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Effect of the vasopressin receptor antagonist conivaptan in rats with heart failure following myocardial infarction

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Abstract

Myocardial infarction often induces congestive heart failure accompanied by a significant increase in plasma vasopressin concentration. To delineate the role of vasopressin in the pathogenesis of congestive heart failure, the acute hemodynamic and aquaretic effects of conivaptan (YM087, 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide monohydrochloride), a combined vasopressin V_{1A} and V_2 receptor antagonist, were assessed in rats with heart failure induced by myocardial infarction. Left coronary artery ligation resulted in decreased left ventricular systolic pressure and first derivatives of left ventricular developed pressure, as well as increased left ventricular end-diastolic pressure, lung and right ventricular weight. Single oral administration of conivaptan (0.3 to 3.0 mg/kg) dose-dependently increased urine volume and decreased urine osmolality in heart failure rats. Furthermore, conivaptan (3.0 mg/kg) attenuated the changes in left ventricular end-diastolic pressure, lung and right ventricular weight induced by heart failure while reducing blood pressure. These results show that vasopressin plays a significant role in elevating vascular tone through vasopressin V_{1A} receptors and plays a major role in retaining free water through vasopressin V_2 receptors in this model of congestive heart failure. Additionally, conivaptan, with its dual vasopressin V_{1A} and V_2 receptor-inhibiting properties, could exert a beneficial effect on cardiac function in the congestive heart failure rat model.

Keywords: Conivaptan; Vasopressin; V_{1A} receptor; V_2 receptor; Nonpeptide antagonist; Congestive heart failure

1. Introduction

Following transmural myocardial infarction, the wall of the left ventricle undergoes progressive stretching and thinning, leading eventually to dilated cardiomyopathy and congestive heart failure. Congestive heart failure is a syndrome characterized by impaired cardiac function, decreased exercise tolerance and quality of life, and high morbidity and mortality. Several vasoactive neurohormonal factors, including those of the renin–angiotensin system and the sympathetic nervous system, participate in this process and contribute to the hemodynamic and metabolic changes that characterize congestive heart failure. Although angiotensin-converting enzyme inhibitors improve hemodynamic profiles and survival times and prevent cardiac dilation in animals and patients with congestive heart failure following myocardial infarction (Pfeffer et al., 1992; Richer et al., 1992; Levine et al., 1984), current therapy for heart failure is still far from optimal.

The hormone vasopressin plays a critical role in water balance, contributing to water retention through effects at the renal vasopressin V_2 receptors (Martin and Schrier, 1997). It also contributes to increased peripheral resistance through the vascular vasopressin V_{1A} receptors, potently constricting blood vessels (Johnston, 1985; Nicod et al., 1985). Interestingly, several experimental and clinical studies have shown that plasma vasopressin concentration is elevated in patients with decompensated heart failure (Yamane, 1968; Riegger et al., 1982; Szatalowicz et al., 1981; Goldsmith et al., 1983). A vasopressin V_{1A} receptor-selective antagonist improved hemodynamics while transiently decreasing systemic vascular resistance and increasing cardiac output in congestive heart failure patients with elevated plasma vasopressin levels (Nicod et al., 1985; Creager et al., 1986). Furthermore, the presence of dilutional hyponatremia is a marker of severe

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decompensated congestive heart failure (Levine et al., 1982). The treatment of patients with this condition is particularly frustrating, because saluretic diuretics tend to further stimulate an inappropriate release of vasopressin, leading to further retention of free water, thus aggravating hypoosmolality of body fluids. A vasopressin V_2 receptor-specific antagonist would offer an additional therapeutic option in congestive heart failure by increasing free water clearance with a minimal saluretic effect (Burrell et al., 1998). These observations suggest that vasopressin is one of the most important neurohormones implicated in the pathophysiology of heart failure.

The recent development of nonpeptide, orally active vasopressin receptor antagonists has allowed reevaluation of the precise role of vasopressin in experimental models of cardiovascular diseases, including heart failure (Burrell et al., 1994, 1995; Naitoh et al., 1994; Yatsu et al., 1997). Until recently, however, all of these nonpeptide antagonists have been selective antagonists of either vasopressin V_{1A} or V_2 receptors, but not both. Recently, Yatsu et al. (1997) developed the orally effective, nonpeptide vasopressin V_{1A} and V_2 receptor antagonist conivaptan (YM087, 4′-(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-*d*][1]benzoazepine-6-carbonyl)-2-phenylbenzanilide monohydrochloride), which exerts potent and long-lasting aquaretic effect and inhibition of vasopressin-induced pressor responses (Tahara et al., 1997; Tomura et al., 1999). Conivaptan is also an effective dual vasopressin V_{1A} and V_2 receptor antagonist in human (Burnier et al., 1999; Tahara et al., 1998b). In the present study, the acute effects of conivaptan in rats with congestive heart failure resulting from ischemic cardiomyopathy were examined.

2. Materials and methods

2.1. Drug

Conivaptan was synthesized at the Yamanouchi Pharmaceutical. (Ibaraki, Japan) and dissolved in 0.5% methylcellurose solution for oral administration. The purity of conivaptan was measured by high-pressure liquid chromatography and was $>98\%$.

2.2. Animals

Male Wistar rats (SLC, Shizuoka, Japan), weighing 280 to 300 g, were used. The animals were fed standard rat chow and tap water ad libitum, housed in communal cages, and maintained on a 12-h light/dark cycle. All experimental procedures involving animals or animal tissues conformed to the regulations of the Animal Ethical Committee of Yamanouchi Pharmaceutical and "The Guide for the Care and Use of Laboratory Animals" (U.S. Department of Health and Human Services, 1985 NIH Publication No. 86-23).

2.3. Surgical production of myocardial infarction

Myocardial infarction was induced by occlusion of the left coronary artery as described previously (Burrell et al., 1996; Nishikimi et al., 1995; Stauss et al., 1994) with a minor modification. In brief, under sodium pentobarbital anesthesia (60 mg/kg i.p.), rats were given positive-pressure ventilation using an artificial ventilator at 10 ml/kg and 60 times/min (model SN-480-4, Shinano Manufacturing Tokyo, Japan). A left thoracotomy was done in the fourth intercostal space and the left coronary artery was ligated approximately 2 to 3 mm from its origin with a 4-0 silk suture. The heart was restored to the normal position and the chest was closed. A sham-operated group underwent the same surgical procedure except for coronary ligation. Hemodynamic and biochemical assessments were performed at 4 to 5 and 7 to 8 weeks after the operation.

2.4. Measurement of aquaretic activity

At 4 or 7 weeks after the operation, rats were consecutively single orally administered with the vehicle (0.5% methylcellurose) or increasing dosages of conivaptan (0.3 to 3.0 mg/kg) at intervals of 3 to 4 days. After treatment, each rat was placed in a metabolic cage and spontaneously voided urine was collected for 4 h. Urine osmolality was measured by the freezing point depression method using an osmometer (model 3C2, Advanced Instruments, MA, USA). Urinary Na^+, K^+ and Cl^- concentrations were measured using an automatic electrolyte analyzer (model 710, Hitachi, Tokyo, Japan).

2.5. Measurement of hemodynamic parameters

At 5 or 8 weeks after the operation, rats were single orally administered vehicle or conivaptan (3 mg/kg). The dose used in this study was based on the significant aquaretic effect of conivaptan in myocardial infarction rats. At 4 h after oral administration, cardiac catheterization was performed under sodium pentobarbital anesthesia. The right carotid artery was exposed and a catheter-tip micromanometer was introduced into the cavity of the left ventricle through the carotid artery. Left ventricular systolic pressure, left ventricular end-diastolic pressure and positive and negative first derivatives of left ventricular developed pressure ($+dP/dt$ and $-dP/dt$) were measured by means of a pressure transducer (model AP-200T, Nihonkohden, Tokyo, Japan) and a differentiator (model EQ-601G, Nihonkohden), respectively. The mean arterial pressure was measured through a cannula placed in the right femoral artery by means of a pressure transducer and heart rate was measured with a tachometer (model AT-600G, Nihonkohden) triggered by the arterial pulse wave. After a 10-min equilibrium period, cardiac and hemodynamic measurements were recorded on a polygraph (model RM-6000, Nihonkohden).

Table 1
The effects of conivaptan on infarct size, heart and lung weights in rats with congestive heart failure (CHF)

Conditions (*n*)	Infarct size (%)	Body wt. (g)	Heart/body wt. (mg/g)	LV/body wt. (mg/g)	RV/body wt. (mg/g)	Lung/body wt. (mg/g)
Fifth week						
Sham (9)	N.D.	291 ± 6	2.75 ± 0.05	1.99 ± 0.04	0.53 ± 0.02	4.04 ± 0.19
CHF/vehicle (5)	15.8 ± 1.2[a]	276 ± 6	3.67 ± 0.17[a]	2.03 ± 0.07	1.05 ± 0.08[a]	8.06 ± 0.56[a]
CHF/conivaptan (5)	16.9 ± 0.8[a]	265 ± 7[a]	3.93 ± 0.08[a]	2.01 ± 0.05	1.25 ± 0.04[a]	8.35 ± 0.42[a]
Eighth week						
Sham (6)	N.D.	325 ± 7	2.42 ± 0.04	1.73 ± 0.03	0.47 ± 0.02	2.98 ± 0.12
CHF/vehicle (4)	16.2 ± 1.3[a]	276 ± 10[a]	3.99 ± 0.12[a]	1.71 ± 0.06	1.40 ± 0.08[a]	9.05 ± 0.18[a]
CHF/conivaptan (4)	14.6 ± 1.4[a]	298 ± 15	3.41 ± 0.11[a,b]	1.64 ± 0.05	1.18 ± 0.08[a,b]	7.41 ± 0.18[a,b]

CHF rats were treated with either the vehicle or conivaptan (3 mg/kg p.o.) at 5 or 8 weeks after the operation. Values are mean ± S.E.M. *n*, number of rats. N.D., not detected. wt., weight; LV, left ventricular; RV, right ventricular.

[a] Significantly different from sham-operated group ($P < 0.05$).

[b] Significantly different from the vehicle control CHF group ($P < 0.05$).

2.6. Measurement of plasma vasopressin concentration

In our preliminary experiment, pentobarbital anesthesia provoked a significant increase in plasma vasopressin concentration. Therefore, another group of myocardial infarction rats and sham-operated rats was used to measure plasma vasopressin concentration under conscious conditions. With the rats under sodium pentobarbital anesthesia, a polyethylene tube (PE-50) was inserted into the left carotid artery for arterial blood sampling at 8 weeks after operation. The catheter was filled with saline containing heparin and tunneled under the skin until exteriorized at the nape of the neck. Blood sampling to measure plasma vasopressin concentration was performed after a 3-day recovery period under conscious and unrestrained conditions. The vasopressin concentration was measured with a vasopressin RIA kit (Mitsubishi Yuka Bio-chemical Laboratories, Tokyo, Japan) after Sep-Pak C18 extraction of plasma.

2.7. Measurement of infarct size and organ weight

After obtaining hemodynamic measurements, the rat was sacrificed and the lung and heart removed. The heart was dissected into three sections: scar tissue, remaining left ventricle including the interventricular septum, and right ventricle. The tissues were rinsed with ice-cold saline, blotted and weighed. Relative values (organ weight/body weight) were used in the evaluation. Rats with an infarct size that was less than 10% of the left ventricle were excluded from analysis.

2.8. Statistical analysis

Data are expressed as mean ± S.E.M. Statistical significance between sham-operated and heart failure groups was estimated by unpaired Student's *t*-test. The effects of conivaptan on tissue weight, hemodynamics and diuresis were analyzed using one-way analysis of variance

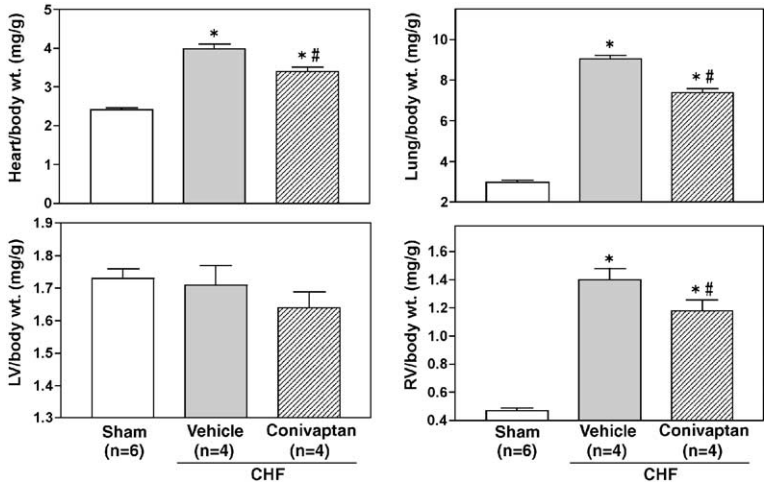

Fig. 1. Effects of conivaptan (3.0 mg/kg p.o.) on heart and lung weight at 8 weeks after coronary ligation. Values are mean ± S.E.M. wt., weight; LV, left ventricular; RV, right ventricular. Statistical comparison was made by a one-way analysis of variance followed by Dunnett's test. * $P < 0.05$ compared with the sham-operated group; # $P < 0.05$ compared with the vehicle control congestive heart failure (CHF) group.

Table 2
The effects of conivaptan on cardiac and hemodynamic parameters in rats with congestive heart failure (CHF)

Conditions (*n*)	MBP (mm Hg)	HR (beats/min)	LVSP (mm Hg)	LVEDP (mm Hg)	+d*P*/d*t* (mm Hg/s)	−d*P*/d*t* (mm Hg/s)
Fifth week						
Sham (9)	129 ± 6	398 ± 12	142 ± 6	3.83 ± 0.87	7340 ± 440	6760 ± 530
CHF/vehicle (5)	116 ± 6	354 ± 21	122 ± 2[a]	16.6 ± 1.2[a]	5080 ± 300[a]	4320 ± 190[a]
CHF/conivaptan (5)	97.8 ± 5.9[a]	348 ± 10[a]	114 ± 2[a]	8.90 ± 2.44[a,b]	4360 ± 390[a]	3680 ± 310[a]
Eighth week						
Sham (6)	124 ± 7	414 ± 14	142 ± 7	4.83 ± 0.31	6950 ± 570	5170 ± 430
CHF/vehicle (4)	109 ± 6	349 ± 14[a]	124 ± 7	33.0 ± 4.3[a]	3930 ± 210[a]	2520 ± 150[a]
CHF/conivaptan (4)	97.3 ± 3.4[a]	354 ± 6[a]	109 ± 4[a]	19.8 ± 5.8[a]	3860 ± 130[a]	2510 ± 200[a]

CHF rats were treated with either the vehicle or conivaptan (3 mg/kg p.o.) at 5 or 8 weeks after the operation. Values are mean ± S.E.M. *n*, number of rats. MBP, mean blood pressure; HR, heart rate; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure.

[a] Significantly different from sham-operated group ($P<0.05$).

[b] Significantly different from the vehicle control CHF group ($P<0.05$).

(ANOVA) followed by Dunnett's multiple-range test, with a level of significance equal to or less than 5%.

3. Results

3.1. Plasma vasopressin concentration

Plasma vasopressin concentration was significantly elevated in congestive heart failure rats at 8 weeks after operation ($P<0.05$). Congestive heart failure rats exhibited a twofold increase in plasma vasopressin concentration (1.39 ± 0.35 pg/ml, $n=7$) compared with sham-operated rats (0.54 ± 0.03 pg/ml, $n=6$).

3.2. Tissue weight and infarct size

The effects of conivaptan treatment on tissue weight of rats with congestive heart failure are shown in Table 1. Both right ventricular and lung weight of rats with congestive heart failure were significantly increased at both 5 and 8 weeks. Single oral administration of conivaptan (3 mg/kg) caused a significant decrease in right ventricular and lung weight at 8 weeks, from 1.40 ± 0.08 and 9.05 ± 0.18 (heart failure) to 1.18 ± 0.08 and 7.41 ± 0.18 (heart failure/conivaptan), respectively (Fig. 1). In contrast, there was no significant difference in left ventricular weight among these groups at 5 or 8 weeks. The infarct area of heart failure rats was approximately 15% of the left ventricle. Conivaptan did

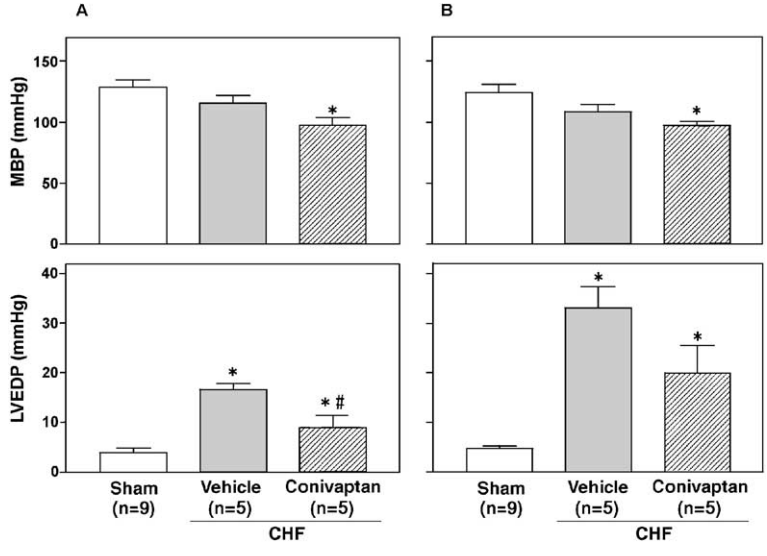

Fig. 2. Effects of conivaptan (3.0 mg/kg p.o.) on hemodynamic parameters at 4 weeks (A) and 8 weeks (B) after coronary ligation. Values are mean ± S.E.M. MBP, mean blood pressure; LVEDP, left ventricular end-diastolic pressure. Statistical comparison was made by a one-way analysis of variance followed by Dunnett's test. *$P<0.05$ compared with the sham-operated group; #$P<0.05$ compared with the vehicle control congestive heart failure (CHF) group.

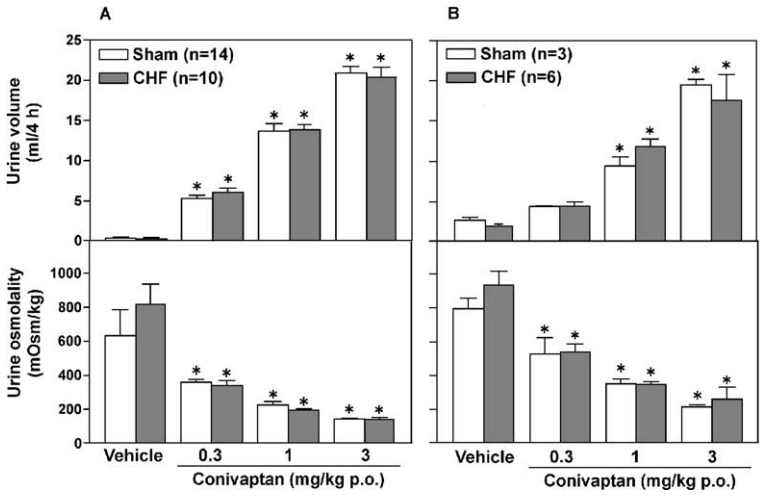

Fig. 3. Effects of conivaptan (0.3–3.0 mg/kg p.o.) on urine volume and osmolality in sham-operated and congestive heart failure (CHF) rats at 4 weeks (A) and 7 weeks (B) after coronary ligation. Values are mean ± S.E.M. Statistical comparison was made by a one-way analysis of variance followed by Dunnett's test. * $P < 0.05$ compared with the vehicle control group.

not change the infarct size of rats with heart failure. No heart of a sham-operated rat had evidence of cardiac damage.

3.3. Changes in hemodynamics

Hemodynamic changes in rats with congestive heart failure, with or without single oral treatment of conivaptan, are shown in Table 2. The left ventricular systolic pressure and dP/dt of rats with congestive heart failure were significantly decreased. The preload parameter left ventricular end-diastolic pressure was markedly increased in rats with heart failure; in conivaptan-treated heart failure rats, left ventricular end-diastolic pressure was significantly decreased at 5 weeks from 16.6 ± 1.2 mm Hg (heart failure) to 8.90 ± 2.44 mm Hg (heart failure/conivaptan) and at 8 weeks from 33.0 ± 4.3 mm Hg (heart failure) to 19.8 ± 5.8 mm Hg (heart failure/conivaptan) (Fig. 2). Moreover, oral administration of conivaptan caused a decrease in mean blood pressure at 5 and 8 weeks. In contrast, there was no significant difference in heart rate, left ventricular systolic pressure and left ventricular dP/dt among these groups at 5 or 8 weeks.

3.4. Urinary parameters

Metabolic cage studies showed no significant differences in terms of urine volume, osmolality, Na^+, K^+ or Cl^- excretion between sham-operated and congestive heart failure rats at both 4 and 7 weeks after operation. Single oral administration of conivaptan (0.3 to 3.0 mg/kg) dose-dependently increased urine volume and decreased urine osmolality in sham-operated and heart failure rats. These effects were seen at both 4 and 7 weeks after operation, and there was no significant difference between sham-operated and heart failure rats (Fig. 3). In contrast, conivaptan had no substantial effects on urine electrolyte

Table 3
The effects of conivaptan on urinary parameters in rats with congestive heart failure (CHF)

Conditions (n)	UV (ml/4 h)	Uosm (mOsm/kg)	$U_{Na}Ex.$ (mEq/4 h)	$U_{K}Ex.$ (mEq/4 h)	$U_{Cl}Ex.$ (mEq/4 h)
Fourth week					
Sham/vehicle (14)	0.31 ± 0.14	631 ± 154	93.8 ± 49.1	202 ± 98	152 ± 80
Sham/conivaptan (14)	20.9 ± 0.8[a]	140 ± 5[a]	163 ± 19	357 ± 20	292 ± 22
CHF/vehicle (10)	0.28 ± 0.16	819 ± 115	102 ± 70	89.3 ± 45.6	66 ± 37
CHF/conivaptan (10)	20.4 ± 1.2[a]	140 ± 11[a]	160 ± 22	352 ± 33[a]	276 ± 35[a]
Seventh week					
Sham/vehicle (3)	2.60 ± 0.40	795 ± 61	213 ± 94	843 ± 152	452 ± 141
Sham/conivaptan (3)	19.5 ± 0.6[a]	215 ± 12[a]	418 ± 58	675 ± 29	592 ± 43
CHF/vehicle (6)	1.93 ± 0.23	935 ± 83	99.8 ± 24.3	647 ± 125	239 ± 33
CHF/Conivaptan (6)	17.6 ± 3.1[a]	261 ± 66[a]	341 ± 87[a]	729 ± 205	484 ± 125

CHF rats were treated with either the vehicle or conivaptan (3 mg/kg p.o.) at 4 or 7 weeks after the operation. Values are mean ± S.E.M. n, number of rats. UV, urine volume; Uosm, urine osmolality; $U_{Na}Ex.$, urinary Na^+ excretion; $U_{K}Ex.$, urinary K^+ excretion; $U_{Cl}Ex.$, urinary Cl^- excretion.

[a] Significantly different from sham-operated group ($P < 0.05$).

excretion in either sham-operated or heart failure rats (Table 3).

4. Discussion

Rats that develop heart failure after induced left ventricular myocardial infarction are widely used as experimental models of human congestive heart failure. The progression of diseases in these animals includes impairment of left ventricular function (Pfeffer et al., 1979), induction of ventricular remodeling (Pfeffer et al., 1992), activation of neurohumoral factors (Hodsman et al., 1988), and reduced long-term survival (Wollert et al., 1994), closely resembling characteristics observed in patients with ischemic heart failure. The present study confirms that myocardial infarction induced in rats results in reduced left ventricular systolic pressure and dP/dt, a cardiac contractility indicator, but increased left ventricular end-diastolic pressure, a preload indicator, at both 5 and 8 weeks after surgery. These physiologic changes are characteristic of cardiac failure (DeFelice et al., 1989), as reported by other investigators who examined these parameters at different times after coronary artery ligation (Burrell et al., 1998; Mulinari et al., 1990).

Elevated plasma vasopressin levels have been reported frequently in patients with congestive heart failure. However, vasopressin levels are very variable, and pathologic levels sometimes overlap with normal values. In several experimental animal models of congestive heart failure, slight increases in plasma vasopressin levels are generally recognized. In dogs with congestive heart failure caused by arteriovenous shunts (Zucker et al., 1979), rapid pacing (Riegger and Liebau, 1982), or inferior vena cava constrictions (Thrasher et al., 1983), vasopressin levels rose to 3 to 5 pg/ml. These observations agree with report that plasma vasopressin concentration rises to 7.8 ± 0.9 pg/ml from normal levels of 2.6 ± 0.2 pg/ml in patients with severe congestive heart failure (Johnston et al., 1988). Also, it is generally recognized that vasopressin levels tend to be higher in patients with severe cardiac failure, as well as those with hypoosmolal or hyponatremic body fluids (Nicod et al., 1986). In the present study, rats that developed congestive heart failure following myocardial infarction exhibited a slight but significant increase in vasopressin level (from a basal level of 0.54 ± 0.03 to 1.39 ± 0.35 pg/ml), analogous to patients with congestive heart failure (Szatalowicz et al., 1981; Goldsmith et al., 1986). Because this increase in vasopressin was presumed to have some significant role in either the hemodynamics or water metabolism of congestive heart failure, the vasopressin V_{1A} and V_2 receptor antagonist conivaptan was used to delineate this role. Conivaptan is an orally active nonpeptide vasopressin receptor antagonist. Conivaptan has shown a high affinity for both vasopressin V_{1A} ($K_i = 0.48$ nM) and V_2 ($K_i = 3.04$ nM) receptors in binding experiments and dose-dependent suppression of the vasopressor action of exogenous vasopressin in rats; this effect lasted more than 8 h (Tahara et al., 1997; Risvanis et al., 1999). Additionally, it acts dose-dependently to increase urine volume and decrease urine osmolality in rats and to exert an aquaretic effect in dogs (Yatsu et al., 1997; Tomura et al., 1999).

In sham-operated and heart failure rats, single oral administration of conivaptan dose-dependently induced a roughly 10-fold increase in urine volume and a decrease in urine osmolality without substantial effects on urinary electrolyte excretion. This aquaretic effect of conivaptan did not differ between the sham-operated and congestive heart failure rats. These results are consistent with a previous report that vasopressin V_2 receptor-selective antagonists exert equal or nearly equal effects in sham-operated and congestive heart failure rats (Pfeffer et al., 1985; Lankhuizen et al., 2001). In contrast, conivaptan significantly lowered both the elevated left ventricular end-diastolic pressure that normally accompanies congestive heart failure and the lung to body weight ratio, a pulmonary congestion indicator. This reduction of cardiac preload might be attributable to the aquaretic action of conivaptan exerted through its vasopressin V_2 receptor antagonism. These results are consistent with the results of Fujita et al. (1995, 1998), who confirmed a preload reduction in congestive heart failure rats given the nonpeptide vasopressin V_2 receptor-selective antagonist OPC-31260.

The present results, together with these previous reports, suggest that, in the pathogenesis of congestive heart failure, vasopressin increases the reabsorption of water in the collecting duct of the kidney, playing an important role in cardiac preload increase due to water retention. Indeed, it has been reported that patients with congestive heart failure exhibit inappropriately high levels of plasma vasopressin even at a plasma osmolality low enough to suppress vasopressin in normal subjects (Szatalowicz et al., 1981). In another study, plasma vasopressin in patients with congestive heart failure was not lowered by acute water loading because of stimulated nonosmotic secretion of vasopressin (Goldsmith et al., 1986). In congestive heart failure, where volume overload exists and leads to deterioration of the dysfunctional ventricle, a preload reduction caused by profuse diuresis induced by vasopressin V_2 receptor antagonism would offer some hemodynamic improvement. Furthermore, the extent of hyponatremia and hypoosmolality in congestive heart failure have been regarded as markers of severity, and an inappropriate and/or elevated vasopressin level is correlated with these metabolic abnormalities through the antidiuretic action of vasopressin. Saluretic diuretics tend to increase free water retention and aggravate hypoosmolality. In contrast, administration of conivaptan to conscious rats with heart failure elicited water diuresis. Conivaptan therefore promises to offer an additional therapeutic benefit for severe congestive heart failure with hyponatremia by increasing free water clearance while exerting a minimal saluretic effect. These results and other

reports suggest that blocking of vasopressin action through vasopressin V_2 receptors to correct abnormal water retention is a promising therapeutic approach to congestive heart failure.

In the present study, groups of rats with heart failure given conivaptan exhibited a lower blood pressure compared with that of the vehicle control group. These results suggest that conivaptan decreases peripheral vascular resistance through its vasopressin V_{1A} and V_2 receptor antagonistic action. In experimental animal models, some researchers reported significant hemodynamic improvement with decreased peripheral vascular resistance and increased cardiac output due to vasopressin V_{1A} receptor-selective antagonist administration and combined administration of vasopressin V_{1A} and V_2 receptor-selective antagonists (Raya et al., 1990; Wilson et al., 1980; Naitoh et al., 1994). This indicates that vasopressin contributes to the raised peripheral vascular resistance and increased ventricular afterload in congestive heart failure (Wang et al., 1991). Furthermore, vasopressin is known to produce potent coronary vasoconstriction via vasopressin V_{1A} receptors, which results in myocardial ischemia and decreased cardiac output (Boyle and Segel, 1986; Walker et al., 1988; Wilson et al., 1980). In human coronary artery smooth muscle cells, conivaptan exhibits high affinity for vasopressin V_{1A} receptors and high potency in inhibiting the vasopressin-induced increase in intracellular free calcium concentration (unpublished observations). Although the results suggest that conivaptan might improve coronary blood flow and cardiac performance through vasopressin V_{1A} receptor antagonism, the present experiments provide no direct information on vasopressin-induced coronary artery contraction in the congestive heart failure model used; to determine this, additional studies are required. Vasoconstrictors, such as angiotensin II, are involved in the regulatory mechanisms of hypertrophy following myocardial infarction (Ambrose et al., 1999; Kalkman et al., 1999). It has been reported that vasopressin also stimulates protein synthesis and induces transcription and translation of proto-oncogenes and growth factors in cardiomyocytes via the vasopressin V_{1A} receptors (Tahara et al., 1998a; Aharonovitz et al., 1998). Such stimulation may lead to ventricular hypertrophy and remodeling. Thus, it is probable that the increase in plasma vasopressin contributes to the process of cardiac remodeling following myocardial infarction in rats, which eventually leads to development of congestive heart failure.

Inappropriate and/or high vasopressin concentrations in congestive heart failure are associated with vasoconstriction, water retention and hyponatremia, and suggest a poor prognosis (Kumar and Berl, 1998; Mayinger and Hensen, 1999). Conivaptan improves cardiac function, reduces preload and afterload, and exerts aquaretic effects in dogs with congestive heart failure (Yatsu et al., 1999). In a clinical study in heart failure patients with hyponatremia, conivaptan reduced urine osmolality and increased free water clearance (Abraham et al., 1999). Moreover, vasopressin antagonism with conivaptan in advanced heart failure significantly decreased pulmonary capillary wedge in pressure (Uldeson et al., 2000). Although proper statistical consideration cannot be derived because of a small number of cases in the present study, these previous findings and the present results suggest that conivaptan, which is able to block the activity of vasopressin at both vasopressin V_{1A} and V_2 receptors, is clinically expected to produce favorable hemodynamic and renal effects in patients with heart failure. However, further studies are needed to evaluate the effect of conivaptan in heart failure.

In conclusion, the results of the present study indicate that in a postinfarction rat model of heart failure vasopressin V_{1A} and V_2 receptor antagonist conivaptan produces significant beneficial hemodynamic changes and profound water diuresis. Therefore, conivaptan is clinically expected to have beneficial effects for treating congestive heart failure.

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