showed that nesiritide improves hemodynamic function and some self-reported symptoms more effectively than intravenous nitroglycerin in patients hospitalized with acutely decompensated heart failure [67].

In contrast, Sackner-Bernstein et al. [68] very recently reported that nesiritide may worsen renal function in patients with acutely decompensated heart failure. They analyzed the data of randomized clinical trials comparing nesiritide with either placebo or active control for acutely decompensated heart failure using thorough review of U.S. Food and Drug Administration files available via the website. Frequency of worsening renal function (an increase in serum creatinine >0.5 mg/dL) was determined from 5 randomized studies that included 1269 patients. They found that low doses of nesiritide (0.015 µg/kg/min) as well as high dose of nesiritide (0.030 µg/kg/min) significantly increased the risk of worsening renal function compared with non-inotrope-based control or any control therapy,
including non-inotrope- and inotrope-based therapies. More recently, Topol [69] criticized the use of the nesiritide for heart failure in USA, where nesiritide was used to many outpatients with heart failure as a tune-up therapy promoted by pharmaceutical company. Such use is not written on the label or not supported by any evidence. We have to be reminded that the production and secretion of ANP and BNP are very tightly regulated in our body and in fact, the plasma ANP and BNP levels are well correlated with atrial pressure and left ventricular end-diastolic pressure. Increased levels of natriuretic peptides compensate for decompensated heart failure as we described in Chapter 5. In decompensated heart failure, further increase of natriuretic peptide levels by exogenous administration may overcome the dominant effects of vasoconstrictive and antidiuretic hormones. Plasma ANP and BNP levels rapidly decline after the effective therapy. If an excess dose of BNP are continuously infused after the effective therapy, we can easily expect that the renal function will worsen or blood pressure will decline considerably as a result of plasma contraction. Therefore, it is possible that worsening renal function or prognosis in the nesiritide therapy may be due to an inappropriate use, ignoring the pathophysiological role of natriuretic peptide. As many other effective drugs that induce side effect if excess dose of them is administered, the dose of ANP and BNP should be strictly monitored so that it does not disturb the homeostasis of the body. Further prospective studies are necessary to answer the controversy about safety of this drug. Indeed, a 2-trial program, the European Trial of Nesiritide in acute decompensated heart failure that will enroll 1900 patients with acute decompensated heart failure to nesiritide or placebo is now ongoing. In FUSION II, a double-blind placebo-controlled trial, will randomly assign approximately 900 severe heart failure patients to treatment with usual care plus nesiritide or usual care plus placebo and will use mortality/cardiorenal hospitalization as a composite end point [70]. The results of these trials will help to understand whether the worsening of renal function is in fact a signal for adverse clinical outcomes.

The beneficial effects of natriuretic peptide may be applicable to acute myocardial infarction. A recent study compared the effect of ANP with the effect of nitroglycerin on left ventricular remodeling after a first anterior acute myocardial infarction [71]. The improvement of left ventricular ejection fraction was greater in the ANP group than in the nitroglycerin group, although the baseline characteristics were similar between the two groups. Furthermore, left ventricular enlargement was prevented by ANP administration, but not by nitroglycerin administration. These findings suggest that ANP infusion can prevent left ventricular remodeling better than nitroglycerin in patients with acute myocardial infarction. Other investigators have also reported similar observations [72]. These investigators injected ANP into the coronary artery immediately after coronary angioplasty, and then infused ANP for 1 week and compared the results with those in a saline-infused group. The rates of premature ventricular contraction, ventricular tachycardia and/or fibrillation in the ANP infusion group were significantly lower than those in the control group. In addition, left ventricular ejection fraction and regional wall motion of the infarcted segments significantly improved in the ANP group compared to the saline group. These findings indicate that ANP infusion can prevent left ventricular remodeling and arrhythmia in patients with a first anterior acute myocardial infarction, and that ANP can be used as an adjunctive therapy in acute myocardial infarction. To determine whether ANP can be used as a therapeutic drug for acute myocardial infarction, a prospective, randomized, and multicenter study is now being carried out in Japan [73]. This study is designed to test whether acute infusion of ANP reduces myocardial infarct size and improves regional wall motion in acute myocardial infarction.

8. Molecular basis for cardioprotection of natriuretic peptides

With regard to a molecular basis of the beneficial effects of natriuretic peptides as therapeutic drugs in heart failure and acute myocardial infarction, cDNA microarray analysis has provided interesting and important information. Using this technique, Kapoun et al. [74] found that BNP treatment inhibited TGF-beta-induced effects on primary human cardiac fibroblasts. BNP treatment resulted in a remarkable reduction in TGF-beta effects. BNP opposed TGF-beta-regulated genes related to fibrosis (collagen 1, fibronectin, CTGF, PAI-1, and TIMP3), myofibroblast conversion (alpha-smooth muscle actin 2 and nonmuscle myosin heavy chain), proliferation (PDGFA, IGF1, FGF18, and IGFBP10), and inflammation (COX2, IL6, TNF alpha-induced protein 6, and TNF superfamily, member 4). In addition, recent studies shows that aldosterone is produced [75] and CYP11B2 (aldosterone synthase) mRNA is induced in the heart [76]. Interestingly, aldosterone increases the mRNA expression of ACE in cultured neonatal cardiac myocytes [77], suggesting a positive regulatory pathway in the intracardiac renin–angiotensin–aldosterone system. In addition, endogenous and exogenous natriuretic peptides have inhibitory effects on CYP11B2 mRNA expression in cultured neonatal rat cardiocytes [78]. These results raise the possibility that the natriuretic peptide system inhibits the cardiac renin–angiotensin–aldosterone system by suppressing the gene expression of CYP11B2 and restraining cardiac hypertrophy and fibrosis. Collectively, the intracardiac natriuretic peptides/cGMP pathway plays a counter-regulatory role against the intracardiac renin–angiotensin–aldosterone system and TGF-beta mediated pathway.

Finally, in addition to the cardiac effects of natriuretic peptides/NPR-A/cGMP pathway, recent studies show that natriuretic peptides have renoprotective effect [79,80] and...
anti-atherosclerotic effects in vivo [81]. Renal dysfunction is an independent prognostic indicator in cardiovascular disease [82], and ischemic heart disease resulting from coronary atherosclerosis is the main cause of death in the Western country. A progression of other organ damage is a risk in cardiac disease and creates a vicious circle in the process of life-threatening cardiovascular disease. Thus, the natriuretic peptides/NPR-A/cGMP pathway likely exerts its cardioprotective effects directly in heart tissues as well as indirectly through its protective effect on other organs in cardiovascular disease (Fig. 2).

In conclusion, both as hormones and as local factors, natriuretic peptides are promising drugs for a clinical use in the prevention of cardiac remodeling and the treatment of cardiac diseases such as heart failure and myocardial infarction.

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