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Natriuretic Peptides Enhance the Production of Adiponectin in Human Adipocytes and in Patients With Chronic Heart Failure

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Objectives We investigated the functional relationship between natriuretic peptides and adiponectin by performing both experimental and clinical studies.

Background Natriuretic peptides are promising candidates for the treatment of congestive heart failure (CHF) because of their wide range of beneficial effects on the cardiovascular system. Adiponectin is a cytokine derived from adipose tissue with various cardiovascular-protective effects that has been reported to show a positive association with plasma brain natriuretic peptide (BNP) levels in patients with heart failure.

Methods The expression of adiponectin messenger ribonucleic acid (mRNA) and its secretion were examined after atrial natriuretic peptide (ANP) or BNP was added to primary cultures of human adipocytes in the presence or absence of HS142-1 (a functional type A guanylyl cyclase receptor antagonist). Changes of the plasma adiponectin level were determined in 30 patients with CHF who were randomized to receive intravenous ANP (0.025 μg/kg/min human ANP for 3 days, n = 15) or saline (n = 15).

Results Both ANP and BNP dose-dependently enhanced the expression of adiponectin mRNA and its secretion, whereas such enhancement was inhibited by pre-treatment with HS142-1. The plasma adiponectin level was increased at 4 days after administration of human ANP compared with the baseline value (from 6.56 ± 0.40 μg/ml to 7.34 ± 0.47 μg/ml, $p < 0.05$), whereas there was no change of adiponectin in the saline group (from 6.53 ± 0.57 μg/ml to 6.55 ± 0.56 μg/ml).

Conclusions Natriuretic peptides enhance adiponectin production by human adipocytes in vitro and even in patients with CHF, which might have a beneficial effect on cardiomyocytes in patients receiving recombinant natriuretic peptide therapy for heart failure. (J Am Coll Cardiol 2009;53:2070–7) © 2009 by the American College of Cardiology Foundation

Plasma natriuretic peptide levels are increased in patients with congestive heart failure (CHF), and the measurement of these peptides is used widely to assess the presence, severity, and prognosis of CHF (1,2). Both atrial natriuretic peptide and brain natriuretic peptide (ANP and BNP, respectively) have a beneficial effect in patients with heart failure because of their various biological actions (3–5).

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Adiponectin is a circulating cytokine derived from adipose tissue that has attracted considerable interest because of its identification as a risk factor for cardiovascular disease (6,7) and CHF (8). Adiponectin production is down-regulated in patients with coronary risk factors that are associated with the development of heart failure (9,10).

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Recently, adiponectin was reported to have a cardioprotective effect against ischemia-reperfusion injury (11) and hemodynamic stress (12,13) in mice. Interestingly, it has been reported that the level of N-terminal pro-brain natriuretic peptide shows a positive correlation with the plasma adiponectin concentration in patients with chronic heart failure (14).

Given these experimental and clinical observations, we hypothesized that natriuretic peptides might increase adiponectin production in patients with heart failure to protect the cardiovascular system. Accordingly, in the present study, we investigated whether natriuretic peptides could directly increase adiponectin production by these adipocytes (and the cellular mechanisms involved) and confirmed this effect on adiponectin in the clinical setting.

Abbreviations and Acronyms

ANP = atrial natriuretic peptide
BNP = brain natriuretic peptide
CHF = congestive heart failure
GC-A = type A guanylyl cyclase receptor
hANP = human atrial natriuretic peptide
NPR = natriuretic peptide receptor
PKG = protein kinase G

Methods

Agents. Both human ANP and BNP were purchased from Sigma-Aldrich (St. Louis, Missouri). HS142-1, a functional guanylyl cyclase-A type receptor antagonist, was provided by Kyowa Hakko Kogyo Co., Ltd. (Mishima, Japan). A cGMP analog (8-pCPT-cGMP) and a selective cGMP-dependent protein kinase G (PKG) inhibitor (R_p-8-Br-PET-cGMP-S) were obtained from Biolog Life Science Institute (Bremen, Germany). An antibody directed against mouse adiponectin (MAB3608) was purchased from Chemicon International, Inc.

Primary culture and in vitro study of human adipocytes. Subcutaneous adipocytes derived from the adipose tissue of 6 women were obtained commercially together with culture medium from Zen-Bio, Inc. (Research Triangle Park, North Carolina. The donors were nonsmokers with a mean body mass index of 27.0 kg/m^2 (range 25.9 to 29.1 kg/m^2) and an average age of 47 years (range 29 to 63 years). Cells were maintained in adipocytes maintenance medium (i.e., AM-1) containing Dulbecco's modified Eagle medium/Ham's F-12 (1:1, v/v), 3% fetal calf serum, 15 mmol/l HEPES (pH 7.4), biotin, pantothenate, human insulin, 1 μmol/l dexamethasone, 100 U/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml amphotericin B at 37°C in a humidified atmosphere of 95% air/5% CO_2. The medium was changed every 2 days. Primary cultures of the adipocytes were used to examine the effects of natriuretic peptides (ANP or BNP) on the expression of adiponectin.

Before these experiments, the cells were plated in adipocyte basal medium (i.e., BM-1) containing Dulbecco's modified Eagle medium/Ham's F-12 (1:1, volume/volume), 15 mmol/l 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (pH 7.4), biotin, and pantothenate for 24 h. Then the indicated concentrations of either natriuretic peptide (from 10^{-11} to 10^{-9} mol/l) were added to the BM-1 medium. After 24 h of incubation, the medium was harvested for Western blotting to measure the secretion of adiponectin, and the cells were also harvested for ribonucleic acid (RNA) analysis. The effect of each natriuretic peptide on adiponectin messenger ribonucleic acid (mRNA) levels was determined by quantitative real-time polymerase chain reaction (PCR).

Measurement of adiponectin. In patients with CHF, the plasma adiponectin concentration was measured by the use of an ELISA kit (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) according to the manufacturer's protocol. Adiponectin secretion by primary cultured human adipocytes was assessed by Western blotting of the culture medium, as previously described (15), and the immunoreactive bands were quantified by densitometry (Molecular Dynamics, Sunnyvale, California).

Reverse transcriptional-PCR. Total RNA was extracted from adipocytes derived from human white fat with the use of RNA-Bee-RNA Isolation Reagent (Tel-Test, Inc., Gainesville, Florida). Then, 200 ng of total RNA was reversed transcribed and amplified by the use of an Omniscript RT kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The forward primers for type A guanylyl cyclase receptor (GC-A) and natriuretic peptide receptor (NPR)-C were 5′-CCAGTTCCAAGTCTTTGCCAAGACAGCA and 5′-GGAAGACATCGTGCGCAATA, respectively, and the reverse primers for GC-A and NPR-C were 5′-CATTGTGTAGAAACAGCATGCCCTTGACGA and 5′-TGCTCCGGATGGTGTCACT, respectively. As a positive control, we used the samples of human cardiac tissue under the protocol approved by the institutional review board of the National Cardiovascular Center (No. 14-18) (16).

Quantitative real-time PCR analysis. Quantitative real-time PCR was performed as described previously (17). Oligonucleotide primers and TaqMan probes for human adiponectin and glyceraldehyde 3-phosphate dehydrogenase were purchased from Applied Biosystems (Foster City, California).

Subjects and design of the clinical study. We prospectively studied 30 consecutive CHF patients who were admitted to the emergency department of the National Cardiovascular Center between April and July 2006. The exclusion criteria were as follows: age >80 years, cardiogenic shock or hypotension (systolic blood pressure <100 mm Hg), and renal failure (serum creatinine >2.0 mg/dl). This study was approved by the Committee on Human Investigation of the National Cardiovascular Center, and all patients who participated gave informed consent. The 30 patients were randomized to 2 groups, a human atrial natriuretic peptide (hANP) group consisting of 15 patients who received administration of hANP and a control group consisting of 15 patients who were administered saline. In the hANP group, from immediately after the diagnosis of

acute exacerbation of CHF, hANP (0.025 μg/kg/min) was infused intravenously for 3 days. The study protocol did not restrict or specify any other diagnostic or therapeutic strategies. Blood for measuring the plasma adiponectin level was sampled before and 1 and 7 days after finishing the administration of hANP or saline (days 1, 4, and 10, respectively) (Fig. 3A).

Statistical analysis. For analysis of differences between the various treatments of adipocytes, analysis of variance was performed, followed by the appropriate post-hoc test. The differences in adiponectin levels between days 1 and 4 in each group were tested with a paired *t* test. The changes in adiponectin levels from day 1 to 4 between ANP group and saline group was tested with an unpaired *t* test. Results are expressed as the mean ± SEM, and p values of <0.05 were considered significant.

Results

Effect of natriuretic peptides on the expression and secretion of adiponectin by primary cultured human adipocytes. First, we checked the expression of GC-A and NPR-C mRNA by using reverse transcriptional-PCR. As shown in Figure 1A, both GC-A and NPR-C mRNA was detectable in primary cultured human adipocytes. To investigate the effects of natriuretic peptides on the regulation of adiponectin production in adipocytes, we incubated primary cultured human adipocytes with recombinant ANP. When ANP was used at a concentration of 10^{-10} mol/l (pathological plasma concentration), it increased adiponectin mRNA expression after 6 h of incubation and reached a maximum after 12 h (Fig. 1B). Next, we incubated human adipocytes with ANP at the concentration of from 10^{-11} mol/l (normal plasma concentration) to 10^{-9} mol/l (pharmacological plasma concentrations) and demonstrated enhanced adiponectin mRNA expression and adiponectin secretion into the medium in a dose-dependent manner, whereas these changes were completely inhibited by pretreatment with HS142-1 (Figs. 1C and 1D). Incubation of adipocytes with BNP also increased the expression of adiponectin mRNA in a dose-dependent manner and this effect was completely blocked by pretreatment with HS142-1 (Figs. 1E and 1F).

Involvement of cGMP/PKG signaling in natriuretic peptide-induced synthesis of adiponectin. Because both ANP and BNP exert their biological effects by promoting cGMP production, to investigate the role of the GC-A/cGMP/PKG signaling pathway in adiponectin production, we measured the changes of cGMP in ANP-treated primary cultured human adipocytes. We found that incubation with ANP increased the cGMP level and that this effect was blunted by co-treatment with HS142-1 (data not shown). Next, we treated human adipocytes with the cGMP analog 8-pCPT-cGMP and the PKG inhibitor (R_p)-8-Br-PET-cGMP-S. The activation of PKG by 8-pCPT-cGMP (50 μmol/l for 12 h) produced an increase of adiponectin mRNA expression similar to that observed after incubation with ANP. The effect of ANP on adiponectin mRNA expression was abolished in the presence of (R_p)-8-Br-PET-cGMP-S (100 nmol/l) (Fig. 2A). Consistent with these findings, adiponectin secretion into the culture medium also was increased by stimulation of the cGMP/PKG-dependent pathway (Fig. 2B). These results suggested that natriuretic peptides promote adiponectin synthesis via the GC-A/cGMP/PKG-dependent pathway.

Increase of plasma adiponectin levels in CHF patients treated with hANP. To confirm the effect of natriuretic peptides on the production of adiponectin, we conducted the clinical study. Thirty consecutive patients who met the inclusion criteria were enrolled in this clinical study. Fifteen patients were randomized to the ANP group, and 15 were assigned to the saline group. Baseline variables and treatments of the 2 groups are shown in Table 1. There were no differences in baseline clinical characteristics, hemodynamics, biochemical data, or medications. There was also no significant difference in the baseline plasma level of adiponectin between the 2 groups. As shown in Figure 3B, the plasma level of adiponectin did not change throughout the study in the saline group. On the other hand, the plasma adiponectin level at 1 day after finishing the administration of hANP (day 4) was significantly increased compared with the baseline value (day 1) in the ANP group, and it returned to baseline by 7 days after the completion of hANP infusion (day 10). These results suggested that hANP infusion led to an increase of the plasma adiponectin level in patients with CHF.

Discussion

In the present study, we demonstrated a novel effect of natriuretic peptides (ANP and BNP) on the production of adiponectin by adipocytes in both experimental and clinical studies. First, we clearly demonstrated that pathophysiological and pharmacological concentrations of either ANP or BNP increased adiponectin synthesis by primary cultured human adipocytes. Second, we showed that administration of recombinant ANP increased the plasma adiponectin level in patients with CHF.

ANP and BNP play an important role in the regulation of cardiovascular homeostasis. Their actions are primarily mediated via GC-A, which is expressed in various tissues and organs, including the kidneys, blood vessels, adrenal glands, and heart (18). Consistent with a previous report (19), we demonstrated that GC-A and NPR-C are expressed by human adipocytes. In the present study, we demonstrated a novel effect of both ANP and BNP on primary cultured human adipocytes, which was that pathophysiological or pharmacological concentrations of both peptides augmented adiponectin production by human adipocytes, with this effect being inhibited by treatment with HS142-1. Furthermore, we demonstrated that natriuretic peptides augment the production of adiponectin via a cGMP-dependent

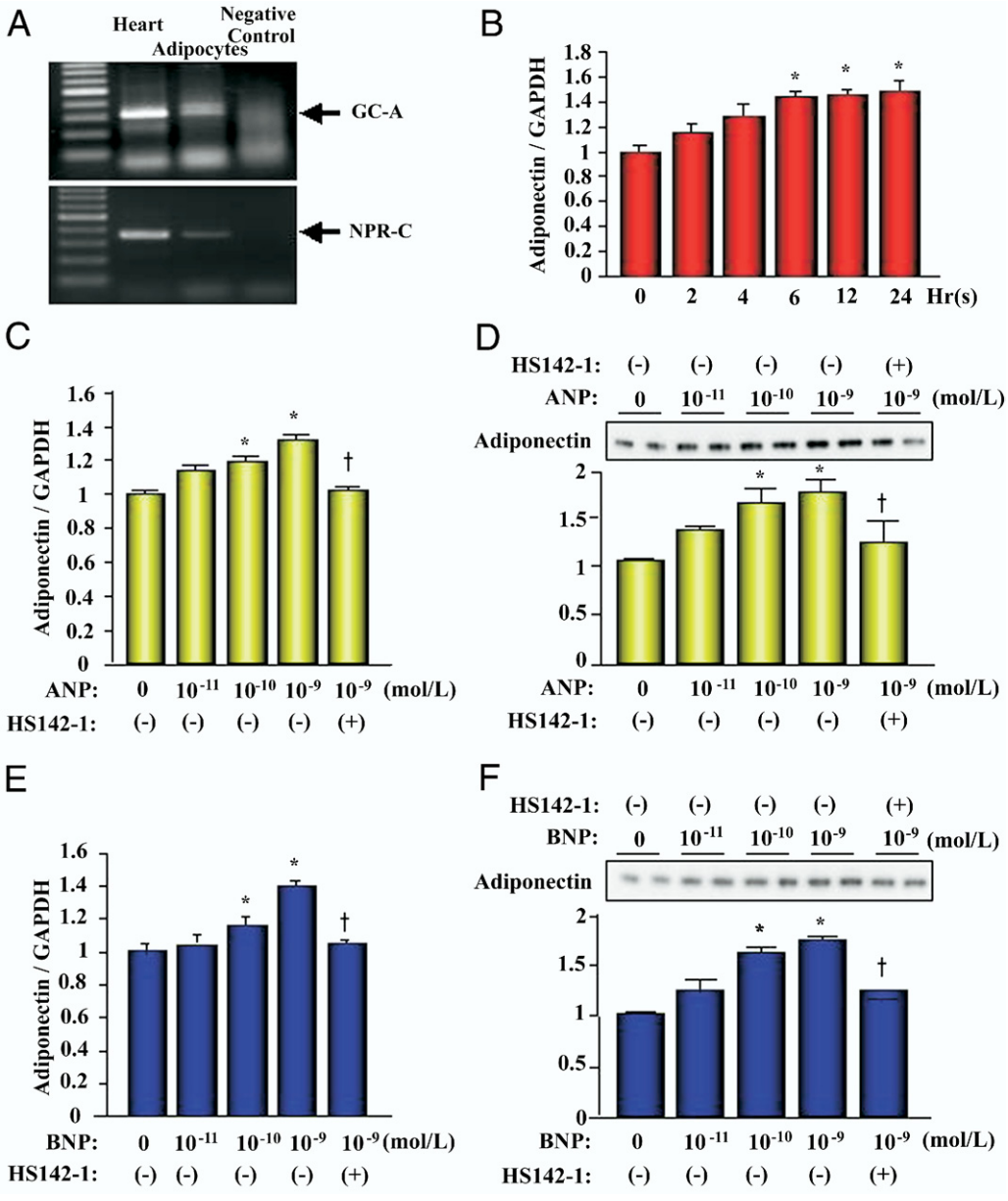

Figure 1 **Effect of Natriuretic Peptides on the Expression and Secretion of Adiponectin by Primary Human Adipocytes**

(A) Expression of GC-A receptors **(top)** and NPR-C **(bottom)** mRNA by primary cultured human adipocytes. Reverse-transcription PCR revealed expression of both GC-A receptors and NPR-C by human adipocytes. **(B)** Effect of ANP (10^{-10} mol/l) on the expression of adiponectin mRNA as determined by quantitative real-time PCR. **(C)** Dose-dependent effect of ANP on adiponectin mRNA expression, as determined by quantitative real-time PCR. Human adipocytes were treated with the indicated concentrations of ANP for 24 h. **(D)** Dose-dependent effect of ANP on adiponectin secretion into the culture medium. **(Top)** A representative Western blot of adiponectin. **(Bottom)** Quantitative analysis of adiponectin by densitometry. Values are normalized to the control. *$p < 0.05$ versus control, †$p < 0.05$ versus ANP 10^{-9} mol/l. **(E)** Dose-dependent effect of BNP on adiponectin mRNA expression, as determined by quantitative real-time PCR. **(F)** Dose-dependent effect of BNP on adiponectin secretion into the culture medium as determined by Western blotting. **(Top)** Representative Western blot of adiponectin. **(Bottom)** Quantitative analysis of adiponectin by densitometry. Values are normalized to the control. *$p < 0.05$ versus control. †$p < 0.05$ versus BNP 10^{-9} mol/l. ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; GC-A = type A guanylyl cyclase receptor; mRNA = messenger ribonucleic acid; NPR-C = natriuretic peptide receptor C; PCR = polymerase chain reaction.

pathway. These findings are important evidence that ANP and BNP regulate adiponectin production by human adipocytes.

Intravenous infusion of nesiritide (recombinant human BNP) has been reported to have beneficial hemodynamic effects in patients with CHF (4,5). The use of ANP also has been reported to have beneficial effects in patients with acute myocardial infarction (20,21). These beneficial effects have been attributed to the cardiovascular-protective actions of natriuretic peptides, including diuresis, natriuresis, vaso-

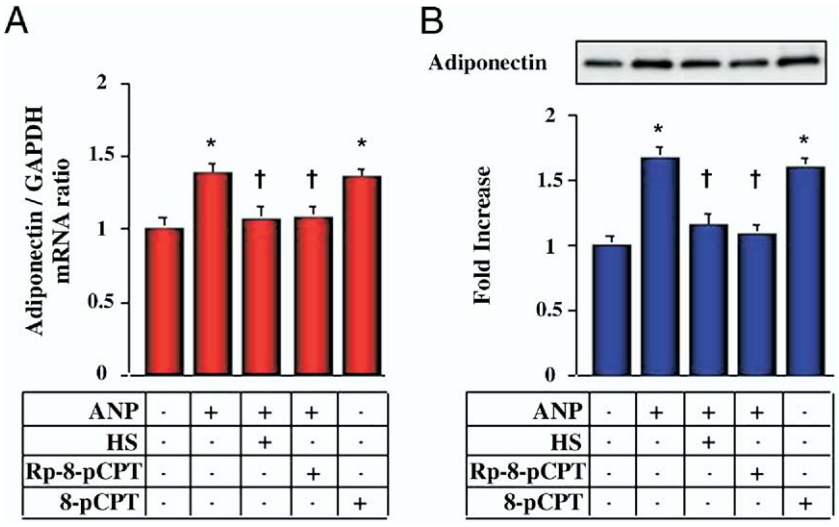

Figure 2 **Involvement of the cGMP/PKG Signaling Pathway in the Induction of Adiponectin Synthesis by ANP**

(A, B) Involvement of PKG was assessed by the treatment of primary cultured human adipocytes with 8-pCPT-cGMP (8-pCPT) and (R_p)-8-Br-PET-cGMP-S (Rp-8-pCPT). Adiponectin mRNA levels were determined by quantitative real-time PCR **(A)** and secretion of adiponectin into the culture medium was determined by Western blotting. Quantitative analysis of adiponectin secretion into the culture medium was done by densitometry **(B)**. Values are normalized to the control. *p < 0.05 versus control. †p < 0.05 versus ANP. HS = HS142-1; other abbreviations as in Figure 1.

dilation, and reduction of activity of the sympathetic nervous system and the renin-angiotensin-aldosterone system (3–5). In the present study, we administered recombinant ANP to patients with CHF and observed the changes of plasma adiponectin. The plasma adiponectin level of the ANP group was increased at 1 day after the finish of ANP administration compared with that in the control group, and then returned to baseline by 7 days after the completion of administration in patients with CHF.

Importantly, Moro et al. (22) showed that ANP did not affect the secretion of adiponectin in human abdominal adipose tissue from overweight women. This result may appear contradict ours, but we believe that is not the case. First, the concentration of ANP they used (10^{-6} mol/l) in the experiment of cultured adipocytes was greater than our concentration. Second, our data that recombinant ANP increased the plasma adiponectin levels were drawn from patients with heart failure, whereas the data of Moro et al. (22) were from cultured fat tissues of overweight women who underwent plastic surgery. However, they also demonstrated the potential stimulatory effect of ANP on adiponectin production from human adipose tissue in the presence of

Table 1 **Clinical Characteristics of the 2 Groups**

	hANP Group (n = 15)	Saline Group (n = 15)	p Value
Age (yrs)	60 ± 19	59 ± 19	NS
Sex (male/female)	9/6	10/5	NS
Heart rate (beats/min)	62 ± 11	66 ± 7	NS
Body mass index (kg/m^2)	21.4 ± 1.1	21.1 ± 1.7	NS
Systolic blood pressure (mm Hg)	116 ± 9	113 ± 9	NS
Diastolic blood pressure (mm Hg)	76 ± 12	74 ± 6	NS
NYHA functional class (II/III)	14/1	10/5	NS
LVEF by echocardiography (%)	32 ± 2	31 ± 8	NS
Plasma BNP (pg/ml)	506 ± 39	537 ± 33	NS
Other medications n (%)			
Loop diuretics	9 (60)	10 (67)	NS
Spironolactone	5 (33)	8 (53)	NS
ACEI or ARB	12 (80)	11 (80)	NS
Beta-blockers	13 (86)	12 (80)	NS

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; BNP = brain natriuretic peptide; hANP = human atrial natriuretic peptide; LVEF = left ventricular ejection fraction; NS = not significant; NYHA = New York Heart Association.

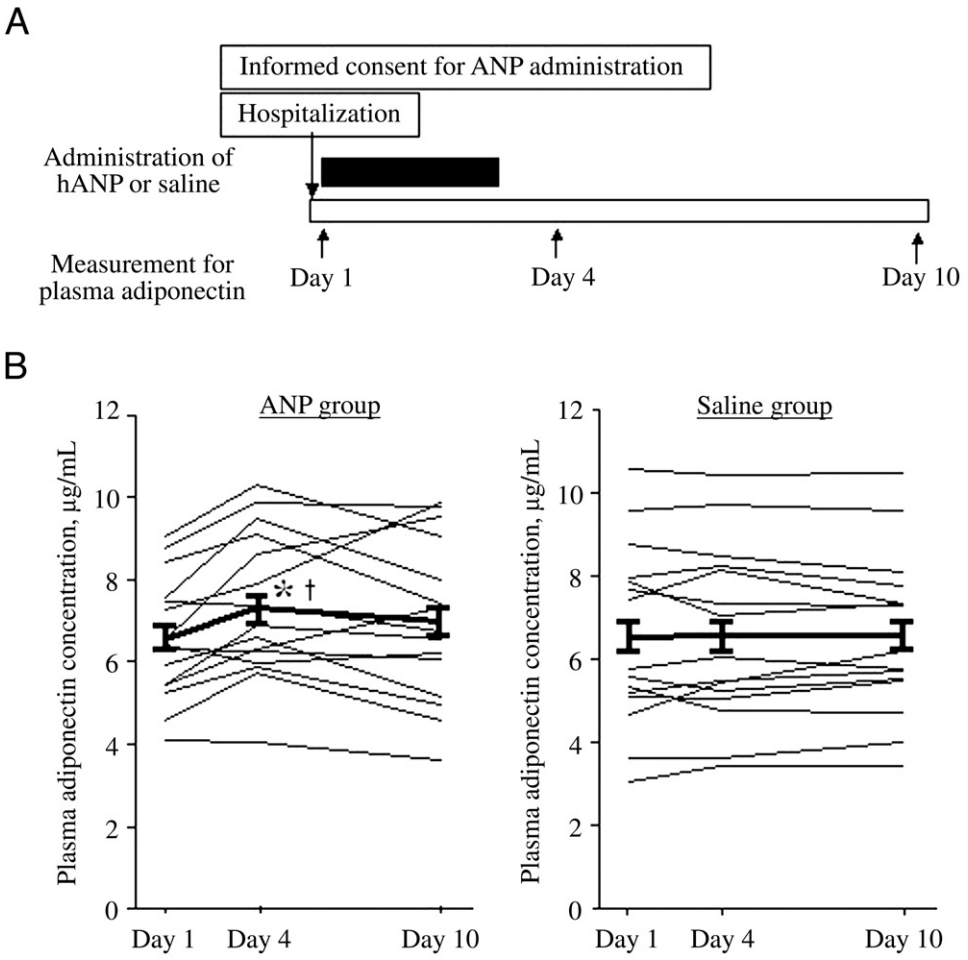

Figure 3 **Increased Plasma Adiponectin Level in Patients With CHF After ANP Treatment**

(A) Outline of the study protocol. hANP or saline was infused continuously for 3 days in the ANP and saline groups, respectively. The **black bar** indicates administration of either hANP (0.025 μg/kg/min) or saline. **(B)** The plasma adiponectin concentration profile after treatment in both groups. *$p < 0.05$ versus baseline in the ANP group; †$p < 0.05$ versus at the corresponding time in the saline group. CHF = congestive heart failure; hANP = human atrial natriuretic peptide; other abbreviations as in Figure 1.

hormone-sensitive lipase inhibitor, which inhibits the formation of lipolysis-derived byproducts by ANP-induced lipolysis (22).

Recently, Yu et al. (23) demonstrated the increased ANP-induced lipolysis rates in large adipocytes compared with small adipocytes. Thus, the difference of adipocyte size between patients with CHF and obesity might contribute to the different pattern of adiponectin secretion. Finally, catecholamines also are involved in the control of lipolysis in humans (24). Thus, the prolonged exposure of high plasma level of catecholamines or the treatment with beta-adrenergic receptor blockers in patients with CHF also might affect the distinct pattern of adiponectin secretion from adipocytes. Although precise mechanisms are unknown, the human adipocytes could secrete adiponectin when the certain stress was loaded. However, it remains possible that factors such as tumor necrosis factor-alpha (25) and alpha-adrenergic stimulation (26), both of which are increased in patients with CHF, may influence the expression of adiponectin or that adiponectin levels are affected by medical treatment, so further investigations are needed.

It is not clear whether ANP augments the plasma adiponectin levels in healthy subjects because of the ethical problems. However, we have reported that the plasma adiponectin level increased along with an increase of plasma BNP levels in 1,538 healthy subjects (27). These results suggest that an increase of natriuretic peptides augments the plasma adiponectin levels and exerts a cardioprotective effect in clinical settings.

Under normal conditions the adult heart utilizes predominantly fatty acids to derive the majority of its energy (28). However, metabolic remodeling such as a marked shift in substrate preference away from fatty acids toward glucose is observed in hypertrophic and failing hearts and the decrease

in fatty acid oxidation is not fully compensated for by an increase in glucose oxidation (29). Thus, the failing heart suffers from chronic energy starvation (30). Insulin resistance also is common in patients with heart failure (31). Adiponectin improves both glucose metabolism and insulin resistance via the AMPK signaling pathway (32). Therefore, we believe that the administration of recombinant natriuretic peptide has beneficial effects on cardiac energy metabolism via adiponectin in patients with CHF.

Interestingly, the plasma adiponectin level was reported to be decreased in patients with risk factors for heart failure (9,33–35) and increased along with BNP after the onset of heart failure (14). Although approximately 10% increase in adiponectin levels in the ANP group seems relatively small, this would not be the case because there was about a 20% reduction in plasma adiponectin levels in patients with coronary artery disease compared with those in control subjects (35), which leads us to believe that the 10% increase in adiponectin is important from the viewpoint of pathophysiology of heart diseases. Therefore, we hypothesized that ANP and/or BNP regulates the plasma level of adiponectin in patients with CHF and conducted this study.

Conclusions

We demonstrated that natriuretic peptides increase the production of adiponectin by human adipocytes, as well as in patients with CHF. These findings may help to shed more light on the pathophysiology of heart failure.

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