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European Journal of Pharmacology 422 (2001) 109–114

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T-1032, a novel specific phosphodiesterase type 5 inhibitor, increases venous compliance in anesthetized rats

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Received 4 April 2001; received in revised form 1 May 2001; accepted 8 May 2001

Abstract

Nitric oxide (NO) donors including organic nitrates dilate capacitance vessels. As inhibition of phosphodiesterase type 5 results in the accumulation of guanosine 3′5′-cyclic monophosphate (cGMP), specific phosphodiesterase type 5 inhibitors are expected to have a vasodilator property similar to that of NO donors. To test this hypothesis, we examined the effect of methyl2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-3-isoquinoline carboxylate sulfate (T-1032), a novel specific phosphodiesterase type 5 inhibitor, on mean arterial pressure and mean circulatory filling pressure (an index of venodilation) compared with that of nitroglycerin and diltiazem in mecamylamine- and noradrenaline-treated anesthetized rats. Intravenous infusion of T-1032 (0.1, 1, 10 μg/kg/min) dose-dependently decreased mean arterial pressure ($-3.8 \pm 0.3\%$, $-9.1 \pm 0.8\%$, $-16.8 \pm 1.5\%$ at doses of 0.1, 1 and 10 μg/kg/min, respectively) and mean circulatory filling pressure ($-6.1 \pm 0.9\%$, $-12.5 \pm 0.7\%$, $-18.6 \pm 3.0\%$ at doses of 0.1, 1 and 10 μg/kg/min, respectively). The mean circulatory filling pressure–mean arterial pressure relationship revealed that T-1032 had a selective action on the mean circulatory filling pressure compared with diltiazem (10, 100 μg/kg/min) and a similar or more selective effect than nitroglycerin (0.3, 3 and 30 μg/kg/min). In the next study, we calculated venous compliance and unstressed volume from the mean circulatory filling pressure–volume relationship. Intravenous infusion of T-1032 (3 μg/kg/min) increased venous compliance (3.35 ± 0.40 in T-1032 vs. 2.31 ± 0.15 ml/kg/mm Hg in vehicle, $P < 0.05$) without changing the unstressed volume (37.2 ± 2.80 in T-1032 vs. 42.6 ± 2.37 ml/kg in vehicle, $P > 0.05$). It was concluded that T-1032 increased venous capacitance by increasing venous compliance, and that this selective phosphodiesterase type 5 inhibitor appeared to have a different vasodilator action from that of an NO donor and a Ca^{2+} channel antagonist in that it had a selective action on the mean circulatory filling pressure.

Keywords: Phosphodiesterase type 5; Mean circulatory filling pressure; Vascular compliance; Unstressed volume

1. Introduction

Cyclic nucleotides play important roles in the regulation of vascular tone. Phosphodiesterases are key enzymes that hydrolyze both cyclic adenosine 3′5′-cyclic monophosphate (cAMP) and cyclic guanosine 3′5′-cyclic monophosphate (cGMP). Phosphodiesterase type 5 is classified as a cGMP binding, cGMP-specific phosphodiesterase (Beavo, 1988; Hamet and Coquil, 1978) that is distributed widely throughout the cardiovascular system (Kotera et al., 1997; Yanaka et al., 1998).

Methyl2-(4-aminophenyl)-1,2-dihydro-1-oxo-7-(2-pyridinylmethoxy)-4-(3,4,5-trimethoxyphenyl)-3-isoquinoline carboxylate sulfate (T-1032) is a novel inhibitor of phosphodiesterase 5 ($IC_{50} = 0.001$ μM; canine lung) and shows a high selectivity for phosphodiesterase type 5 over other phosphodiesterases (IC_{50}: phosphodiesterase type 1: 3 μM; phosphodiesterase type 2: 9.7 μM; phosphodiesterase type 3: > 100 μM; phosphodiesterase type 4: 3.3 μM (Kotera et al., 2000)). The vasodilator action of T-1032 has been investigated in isolated vessels (Takagi et al., 2001), where it was found to relax rat aorta with a concomitant increase in tissue cGMP (Takagi et al., 2001). In contrast, vasodilation failed to occur in the presence of N^G-nitro-L-arginine methyl-ester (L-NAME), a nitric oxide synthase inhibitor, or after endothelium denudation. These vasodilator properties were similar to those of sildenafil, a selective inhibitor of phosphodiesterase type 5 used in the treatment of male erectile dysfunction. In addition, T-1032 potentiated the vasorelaxation elicited by sodium nitroprusside, but not that elicited by isoproterenol in rat aorta, and potentiated the electrical stimulation-induced relaxation of isolated

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0014-2999/01/$ - see front matter
PII: S0014-2999(01)01044-5

rabbit corpus cavernosum. We also have reported that T-1032 potentiates pelvic nerve stimulation-induced tumescence in an NO cGMP-dependent manner (Noto et al., 2000). These observations suggest that the vasodilator property of T-1032 is due to an NO-dependent mechanism.

The hemodynamic actions of cGMP-generating agents such as nitrovasodilator, atrial natriuretic peptide and phosphodiesterase type 5 inhibitor have been investigated. In particular, organic nitrate, including nitroglycerin, has been reported to preferably dilate capacitance—rather than resistance vessels (Hirano et al., 1997; Ng and Pang, 1998a). The venodilator actions were examined by measuring the mean circulatory filling pressure, an index of venodilation. Nitroglycerin reduced the mean circulatory filling pressure and venous resistance in anesthetized rats (Hirano et al., 1997; Ng and Pang, 1998a). Moreover, in a rat model of heart failure, nitroglycerin reduced the mean circulatory filling pressure accompanied by an increased vascular compliance and decreased unstressed volume (Chien et al., 1992a). As phosphodiesterase type 5 inhibitors are expected to facilitate the accumulation of cGMP in vascular tissues, it is of interest to determine the vasodilator actions of phosphodiesterase type 5 inhibitors in vivo.

Zaprinast, a relatively specific phosphodiesterase type 5 inhibitor (Souness et al., 1989), was reported to decreased venous resistance in ganglion-blocked anesthetized rats (Ng and Pang, 1998b). However, the enzyme specificity and potency of zaprinast are insufficient as compared with those of T-1032. Therefore, in the present study, we examined the effect of T-1032, a highly specific phosphodiesterase type 5 inhibitor, on venous capacitance in rats. We used the ganglion-blocked, noradrenaline-infused anesthetized rat model to prevent any possible baroreflex. First, we examined the effect of T-1032 on mean circulatory filling pressure as compared with nitroglycerin and diltiazem to characterize the venodilator action of T-1032. Second, to find out the mechanism underlying the venodilator action of T-1032, we evaluated the effect of T-1032 on venous compliance and unstressed volume.

2. Material and methods

This study was approved by the Animal Research Committee of Tanabe Seiyaku.

2.1. Animal preparation

Male Wistar rats (230–400 g, $N = 41$) were anesthetized with thiobutabarbital sodium (100 mg/kg, i.p.). A tracheotomy was performed, and a polyethylene tube was inserted into the trachea. Polyethylene tubes were cannulated into the following vessels: femoral artery for measuring mean arterial pressure, inferior vena cava via left femoral vein for measuring central venous pressure, right femoral vein for administration of test drugs and noradrenaline. In a second series of experiments, the left common carotid artery was cannulated for blood administration. A double-lumen catheter (DP 4, Natsume, Tokyo, Japan) was used to cannulate the right femoral vein. A balloon-tip catheter (3F) was inserted into the right atrium from the right jugular vein. The catheters inserted in the femoral- and common carotid arteries and in the femoral vein were filled with heparinized saline.

2.2. Measurement of hemodynamics

Mean arterial pressure and central venous pressure were measured with a pressure transducer (Life Kit, type DX-100; Nihon Kohden, Tokyo, Japan). Heart rate was monitored from arterial pulsation. These parameters were recorded on a polygraph (WR3300, Graph Tec, Tokyo, Japan).

Mean circulatory filling pressure is well described as an index of venodilation (Yamamoto et al., 1980). The mean circulatory filling pressure is defined as that pressure in the circulation during a transient circulatory arrest with the blood redistributed instantaneously so that all pressures in the circulation are equal (Rothe, 1993). The determination of the mean circulatory filling pressure has been validated by previous reports [Chien, 1992 #10; Ng, 1998 #1; Ng, 1998 #16]. To measure mean circulatory filling pressure, the balloon was immediately inflated (6–10 s) and transiently stopped the circulation while mean arterial pressure and central venous pressure were recorded. Mean circulatory filling pressure (MCFP) was calculated using the venous plateau pressure (VPP) and final arterial pressure (FAP) by means of the following equation: $MCFP = VPP + 1/75(FAP - VPP)$ (Chien et al., 1992a).

To determine the mean circulatory filling pressure–blood volume relationship, we made a minor modification of the method described previously (Chien et al., 1992a). Mean circulatory filling pressure was measured immediately after an increase or decrease in blood volume of 10% (6.2 ml/kg) of total. Fresh blood from a donor rat was immediately infused and withdrawn via an arterial catheter. Mean circulatory filling pressure was measured at baseline, and after a 10% increase or 10% decrease in blood volume, and these values were used to determine the mean circulatory filling pressure–blood volume relationship for each rat. Total vascular compliance was obtained from the reciprocal of the slope of the mean circulatory filling pressure–blood volume relationship. Unstressed volume was obtained by linear extrapolation of the mean circulatory filling pressure–blood volume relationship to the mean circulatory filling pressure of 0 mm Hg (Rothe, 1993).

Total blood volume was measured by the Evans blue technique as previously described (Chien et al., 1992b). Briefly, a 0.5% (wt./vol.) solution of Evans blue in a volume of 0.13–0.15 ml was injected through a venous catheter. Ten minutes later, a 0.35-ml arterial blood sample was obtained via the common carotid arterial catheter.

Table 1
Basal hemodynamic variables in mecamylamine- and noradrenaline-treated anesthetized rats

	N	MCFP (mm Hg)	MAP (mm Hg)	CVP (mm Hg)	HR (beats/min)
Before mecamylamine treatment					
T-1032	7	6.92 ± 0.33	134.1 ± 3.0	1.8 ± 0.2	450 ± 3
Nitroglycerin	7	6.48 ± 0.16	123.0 ± 6.9	1.7 ± 0.2	420 ± 18
Diltiazem	7	6.78 ± 0.40	135.6 ± 8.2	1.7 ± 0.1	432 ± 17
After mecamylamine treatment					
T-1032	7	4.86 ± 0.35	73.6 ± 2.5	1.7 ± 0.1	283 ± 11
Nitroglycerin	7	4.31 ± 0.18	68.4 ± 2.6	1.8 ± 0.2	291 ± 8
Diltiazem	7	4.59 ± 0.31	68.9 ± 3.8	1.7 ± 0.1	323 ± 14
After mecamylamine and norepinephrine treatment					
T-1032	7	9.37 ± 0.50	127.3 ± 6.3	2.3 ± 0.3	432 ± 12
Nitroglycerin	7	9.27 ± 0.28	134.6 ± 4.3	2.1 ± 0.2	397 ± 11
Diltiazem	7	9.01 ± 0.34	129.1 ± 6.7	2.1 ± 0.2	408 ± 11

Basal hemodynamics before and after mecamylamine or noradrenaline treatment in anesthetized rats.
Values are means ± S.E.M. *N*: number of rats. MAP; mean arterial pressure, HR; heart rate, MCFP; mean circulatory filling pressure. There were no statistical differences among drugs in each treatment state (one-way ANOVA).

After centrifugation, the Evans blue dye concentration in the plasma was spectrophotometrically determined. Total blood volume was calculated as previously described (Chien et al., 1992b).

2.3. Experimental protocol

2.3.1. Experiment 1. Effect of T-1032, nitroglycerin, and diltiazem on mean circulatory filling pressure in anesthetized rats

After the rats recovered from the cannulation procedure, baseline hemodynamics were measured. Then mecamylamine (3.0 mg/kg) was administered intravenously. After mecamylamine, noradrenaline (1.5 μg/kg/min, 10 μl/kg/min; Harvard infusion pump, model 11) was infused intravenously. All tested drugs were administered intravenously (10 μl/kg/min; Harvard infusion pump, model 11). In the case of cumulative injection, the drugs were administered at 10- to 15-min intervals. The vehicle was 0.001 N HCl/saline. The doses of test drugs were determined in our preliminary study. We selected doses that caused a dose-dependent reduction in mean circulatory filling pressure or mean arterial pressure.

2.3.2. Experiment 2. Effect of T-1032 on mean circulatory filling pressure–blood volume relationship

T-1032 (0.1, 1, 10 μg/kg/min, 10 μl/kg/min) or its vehicle (0.001 N HCl/saline, 10 μl/kg/min) was infused into the mecamylamine- and noradrenaline-treated rats. After all hemodynamics reached steady state, the mean circulatory filling pressure–blood volume relationship was obtained by 10% blood volume changes (increase and decrease). At the end of these measurements, blood volume and hematocrit were measured.

2.4. Drugs

T-1032 and diltiazem hydrochloride were provided by Tanabe Seiyaku, and nitroglycerin was purchased from Nihon Kayaku (milislole injection). T-1032 was dissolved in 0.001 N HCl/saline, and nitroglycerin and diltiazem were dissolved in saline.

2.5. Statistical analysis

Data are shown as percent changes or delta changes from baseline values. Both values are presented as means ± S.E.M. Statistical differences were analyzed by one-way analysis of variance (ANOVA) and Dunnett's method for multiple comparisons. The slope of the mean arterial pres-

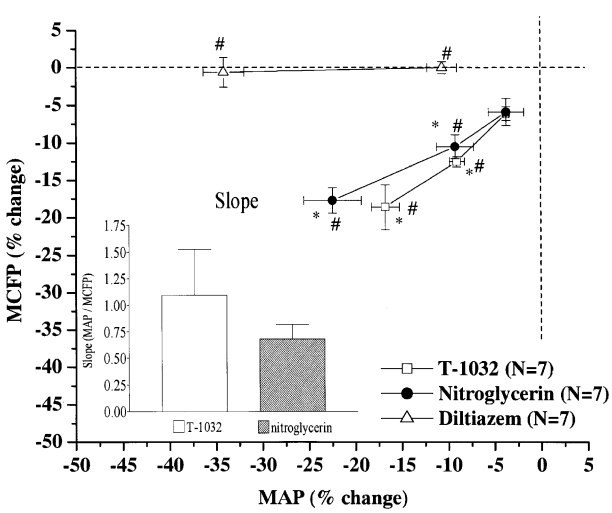

Fig. 1. Relationships between mean arterial pressure (MAP) and mean circulatory filling pressure (MCFP) in T-1032 (0.1, 1, 10 μg/kg/min, $N = 7$)-, nitroglycerin (0.3, 3, 30 μg/kg/min, $N = 7$)- and diltiazem (10, 100 μg/kg/min, $N = 7$)-treated rats. Values are presented as percent changes from baseline values and expressed as means ± S.E.M. Statistical differences from vehicle treatment values were analyzed by Dunnett's test. *: $P < 0.05$ vs. vehicle in mean circulatory filling pressure, #: $P < 0.05$ vs. vehicle in mean arterial pressure. Inner panel: Slope of the MAP/MCFP relationship was determined by regression analysis for each mean circulatory filling pressure–blood volume relationship. Statistical analysis was performed by unpaired *t*-test.

Table 2
Effect of T-1032, NTG and diltiazem on heart rate in mecamylamine- and noradrenaline-treated anesthetized rats

Heart rate (% changes from baseline value)					
T-1032		Nitroglycerin		Diltiazem	
0.1 μg/kg/min	1.0 ± 0.4	0.3 μg/kg/min	1.7 ± 0.5	10 μg/kg/min	−0.4 ± 0.8
1 μg/kg/min	2.7 ± 0.7	3 μg/kg/min	3.4 ± 1.1	100 μg/kg/min	−13.0 ± 1.1[a]
10 μg/kg/min	4.2 ± 0.8	30 μg/kg/min	5.0 ± 1.1		

Values are presented as percent changes from baseline values and expressed as means ± S.E.M. There was statistical difference from vehicle treatment.
[a] $P < 0.05$, Dunnett's test.

sure/mean circulatory filling pressure relationship, vascular compliance and unstressed volume were determined by regression analysis for each mean circulatory filling pressure–blood volume relationship. When the P value was less than 0.05, it was considered statistically significant. All data were analyzed with Stat View ver. 5.0 (SAS Institute Japan).

3. Results

The baseline hemodynamics are shown in Table 1. There were no significant differences among the three compounds in each treatment state (T-1032, nitroglycerin, and diltiazem, one-way ANOVA, $P > 0.05$). The relationship between mean arterial pressure and mean circulatory filling pressure is shown in Fig. 1. Intravenous infusion of vehicle at 10- to 15-min intervals had no effects on mean arterial pressure (0.0 ± 0.1%), heart rate (2.5 ± 0.1%) and mean circulatory filling pressure (−0.5 ± 0.8%) (data not shown). T-1032 (0.1, 1 and 10 μg/kg/min) produced a dose-dependent reduction of both mean arterial pressure ($P < 0.05$ vs. vehicle, Dunnett's test) and mean circulatory filling pressure ($P < 0.05$ vs. vehicle, Dunnett's test). Nitroglycerin (0.3, 3 and 30 μg/kg/min) produced a dose-dependent reduction of both mean arterial pressure ($P < 0.05$ vs. vehicle, Dunnett's test) and mean circulatory filling pressure ($P < 0.05$ vs. vehicle, Dunnett's test), but a further reduction of mean circulatory filling pressure was not seen with the highest dose. Diltiazem (10, 100 μg/kg/min) produced a dose-dependent reduction of mean arterial pressure ($P < 0.05$ vs. vehicle, Dunnett's test) but had no effects on mean circulatory filling pressure ($P > 0.05$ vs. vehicle Dunnett's test). Slope analysis for T-1032 and nitroglycerin revealed that there was a slight difference between T-1032 and nitroglycerin, but the difference was not statistically significant ($P > 0.05$, t-test; Fig. 1, inner panel). Both T-1032 ($P > 0.05$ vs. vehicle, Dunnett's test) and nitroglycerin ($P > 0.05$ vs. vehicle, Dunnett's test) had little effect on heart rate. However, diltiazem produced a significant decrease in heart rate at a high dose (100 μg/kg/min, $P < 0.05$ vs. vehicle, Dunnett's test, Table 2).

In the next study, we examined whether T-1032 changed the mean arterial pressure–blood volume relationship. In this study, we used mecamylamine- and noradrenaline-treated rats, as in the first experiment. There were no statistical differences in baseline hemodynamics between the vehicle- and T-1032-treated groups (one-way ANOVA, $P > 0.05$, Table 3). When T-1032 (3 μg/kg/min) was infused intravenously, mean arterial pressure and mean circulatory filling pressure were significantly decreased compared with those of vehicle-treated rats ($P < 0.05$, Table 4). The slope of the mean circulatory filling pres-

Table 3
Basal hemodynamics in mecamylamine- and noradrenaline-treated anesthetized rats

	N	MCFP (mm Hg)	MAP (mm Hg)	CVP (mm Hg)	HR (beats/min)
Before mecamylamine treatment					
Vehicle	7	9.07 ± 0.73	144.5 ± 5.9	1.8 ± 0.2	433.7 ± 10.7
T-1032	7	8.30 ± 0.27	144.3 ± 6.6	1.7 ± 0.1	433.6 ± 9.00
After mecamylamine treatment					
Vehicle	7	6.20 ± 0.71	59.1 ± 3.3	1.7 ± 0.1	323.0 ± 15.9
T-1032	7	5.21 ± 0.39	61.0 ± 1.5	1.7 ± 0.1	336.6 ± 9.40
After mecamylamine and norepinephrine treatment					
Vehicle	7	10.1 ± 1.08	126.6 ± 6.9	2.3 ± 0.3	416.7 ± 12.4
T-1032	7	9.58 ± 0.47	129.6 ± 8.0	2.1 ± 0.1	428.9 ± 9.50

Basal hemodynamics before and after mecamylamine or noradrenaline treatment in anesthetized rats. Values are means ± S.E.M. N: number of rats. MAP; mean arterial pressure, HR; heart rate, MCFP; mean circulatory filling pressure. There were no statistical differences between T-1032 and vehicle in each treatment state ($P > 0.05$, one-way ANOVA).

Table 4
Effects of T-1032 on hemodynamic and blood volume in mecamylamine- and noradrenaline-treated anesthetized rats

	T-1032 ($N = 7$)	Vehicle ($N = 7$)
MAP (Δmm Hg)	−16.9 ± 3.8[a]	−4.6 ± 1.6
HR (Δbeats/min)	4.9 ± 1.0	3.9 ± 2.6
MCFP (Δmm Hg)	−0.93 ± 0.13[a]	−0.11 ± 0.08
Venous compliance (ml/kg/mm Hg)	3.35 ± 0.40[a]	2.31 ± 0.15
Unstressed volume (ml/kg)	37.2 ± 2.8	42.6 ± 2.4
Total blood volume (ml/kg)	65.4 ± 2.3	65.0 ± 1.5
Hematocrit	49.4 ± 0.7	47.1 ± 1.9

Values are means ± S.E.M. N: number of rats. MAP; mean arterial pressure, HR; heart rate, MCFP; mean circulatory filling pressure. There were statistical differences between T-1032 and vehicle in each treatment state.
[a] $P < 0.05$, one-way ANOVA.

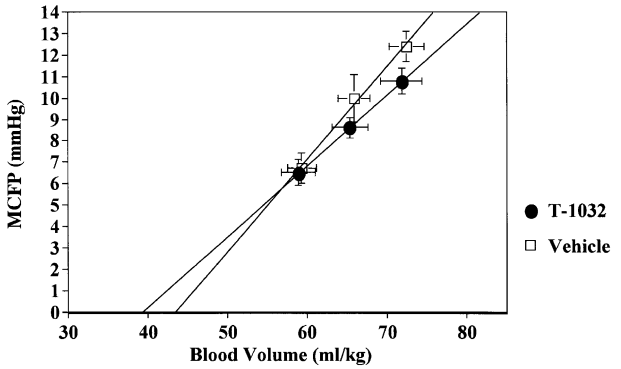

Fig. 2. Mean circulatory filling pressure (MCFP)–blood volume relationship in mecamylamine- and noradrenaline-treated rats. Values are presented as means ± S.E.M. Vehicle ($N = 7$); open square, T-1032 (3 μg/kg/min, $N = 7$); closed circle.

sure–blood volume relationship revealed that T-1032 increased vascular compliance ($P < 0.05$, Fig. 2, Table 4) without changing the blood volume ($P > 0.05$, Table 4), hematocrit ($P > 0.05$, Table 4), or unstressed volume ($P > 0.05$, Fig. 2, Table 4).

4. Discussion

In the present study, we examined whether T-1032 changed venous capacitance in anesthetized rats. In the first experiment, to test whether T-1032 had venodilator activity, we examined the effect of T-1032 on mean arterial pressure and mean circulatory filling pressure, and their relationship, in comparison with that of two types of vasodilator, nitroglycerin and diltiazem. Our results suggested that both T-1032 and nitroglycerin but not diltiazem reduced mean circulatory filling pressure. Diltiazem reduced mean arterial pressure profoundly, but T-1032 and nitroglycerin reduced it weakly.

There are several reports suggesting that NO-generating agents, such as nitroglycerin or sodium nitroprusside, have venodilator activity in animal models (Muikku et al., 1992; Ng and Pang, 1998a; Ogilvie and Zborowska Sluis, 1991). In the present experiment, nitroglycerin produced a dose-dependent decrease of mean circulatory filling pressure. In contrast, there was little difference in the slope of the mean arterial pressure–mean circulatory filling pressure relationship between T-1032 and nitroglycerin (Fig. 1). Diltiazem, an L-type calcium channel blocker, dose-dependently decreased the mean arterial pressure but had no effect on the mean circulatory filling pressure. This result suggests that diltiazem has no venodilator activity. Several investigators reported the venous action of Ca^{2+} channel antagonists (Hirano et al., 1997; Ito and Hirakawa, 1984; Waite et al., 1988). Pranidipine and amlodipine, dihydropyridine Ca^{2+} channel antagonists, decreased the mean circulatory filling pressure in ganglion-blocked, noradrenaline-infused rats (Hirano et al., 1997). However, another dihydropyridine derivative, nifedipine, had no effect on the mean circulatory filling pressure (Ogilvie and Zborowska Sluis, 1990). Because we aimed to clarify the vasodilator property of T-1032 as compared with that of other venodilator and/or arterial vasodilators, we used diltiazem, which might not have an effect on the mean circulatory filling pressure in this model. Heart rate was not affected by T-1032 and nitroglycerin, except at a high dose of diltiazem. These results indicate that T-1032 does not have a direct chronotropic action.

In the second study, we examined how T-1032 changed the mean circulatory filling pressure in the first study. The baseline hemodynamics were not different between vehicle- and T-1032-treated groups ($P > 0.05$, Table 3). However, absolute values of the mean circulatory filling pressure in before mecamylamine treatment state were different between first- and second experiment. In the second study, additional catheter was inserted into common carotid artery to infuse and withdraw the 10% of donor blood for the construction of MCFP–blood volume relationships. MAP and MCFP might increase by stopping the blood flow in carotid artery. Therefore, it is possible that this difference was due to the difference of surgical preparation between two series of experiments.

Intravenous infusion of T-1032 (3 μg/kg/min) displaced the mean circulatory filling pressure-blood volume relationship toward the pressure axis, especially when the mean circulatory filling pressure was high. These data indicated that T-1032 changed venous compliance. However, unstressed volume was not changed significantly. The total blood volume or hematocrit was not changed as compared with that of vehicle-treated rats, either. Therefore, these results suggested that T-1032 changed venous compliance, but not unstressed volume.

The reported action of nitroglycerin on venous capacitance is inconsistent, probably due to differences in experimental conditions. It was reported that intravenous infusion of nitroglycerin reduced the mean circulatory filling pressure through an increased venous compliance and a decreased unstressed volume in a rat model of heart failure (Chien et al., 1992a). Total blood volume and hematocrit were decreased, which indicated hemodilution, suggesting that nitroglycerin caused venodilation. However, in other studies, nitroglycerin and sodium nitroprusside decreased venous return without changing venous compliance in ganglion-blocked anesthetized dogs (Ogilvie and Zborowska Sluis, 1991). In addition, several NO-generating agents (diethylamine/NO, *S*-nitroso-*N*-acethylpenicillamine, and sodium nitroprusside) decreased venous resistance in ganglion-blocked, noradrenaline-infused normal rats (Ng and Pang, 1998a).

Zaprinast, a relatively potent inhibitor of phosphodiesterase type 5 (IC_{50}: 200 nM, bovine aorta) (Souness et al., 1989), potentiated the action of NO. Recently, it was reported that zaprinast dilated capacitance vessels in ganglion-blocked, noradrenaline-infused rats (Ng and Pang, 1998b). However, the mechanisms underlying the reduc-

tion in mean circulatory filling pressure produced by phosphodiesterase type 5 inhibitors have not been clarified. In the present study, we demonstrated that phosphodiesterase type 5 inhibitors reduce the mean circulatory filling pressure through a decrease in venous compliance in anesthetized rats.

We used ganglion-blocked rats to minimize autonomic reflex effects. Because ganglion blockade results in a low level of venous tone, which may have masked possible venodilation by the drugs, noradrenaline was infused to elevate both venous and arterial vascular tone. The venodilator property of T-1032 in intact animals is still unknown. Intravenous administration of nitroglycerin and NO donor reduced the mean circulatory filling pressure in ganglion-blocked rats but failed to do so in intact rats (D'Oyley et al., 1989). It was speculated that the lack of venodilation by nitroglycerin and NO donors might be partly explained by the sympathetic baroreflex. Further studies will be necessary to determine the venous action of T-1032 in conscious rats.

A decreased venous capacitance was reported in various models of heart failure (Gay et al., 1986; Ogilvie and Zborowska Sluis, 1992, 1995; Raya et al., 1989). An increased venous capacitance results in decreased resistance to venous return and cardiac preload. In this regard, the venodilator action of T-1032 might improve the decreased cardiac performance of patients with heart failure.

In conclusion, T-1032 decreased mean circulatory filling pressure in anesthetized rats. The mechanisms of the reduction in mean circulatory filling pressure are based on an increased venous compliance. The reduction of mean circulatory filling pressure vs. mean arterial pressure produced by T-1032 was clearly different from that produced by diltiazem. The vasodilator action of phosphodiesterase type 5 inhibitors might be more selective than that of NO donors such as nitroglycerin.

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