The Mechanism of the Increasing Action of TA-993, a New 1,5-Benzothiazepine Derivative, on Limb Blood Flow in Anesthetized Dogs: Selective Suppression of Sympathetic Nerve Activity

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ABSTRACT

TA-993, (cis)-3-acetoxy-5-(2-(dimethylamino)ethyl)-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-benzothiazepin-4(5H)-one maleate, a new 1,5-benzothiazepine derivative with cis configuration, has a unique and selective increasing action on limb blood flow with little influence on arterial pressure besides an antiplatelet action. We studied the mechanism of increasing action of TA-993 on limb blood flow in anesthetized dogs. In a canine blood-perfused hindlimb preparation with a donor dog, TA-993 (100 μg/kg i.v.) did not increase femoral blood flow when administered to the donor dog, but did when administered to a recipient dog. TA-993 did not show the increasing action on femoral blood flow in the presence of hexamethonium or phentolamine, whereas it did in the presence of propranolol or atropine. TA-993 also showed a weak increasing effect on heart rate, which was inhibited by any one of these blockers. TA-993 (300 μg/kg i.v.) did not alter the phenylephrine (1–100 ng/kg i.a.)- or the talipexole (3–100 ng/kg i.a.)-induced increase in perfusion pressure in an autoperfused hindlimb. These results suggest that the increasing action of TA-993 on limb blood flow is mediated by the sympathetic nervous system but that the adrenergic receptors are not likely to be the central point of action of this new agent. There is a possibility that the mechanism of the increasing action on heart rate is different from that of its increasing action on limb blood flow.

TA-993, (cis)-3-acetoxy-5-(2-(dimethylamino)ethyl)-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-benzothiazepin-4(5H)-one maleate, is a new 1,5-benzothiazepine derivative with cis configuration (Fig. 1). TA-993 has a selective increasing action on limb blood flow, such as femoral and brachial blood flow (Kaburaki et al., 1998c), and an inhibitory effect on platelet aggregation (Odawara et al., 1996). Moreover, TA-993 showed an antithrombotic effect in some models of arterial thrombosis (Narita et al., 1995; Odawara et al., 1996; Kaburaki et al., 1998a). The cardiovascular action of TA-993 is quite different from that of 1,5-benzothiazepine derivatives with d-cis configuration, such as diltiazem and clentiazem, which show potent spasmolytic and vasodilating actions on coronary and vertebral arteries, as well as hypotensive action (Sato et al., 1971; Nagao et al., 1977; Rosenthal et al., 1983; Murata et al., 1988). As we reported previously (Kaburaki et al., 1998c), the cardiovascular action of TA-993 has unique characteristics. TA-993 selectively increases blood flow of femoral, brachial, and common carotid arteries with little influences on blood pressure and blood flow in other vascular beds. This action manifests itself slowly and is long-lasting, even after i.v. administration. We know of no other vasodilating agents with characteristics such as those seen with TA-993.

It has been reported that the cardiovascular effects of d-cis isomers of 1,5-benzothiazepine derivatives are due to their potent antagonistic action on voltage-dependent L-type calcium channels (Ito et al., 1978; Fujiwara et al., 1982; Kikkawa et al., 1988). However, the increasing action of TA-993 on limb blood flow cannot be explained by calcium antagonistic action because antagonistic activity of TA-993 on Ca⁺⁺-induced contraction in the isolated K⁺-depolarized saphenous artery was much weaker than that of diltiazem (Kaburaki et al., 1998b).

In the present study, we investigated the mechanism of the increasing action of TA-993 on limb blood flow in anesthetized dogs.

Materials and Methods

Fifty-five mongrel dogs of either sex weighing from 10.5 to 18.3 kg were each anesthetized by i.v. administration of sodium pentobarbi-
tal (30–35 mg/kg and 5.0–5.5 mg/kg/h), and were placed on a heated operating table in the supine position. The trachea was intubated and the dog was artificially ventilated (15 ml/kg/stroke, 20 strokes/min) with room air. Polyethylene tubes were inserted into the intermediate antebrachial, brachial, and medial saphenous veins for infusion of pentobarbital and injection of drugs. Arterial blood pressure was measured with a pressure transducer (TP-400T; Nihon Kohden, Tokyo, Japan) that was connected to a polyethylene catheter inserted into the right brachial artery and a carrier amplifier (AP-621G; Nihon Kohden). Heart rate was measured with a heart rate counter (AT-601G; Nihon Kohden) triggered by arterial pressure pulses. All measurements were simultaneously recorded on a multichannel thermal pen recorder (WR3310; Graphtec, Tokyo, Japan).

Effect of TA-993 on Blood Flow of Blood-Perfused Hindlimb Preparation with a Donor Dog.

A scheme of the preparation is shown in Fig. 2. Briefly, the left common carotid artery, the left lateral jugular vein, and the left femoral artery were exposed in the donor dog. After celiotomy, the left external iliac artery and the left external iliac vein were exposed in the recipient dog. In the donor, the distal parts of the common carotid artery and the lateral jugular vein were ligated and silicone tubes filled with 0.9% sodium chloride solution were inserted into the proximal parts of the artery and the vein. In the recipient, the proximal parts of left external iliac artery and left external iliac vein were ligated, and the distal parts of the external iliac artery and the external iliac vein were connected via silicone tubing to the proximal parts of the common carotid artery and the lateral jugular vein of the donor, respectively. Thus, the left hindlimb of the recipient was perfused by the blood of the donor. Flow probes (2.5–3.0 mm in inner diameter) of electromagnetic flowmeters (MFV-2100; Nihon Kohden, Tokyo, Japan) were placed on the left femoral artery of the donor and the femoral arteries of perfused and contralateral limbs of the recipient to measure their blood flows. Both dogs received heparin (200 I.U./kg i.v., initially and 100 I.U./kg i.v., thereafter) every 1.5 h throughout the experiment to prevent coagulation of blood.

After an equilibration period, TA-993 (100 μg/kg) was administered i.v. to the donor. An i.v. administration of TA-993 (100 μg/kg) to the recipient was also carried out more than 60 min after the administration of TA-993 to the donor.

Influences of Adrenergic and Cholinergic Blocking Agents on the Increasing Action of TA-993 on Femoral Blood Flow in Anesthetized Dogs. The right femoral artery was exposed and an electromagnetic flow probe was placed on it (inner diameter of probes; 2.5–3.0 mm) for measurement of femoral blood flow. A polyethylene tube was also inserted into the muscular branch of the femoral artery as the occasion demanded for intra-arterial administration of drugs to the femoral artery. After an equilibration period, hexamethonium (5 mg/kg i.v. bolus and 6 mg/kg/h i.v. infusion), phentolamine (5 mg/kg i.v. bolus and 2–3 mg/kg/h i.v. infusion), propranolol (0.5 mg/kg i.v. bolus and 0.1 mg/kg/h i.v. infusion), or atropine (0.5 mg/kg i.v. bolus, and 0.1 mg/kg i.v., intermittently) was administered. After waiting 10 to 30 min to allow plateauing of the cardiovascular responses to these drugs, TA-993 (300 μg/kg) was administered i.v. in some experiments, [Arg₁]-vasopressin (AVP) (60–1800 ng/kg/h) was also infused i.v. after the administration of hexamethonium, phentolamine, or atropine to restore the vascular resistance of the femoral artery, which was decreased by the treatment of these blockers. In the control group, TA-993 was administered i.v. without any pretreatment. The efficacy of each blocker was confirmed by intermittent application of the corresponding agonist; 1,1-dimethyl-4-phenylpiperazinium (10–30 μg/kg i.v.), phenylephrine (100 ng/kg i.a.), talipexole (10–30 ng/kg i.a.), isoproterenol (0.3–1.0 ng/kg i.a.), or acetylcholine (0.3–1.0 ng/kg i.a.).

Influence of TA-993 on Pressor Response to Adrenergic α₁ or α₂ Stimulation in a Canine Hindlimb Autoperfusion Model.

A scheme of the preparation is shown in Fig. 3. Briefly, the right
common carotid artery and the right femoral artery were exposed. The distal part of the common carotid artery and the proximal part of the femoral artery were ligated, and the proximal part of the common carotid artery was connected via silicone tubing to the distal part of the femoral artery to prepare a shunt between the arteries. The hindlimb was autoperfused with a fixed rate (49–110 ml/min) by means of a variable speed peristaltic pump (1210; Harvard Apparatus Co., Inc., Millis, MA). A flow probe (3.0 mm in inner diameter) of an electromagnetic flowmeter and a pressure transducer were placed on the shunt so that both blood flow and perfusion pressure of the perfused hindlimb were measured. Mean perfusion pressure of the femoral artery was adjusted as close as possible to the mean arterial pressure. Blood flow of the contralateral femoral artery was also measured with an electromagnetic flowmeter for reference. The dogs received heparin (200 I.U./kg i.v., initially and 100 I.U./kg i.v., thereafter) every 1.5 h throughout the experiment to prevent coagulation of blood. After an equilibration period, both phenylephrine and talipexole were administered to the shunt and then TA-993 (300 μg/kg) was administered i.v. The pressor responses to phenylephrine and talipexole were studied again 60 min after the administration of TA-993.

**Drugs.** The following drugs were used: TA-993 (Tanabe Seiyaku, Co., Ltd., Osaka, Japan), sodium pentobarbital (Tokyo Kasei Co., Ltd., Tokyo, Japan), sodium heparin (1000 I.U./ml; Mochida Seiyaku Co., Ltd., Tokyo, Japan), hexamethonium bromide (Nacalai Tesque Inc., Kyoto, Japan), phenolamine hydrochloride (Sigma Chemical Co., St. Louis, MO), dl-propranolol hydrochloride (Nacalai Tesque Inc., Kyoto, Japan), atropine sulfate (Wako Pure Chemical Industries, Ltd., Osaka, Japan), 1,1-dimethyl-4-phenylpiperazinium iodide (Nacalai Tesque Inc.), phenylephrine hydrochloride (Kowa Co., Ltd., Nagoya, Japan), talipexole dihydrochloride (Discovery Research Laboratory, Tanabe Seiyaku Co., Ltd., Saitama, Japan), dl-isoproterenol hydrochloride (Nacalai Tesque Inc.), acetylcholine chloride (Daiichi Seiyaku Co., St. Louis, MO), dl-propranolol hydrochloride (Nacalai Tesque Inc., Kyoto, Japan), phentolamine hydrochloride (Sigma Chemical Co., Ltd., Osaka, Japan), sodium pentobarbital (Tokyo Kasei, Co., Ltd., Osaka, Japan), sodium heparin (1000 I.U./ml; Mochida Seiyaku Co., Ltd., Tokyo, Japan), sodium pentobarbital (Tokyo Kasei Co., Ltd., Osaka, Japan), and L- (+) ascorbic acid (Wako Pure Chemical Industries, Ltd., Japan). Isoproterenol was dissolved in 0.9% sodium chloride solution containing 0.1% ascorbic acid. The other drugs were dissolved in 0.9% sodium chloride solution. The volume of drugs administered was as follows: i.v. administration, 0.1 ml/kg (except phenolamine, 0.5 ml/kg); and intra-arterial administration, 0.01 ml/kg. Doses of all drugs were expressed in terms of the salt.

**Data Analysis.** Vascular resistance of femoral artery was calculated according to the following formula:

\[
\text{Vascular resistance of femoral artery} \left( \text{mm Hg} \times \text{min/ml} \right) = \frac{\text{Mean arterial pressure (mm Hg)/femoral blood flow (ml/min)}}{1}
\]

Values were represented as means ± S.E.M. A paired t test was performed to compare data before and after the drug administration. The time course data were analyzed by repeated measures ANOVA, followed by post hoc multiple comparison with Bonferroni’s method for comparison with the control experiment. The results were considered to be statistically significant when \( p < 0.05 \).

**Results**

**Effect of TA-993 on Blood Flow of Blood-Perfused Hindlimb Preparation with a Donor Dog.** Figure 4 shows the time course of the effects of TA-993 on the femoral blood flow of the donor and on the perfused and contralateral hindlimbs of the recipient after i.v. administration to the donor dog (A) and the recipient dog (B). When TA-993 (100 μg/kg i.v.) was administered to the donor, it influenced neither blood flow nor vascular resistance of either the perfused or the contralateral hindlimb of the recipient, although it progressively increased the femoral blood flow and decreased the vascular resistance of the femoral artery in the donor (Fig. 4A). In contrast, when TA-993 (100 μg/kg i.v.) was administered to the recipient, it progressively increased blood flow and decreased the vascular resistance of the perfused hindlimb of the recipient with a potency similar to that in the contralateral hindlimb (Fig. 4B). In addition, TA-993 administered to either dog did not affect the mean arterial pressure or heart rate.

**Influences of Adrenergic and Cholinergic Blocking Agents on the Increasing Action of TA-993 on Femoral Blood Flow in Anesthetized Dogs.** Table 1 shows baseline values of cardiovascular parameters and the values after the treatment with blockers (just before the administration of TA-993) in each drug-treated group. In the control group, TA-993 (300 μg/kg i.v.) showed an increasing effect on femoral blood flow that manifested slowly and was persistent. TA-993 also showed a decreasing effect on vascular resistance of the femoral artery and a weak increasing effect on heart rate (Fig. 5).

Treatment with hexamethonium induced a significant hypotension and tended to increase femoral blood flow and decrease the vascular resistance of the femoral artery. The vascular resistance of the femoral artery was made nearly equal to the baseline value by i.v. infusion of AVP (Table 1). After treatment with a combination of hexamethonium and AVP, TA-993 (300 μg/kg i.v.) neither increased femoral blood flow nor decreased the vascular resistance of the femoral artery. In addition, a weak but persistent increase in heart rate observed in the control group also disappeared (Figs. 5 and 6). Similar results were obtained after treatment with hexamethonium alone (Fig. 6). AVP itself did not interfere with the increasing action of TA-993 on the femoral blood flow (Fig. 6).

Phentolamine caused similar changes in cardiovascular parameters to those caused by hexamethonium but also displayed a tendency to induce tachycardia (Table 1). After treatment with phentolamine either alone or combined with AVP, TA-993 did not show any effects on femoral blood flow, vascular resistance of the femoral artery, and heart rate as in the case of hexamethonium described above (Figs. 6 and 7).

Propranolol caused significant decreases in the mean arterial pressure, heart rate and femoral blood flow (Table 1). ß-Adrenergic blockade with propranolol had no influence on the increasing action of TA-993 on femoral blood flow, but inhibited the TA-993-induced increase in heart rate (versus control, \( p < 0.05 \)) (Fig. 6). After the treatment with atropine, which induced significant increases in heart rate and femoral blood flow and a decrease in the vascular resistance of the femoral artery, TA-993 showed an evident increasing effect on femoral blood flow. A TA-993-induced weak increase in heart rate was inhibited by treatment with atropine (versus control, \( p < 0.05 \)) (Fig. 6). A similar result was obtained when the decreased vascular resistance by atropine was restored by AVP, except that TA-993 showed a slight but persistent hypertensive effect.

**Influence of TA-993 on Pressor Response to Adrenergic α₁ or α₂ Stimulation in a Canine Hindlimb Autoperfusion Model.** In a canine autoperfused hindlimb, TA-993 (300 μg/kg i.v.) caused a gradual and persistent decrease in the perfusion pressure of the femoral artery without any influences on arterial pressure (Table 2). In this preparation, phenylephrine and talipexole induced a dose-dependent increase in the perfusion pressure of the femoral artery. TA-993 did not influence either phenylephrine- or talipexole-
induced increases in the perfusion pressure of the femoral artery (Fig. 8).

Discussion

We previously reported (Kaburaki et al., 1998c) that TA-993, a new 1,5-benzothiazepine derivative having l-cis configuration, had the following cardiovascular effects: TA-993 increased common carotid blood flow and limb blood flow selectively; the blood flow-increasing action of TA-993 manifested slowly and was long-lasting in spite of i.v. administration; and TA-993 also increased cardiac output slightly in a fashion similar to its effects on limb blood flow.

Thus, the cardiovascular effect of TA-993 was much different from that of diltiazem, a representative 1,5-benzothiazepine derivative having d-cis configuration. It has been reported that the cardiovascular action of diltiazem is due to its antagonistic action on voltage-dependent L-type calcium channels (Nagao et al., 1977; Ito et al., 1978; Fujiwara et al., 1982). However, the cardiovascular action of TA-993 could not be explained by an antagonistic action on voltage-dependent L-type calcium channels because its antagonistic activity on Ca\(^{2+}\)-induced contraction in the isolated and K\(^+\)-depolarized canine saphenous artery was much weaker than that of diltiazem (Kaburaki et al., 1998b). In the present study, we further investigated the mechanism of the increasing action of TA-993 on limb blood flow in anesthetized dogs using femoral blood flow as an index of limb blood flow.

In a canine blood-perfused hindlimb preparation with a donor dog, TA-993 did not increase femoral blood flow in the recipient dog when it was administered to the donor dog, but it did when it was administered to the recipient dog. This result was confirmed by the fact that TA-993 also increased femoral blood flow in the recipient’s hindlimb that was perfused with the donor’s blood when it was administered to the recipient without the previous administration to the donor (data not shown). These results suggest that the increasing action of TA-993 on limb blood flow is neither a direct action on blood vessels nor an action mediated by any endocrine systems, but is an action mediated by the nervous system.

As partially reported in the previous study (Kaburaki et al., 1998c), TA-993 did not show an increasing action on femoral blood flow under the blockade of autonomic ganglia with hexamethonium, suggesting that the increasing action of TA-993 on limb blood flow is mediated by the autonomic nervous system. TA-993 did not show an increasing action on femoral blood flow even if the vascular resistance of the femoral artery, which tended to decrease due to hexamethonium, was made nearly equal to the baseline value by i.v.

![Fig. 4. Influence of TA-993 on the blood flow of the perfused hindlimb of the recipient. Donor (■), recipient (perfused limb; ○), recipient (contralateral limb; ●). Each point and vertical bar represents the mean ± S.E.M. of four experiments. A, TA-993 (100 μg/kg i.v.) was administered to the donor. B, TA-993 (100 μg/kg i.v.) was administered to the recipient. Baseline values were as follows. A, mean arterial pressure (mm Hg): ■ 125.0 ± 8.2, ○ 131.5 ± 10.8; heart rate (beats/min): ■ 164.3 ± 3.5, ○ 137.3 ± 22.8; femoral blood flow (ml/min): ■ 44.0 ± 14.6, ○ 48.3 ± 9.6, ● 72.5 ± 13.1; vascular resistance of femoral artery (mm Hg × min/ml): ■ 3.84 ± 1.07, ○ 3.32 ± 1.09, ● 2.09 ± 0.56. B, mean arterial pressure (mm Hg): 134.5 ± 8.5; heart rate (beats/min): 154.8 ± 8.5; femoral blood flow (ml/min): ○ 43.8 ± 11.6, ● 68.0 ± 27.2; vascular resistance of femoral artery (mm Hg × min/ml): ○ 4.29 ± 1.73, ● 3.17 ± 0.75. * p < .05, ** p < .01 versus contralateral limb of the recipient (repeated measures ANOVA, followed by Bonferroni’s method).](image-url)
TABLE 1
Influences of various treatments on hemodynamics in anesthetized dogs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Arterial Pressure</th>
<th>Heart Rate</th>
<th>Femoral Blood Flow</th>
<th>Vascular Resistance of Femoral Artery</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>mmHg</td>
<td>beats/min</td>
<td>ml/min</td>
<td>mm Hg · min/ml</td>
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<tr>
<td>Control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hexamethonium</td>
<td>129.0 ± 8.3</td>
<td>117.8 ± 5.4</td>
<td>78.8 ± 8.6</td>
<td>1.76 ± 0.28</td>
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<tr>
<td></td>
<td>Baseline</td>
<td>122.8 ± 7.3</td>
<td>125.8 ± 5.5</td>
<td>73.3 ± 11.8</td>
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<tr>
<td></td>
<td>After treatment</td>
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<td>119.8 ± 8.9</td>
<td>89.0 ± 15.6</td>
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<tr>
<td>Phentolamine</td>
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<td>121.0 ± 12.5</td>
<td>74.8 ± 8.5</td>
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<tr>
<td></td>
<td>After treatment</td>
<td>107.6 ± 5.2*</td>
<td>136.8 ± 15.5</td>
<td>108.2 ± 14.6</td>
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<tr>
<td>Propranolol</td>
<td>Baseline</td>
<td>132.8 ± 7.0</td>
<td>137.8 ± 4.8</td>
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<td></td>
<td>After treatment</td>
<td>122.0 ± 7.2**</td>
<td>116.0 ± 5.8*</td>
<td>68.0 ± 6.9*</td>
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<tr>
<td>Atropine</td>
<td>Baseline</td>
<td>119.2 ± 8.2</td>
<td>106.4 ± 11.4</td>
<td>62.0 ± 10.2</td>
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<td>After treatment</td>
<td>119.8 ± 8.9</td>
<td>142.0 ± 8.4**</td>
<td>81.8 ± 15.4*</td>
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<tr>
<td>AVP</td>
<td>Baseline</td>
<td>118.2 ± 5.0</td>
<td>108.2 ± 8.1</td>
<td>90.4 ± 17.0</td>
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<tr>
<td></td>
<td>After treatment</td>
<td>123.2 ± 3.9</td>
<td>79.0 ± 9.3**</td>
<td>58.8 ± 15.3**</td>
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<tr>
<td>Hexamethonium + AVP</td>
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<td>112.8 ± 3.7</td>
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<td>106.6 ± 5.1**</td>
<td>87.6 ± 9.5**</td>
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<tr>
<td>Atropine + AVP</td>
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<td>After treatment</td>
<td>123.8 ± 7.1</td>
<td>117.0 ± 9.4</td>
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</table>

Values are means ± S.E.M. (n = 4–5). *p < .05 and **p < .01 versus baseline value (paired t test).
infusion of AVP. Therefore, we could deny a possibility that a tendency to decrease in vascular resistance of femoral artery by the treatment with hexamethonium affected the result. Furthermore, TA-993 did not show an increasing action on femoral blood flow under $\alpha$-adrenergic blockade with phentolamine, but showed it under $\beta$-adrenergic blockade with propranolol or blockade on muscarinic receptors with atropine. The inhibitory effect of phentolamine on TA-993-induced increase in femoral blood flow was not influenced by i.v. infusion of AVP for restoration of vascular resistance of femoral artery. These results suggest that sympathoadrenergic innervation mediated by $\alpha$-adrenoceptors is involved in the mechanism of increasing action of TA-993 on limb blood flow.

However, because TA-993 had no influences on the increase in perfusion pressure induced by stimulation of either $\alpha_1$- or $\alpha_2$-adrenoceptors in the canine autoperfused hindlimb, the increasing action of TA-993 on limb blood flow was not due to an antagonistic action against $\alpha$-adrenergic receptors. These results are consistent with the results obtained in the blood-perfused hindlimb preparation with a donor dog. Therefore, it is suggested that TA-993 acts somewhere in either the peripheral sympathetic nervous system superior to $\alpha$-adrenoceptors or in the central nervous system. It is necessary to elucidate whether the central nervous system would be involved in the increasing action of TA-993 on limb blood flow or not.

TA-993 also showed a weak but persistent increasing effect on heart rate which was almost abolished under either adrenergic or cholinergic blockade. Therefore, it is possible that the mechanism of this increasing effect of TA-993 on heart rate is different from that of the increasing action on limb blood flow. Further studies on the mechanism of the increasing effect on heart rate are required. In addition, TA-993 also

**TABLE 2**

<table>
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<th>Mean Arterial Pressure</th>
<th>Heart Rate</th>
<th>Perfusion Pressure of Femoral Artery</th>
<th>Contralateral Femoral Blood Flow</th>
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</thead>
<tbody>
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<td>mm Hg</td>
<td>beats/min</td>
<td>mm Hg</td>
<td>ml/min</td>
</tr>
<tr>
<td>Baseline</td>
<td>140.5 ± 2.7</td>
<td>140.3 ± 15.6</td>
<td>141.5 ± 3.2</td>
<td>81.3 ± 29.1</td>
</tr>
<tr>
<td>60 min after TA-993</td>
<td>142.0 ± 2.9</td>
<td>160.8 ± 10.7*</td>
<td>115.0 ± 1.8*</td>
<td>195.0 ± 44.6**</td>
</tr>
</tbody>
</table>

TA-993, 300 $\mu$g/kg i.v. Values are means ± S.E.M. ($n = 4$). *$p < .05$ and **$p < .01$ versus baseline value (paired t test).
showed a slight but persistent hypotensive effect under a combined treatment with atropine and AVP. Because this effect was not observed after treatment with either atropine or AVP, the cardiovascular action of TA-993 seems to be a subject of some modification of the treatment of atropine combined with AVP.

In conclusion, the present study indicates that the increasing action of TA-993 on limb blood flow is mediated by the sympathetic nervous system and that TA-993 acts somewhere in sympathoadrenergic nerves superior to α-adrenoceptors. There is a possibility that the mechanism of the weak increasing effect of TA-993 on heart rate is different from that of its increasing action on limb blood flow.

References

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