PDGF-BB decreases systolic blood pressure through an increase in macrovascular compliance in rats

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PDGF-BB decreases systolic blood pressure through an increase in macrovascular compliance in rats. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H1719–H1726, 1997.—The cardiovascular roles of platelet-derived growth factor (PDGF) were examined in anesthetized rats by monitoring blood pressure and in isolated blood vessels and heart preparations. Intravenous injection of PDGF decreased blood pressure. The decrease in systolic pressure was greater than that in diastolic pressure, so the pulse pressure decreased. PDGF-AA and -AB, other isoforms of PDGF, did not have any effect on blood pressure. Pretreatment of rats with N-nitro-L-arginine methyl ester (L-NAME), an inhibitor of nitric oxide (NO) synthase, shortened duration of the hypotensive effect of PDGF-BB. The administration of L-arginine with L-NAME partially prevented the effect of L-NAME. PDGF-BB relaxed aortic rings precontracted with phenylephrine with a 50% effective concentration of 3 ng/ml. In contrast, in isolated mesenteric vascular preparations, the vasodilating activity of PDGF-BB was observed only at a high concentration (>12.5 ng/ml). In isolated heart preparations, PDGF-BB had no effect on the beat rate or contractile activity. These results suggest a new role of PDGF-BB that may contribute to the regulation in circulation through the increase in macrovascular compliance mediated by NO.

nitric oxide; endothelium; macrovessel; hypotension; β-receptor

PLATELET-DERIVED GROWTH FACTOR (PDGF), a potent mitogen in various cell types, is released from the cells involved in the regulation of circulation, including platelets, monocytes and macrophages, endothelial cells, and vascular smooth muscle cells (19). Recently, Cunningham et al. (10) have shown that PDGF-BB causes contraction in aortic rings denuded of endothelium and relaxation in intact aortas. In addition, it has been reported that PDGF and nitric oxide (NO) may have an interaction: PDGF, which is released from the platelets, inhibits NO production in interleukin-1β-stimulated rat vascular smooth muscle cells in culture (11); and NO prevents the expression of the PDGF-B chain gene in cultured human endothelial cells (15). These data suggest that PDGF plays a role in the regulation of vascular tone. However, the role of PDGF in circulation in vivo remains to be elucidated. To delineate the cardiovascular action of PDGF in vivo, we measured blood pressure when PDGF was intravenously administered to anesthetized rats and also examined the effect of PDGF on isolated aorta, mesenteric artery, and heart preparations.

METHODS

Animals. Male Wistar rats (6–7 wk old) were purchased from Japan SLC (Shizuoka, Japan) and used in all experiments. Animals were fed a normal diet and tap water ad libitum.

In vivo experiments. Rats were anesthetized with pentobarbital sodium (50 mg/kg ip), and two polyethylene cannulas were placed, one in the left femoral artery for measuring blood pressure and the other in the left femoral vein for injecting drugs. The arterial cannula was connected to a pressure transducer (TP-200T, Nihon Kohden, Tokyo, Japan), and blood pressure and heart rate (HR) were continuously recorded on a thermal pen-writing recorder (RJ G-4128, Nihon Kohden). PDGF was injected intravenously within 3 s with a volume of 0.02 ml/kg. The dose-response curve for PDGF was obtained by repeating the administrations from a low dose to high doses after the initial and previous doses caused no further change in blood pressure. A bolus injection (0.1 ml/kg) of 0.9% saline, N-nitro-L-arginine methyl ester (L-NAME), or L-NAME + L-arginine was given 10–16 min before the administration of PDGF. In another series of experiments, L-NAME or phenylephrine (PE) was infused with the use of an infusion pump (STC-521, Terumo, Tokyo, Japan) at a rate of 0.3 ml·kg⁻¹·min⁻¹ through the catheter inserted into the left femoral vein. PDGF was injected after a stable elevation of blood pressure was obtained with L-NAME or PE.

In vitro experiments. isolated rat aorta preparation. Rats were stunned by a blow on the neck, and their thoracic aortas were removed immediately after bleeding from the common carotid arteries. The aortas were cleaned of adherent connective tissue and cut into transverse rings 3 mm in length. The endothelium was removed from some rings by gently rubbing the rings with a cotton swab. The preparation was suspended with 1 g tension in an organ bath containing 20 ml Krebs-Henseleit solution (KHS) maintained at 37°C and aerated with 5% CO₂–95% O₂. KHS had the following composition (in mM): 119.8 NaCl, 4.7 KCl, 2.5 CaCl₂, 1.2 MgSO₄, 1.2 K₂HPO₄, 25.0 NaHCO₃, and 11.1 glucose. The developed tension was measured with the use of a force-displacement transducer (TB-612T, Nihon Kohden) and recorded on the thermal pen-writing recorder.

After an equilibration period of 120 min or longer, the rings were contracted with a submaximal dose of PE (0.5 µM). After stable contraction was obtained, PDGF, acetylcholine (ACH), and sodium nitroprusside (SNP) were added to the bath in subsequent order. The dose-response curve for PDGF was determined by administering two or three doses of PDGF in an ascending order in one preparation to avoid a desensitization of response (10). The dose-response curve for ACH was obtained by adding ACH to the bath in a cumulative manner. To test the effect of L-NAME, L-NAME + L-arginine, methylene blue, or carboxy-2-phenyl-4,4,5,5-tetramethyl-imidazole-1-oxyl-3-oxide (carboxy-PTIO), we applied each drug 10 min before the addition of PDGF (10 ng/ml). Maximum relaxation was evoked by the addition of papaverine (100 µM) at the end.
of each experiment to calculate the relative vasorelaxant activity of the test drugs.

In another series of experiments, after stabilization of the preparation, high-K KHS (60 mM K⁺ substituted for Na⁺) was applied to the bath to obtain a control response. PDGF-BB was then added to the bath. PDGF-BB-induced contraction was expressed as a percentage of the control response.

In vitro experiments: isolated rat mesenteric vascular bed preparation. The mesenteric vascular beds were removed and perfused by McGregor's method (17). The isolated mesenteric vascular preparations were placed in a 5-ml water-jacketed organ bath maintained at 37°C, and only four main arterial branches from the superior mesentry running to the terminal ileum were perfused with KHS by means of a pump (Miniplus 2, Gilson, Villiers le Bel, France) at a constant flow rate of 5 ml/min and superfused with the same solution at a rate of 0.5 ml/min to prevent drying. The perfusate was aerated with 5% CO₂-95% O₂. Changes in the perfusion pressure were monitored with the pressure transducer. After 20 min of equilibration, the mesenteric vascular bed was routinely perfused with KHS containing guanethidine (5 µM) to block adrenergic neurotransmission and methoxamine (40 µM) to induce submaximal vasoconstriction. After the elevated perfusion pressure was allowed to stabilize, the preparation was subjected to an infusion of drugs. PDGF (0.75, 2.5, 7.5, and 75 ng) and ACh (10, 30, and 100 pmol), which were diluted with KHS containing methoxamine and guanethidine, were infused directly into the perfusate proximal to the arterial cannulas by the infusion pump for 9 s. The infused volume was 0.05 ml. Maximum relaxation was evoked by adding papaverine (100 µM) to calculate the relative vasorelaxant activity of the test drugs.

In vitro experiments: isolated rat heart preparation. The heart was isolated immediately after the rat was stunned by a blow on the neck. The right atrium and ventricular papillary muscles were dissected and mounted in a 30-ml organ bath containing KHS aerated with 5% CO₂-95% O₂ at 37°C. The right ventricular papillary muscle was stimulated with square pulses at a frequency of 1 Hz and 2 ms in duration using a threefold-threshold voltage. The developed tensions of the heart preparations were measured by means of a force-displacement transducer, and the beat rate of the right atrium was measured using a tachometer (AT-601G, Nihon Kohden). These data were recorded on the thermal pen-writing recorder. The initial resting tension was set at 500 mg. After a 10-min equilibration period, PDGF-BB at a dose of 10 or 30 ng/ml was added to the bath.

Reagents. Human recombinant PDGF-AA, -AB, and -BB were obtained from Boehringer Mannheim (Mannheim, Germany). L-NAME, L-arginine hydrochloride, PE hydrochloride, methylene blue, and SNP were from Sigma Chemical (St. Louis, MO). ACh hydrochloride (Ovisot) was from Daiichi (Tokyo, Japan), methoxamine hydrochloride (Mexan) was from Nihon Shinyaku (Kyoto, Japan), papaverine hydrochloride was from Wako Pure Chemical (Osaka, Japan), carboxy-PTIO was from Dojirin (Kumamoto, Japan), and guanethidine sulfate was from Tokyo Kasei (Tokyo, Japan).

Data analysis. All data are expressed as means ± SE. For all experiments, n indicates the number of rats. Statistical mean comparison was done by Student's t-test between two groups and by Dunnett's method between three or more groups. The 50% effective concentration (EC₅₀) in the isolated rat mesenteric vascular bed experiment was calculated by dividing the 50% effective dose (ED₅₀) by the volumes of infusate and perfusate during drug applications.

RESULTS

In vivo experiments. When administered intravenously, PDGF-BB (0.3–3 µg/kg) gradually decreased mean arterial blood pressure (MBP), with systolic blood pressure (SBP) being more affected than diastolic blood pressure (DBP), resulting in a reduction of pulse pressure (PP) (Figs. 1 and 2). This hypotension reached a maximum within 5–7 min after PDGF-BB administration and recovered to the pretreatment level within 12 min (Fig. 2A). HR increased slightly in response to PDGF-BB. Figure 1A shows the peak amplitudes of HR, SBP, DBP, and MBP plotted against a logarithmic dose of PDGF-BB. PDGF lowered blood pressure in a dose-dependent manner, and its threshold dose was around 0.3 µg/kg. Figure 1B summarizes the effects of three isoforms of PDGF when each was injected intravenously at a dose of 3 µg/kg. Among three isoforms of PDGF, only PDGF-BB caused hypotension.

Next, we examined whether the response to PDGF-BB involved NO. Intravenous bolus injection of L-NAME (1–2 mg/kg), an inhibitor of NO synthase (18), caused a
gradual increase in blood pressure and a decrease in HR (Fig. 2B, Table 1), which attained a maximum within 6–7 min. After the response to L-NAME was stabilized, PDGF-BB was injected intravenously. PDGF-BB produced a transient reduction of SBP, followed by a rapid return to the original level (Fig. 2B). In contrast, after L-arginine (100–200 mg/kg) was injected in combination with L-NAME, PDGF-BB caused a gradual reduction in SBP, which then returned to the original level as observed in the vehicle pretreatment (saline; Figs. 2A and C). Figure 4A summarizes the effect of bolus injection of L-NAME. L-NAME shortened the PDGF response, whereas the absolute amplitude of change in SBP induced by PDGF-BB was greater in the rats pretreated with L-NAME than those pretreated with saline and L-NAME + L-arginine (Table 1). This was probably caused by the increase in blood pressure induced by L-NAME. To verify the action of L-NAME on the PDGF-induced response to that of PE (Figs. 3 and 4B, Table 2). In this experiment, both drugs were infused by an infusion pump before injection of PDGF. The elevation of blood pressure induced by the infusion of PE (10 µg·kg⁻¹·min⁻¹) was comparable to that induced by L-NAME (0.15 mg·kg⁻¹·min⁻¹). The peak reduction of SBP in response to PDGF-BB in L-NAME-pretreated rats was the same as that in PE-pretreated rats (Table 2). However, the duration of PDGF-induced reduction of blood pressure was shorter in the L-NAME-treated rats than in the PE-treated rats (Fig. 4B). It is noteworthy that the duration of the PDGF response in the PE-treated rats was similar to that in the rats injected with vehicle (Fig. 4).

Next, we tried to examine effects of methylene blue and carboxy-PTIO, which are the inhibitors of NO action on the PDGF-induced hypotension (2, 14). Unfortunately, we failed, because these compounds could not induce an elevation of blood pressure and higher doses...
of these compounds led to animal death. Therefore, we did not further evaluate the involvement of NO in the PDGF-induced hypotension.

In vitro experiments: isolated rat aorta preparation. PDGF-BB-induced relaxation was only observed in the intact aortic rings precontracted with PE (Fig. 5, A and B), and its EC50 value was ∼3 ng/ml (Table 3). At the concentration at which PDGF-BB showed the maximum response (>10 ng/ml), PDGF-AB caused a slight relaxation and PDGF-AA had virtually no effect (Fig. 5B).

In endothelium-denuded aortic rings, a higher dose (60 ng/ml) of PDGF-BB elicited a transient contraction (29.5 ± 8.8%, expressed as the percentage of high-KKHS-induced contraction; n = 3). However, we did not observe the PDGF-BB-induced contraction at a concentration, 10 ng/ml.

PDGF-BB-induced relaxation (10 ng/ml) was abolished by pretreatment with L-NAME (30 µM; 0 ± 0%, expressed as the papaverine-induced relaxation; n = 4). This inhibitory effect of L-NAME was partially recovered by concomitant addition of L-arginine (3 mM; 15.3 ± 6.9%; n = 4). A similar result was obtained when methylene blue (10 µM), an inhibitor of guanylate cyclase (14), was administered before the addition of PDGF-BB (0 ± 0%; n = 4). A pretreatment with

<table>
<thead>
<tr>
<th>SBP, mmHg</th>
<th>Basal</th>
<th>Test Drug Injection</th>
<th>PDGF Injection</th>
<th>ΔSBP (PDGF-Test Drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (5)</td>
<td>143.4 ± 4.9</td>
<td>140.2 ± 3.8</td>
<td>127.4 ± 2.3</td>
<td>−12.8 ± 2.2</td>
</tr>
<tr>
<td>L-NAME (5)</td>
<td>137.6 ± 4.3</td>
<td>184.4 ± 9.5†</td>
<td>157.0 ± 8.7†</td>
<td>−27.4 ± 4.0†</td>
</tr>
<tr>
<td>L-NAME + L-Arg (4)</td>
<td>139.0 ± 1.7</td>
<td>146.3 ± 4.1</td>
<td>134.0 ± 2.9</td>
<td>−12.3 ± 1.9</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>Vehicle</td>
<td>104.8 ± 4.0</td>
<td>103.0 ± 2.8</td>
<td>96.6 ± 2.2</td>
</tr>
<tr>
<td>L-NAME</td>
<td>100.2 ± 2.4</td>
<td>135.0 ± 4.2†</td>
<td>122.6 ± 6.0†</td>
<td>−12.4 ± 2.5</td>
</tr>
<tr>
<td>L-NAME + L-Arg</td>
<td>102.0 ± 1.1</td>
<td>110.8 ± 1.4</td>
<td>104.5 ± 1.3</td>
<td>−6.3 ± 1.3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>Vehicle</td>
<td>437.6 ± 16.5</td>
<td>437.2 ± 16.9</td>
<td>447.4 ± 16.4</td>
</tr>
<tr>
<td>L-NAME</td>
<td>390.4 ± 21.2</td>
<td>330.2 ± 7.2†</td>
<td>346.4 ± 6.7†</td>
<td></td>
</tr>
<tr>
<td>L-NAME + L-Arg</td>
<td>416.8 ± 7.3</td>
<td>380.8 ± 7.1*</td>
<td>390.3 ± 3.9†</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Nos. in parentheses represent nos. of rats. See text for details. PDGF-BB, platelet-derived growth factor BB; ΔSBP, change in blood pressure; L-NAME, N-nitro-L-arginine methyl ester; L-Arg, L-arginine; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate. *P < 0.05, †P < 0.01, and ‡P < 0.001 vs. vehicle (Dunnett’s method).

Fig. 3. Effects of continuously infused L-NAME (A) and phenylephrine (PE; B) on PDGF-BB-induced hypotension. PDGF was injected after stable elevations of BP were obtained. Arrowheads and arrows indicate times of injection and infusion, respectively.
carboxy-PTIO (300 µM), a newly developed NO-scavenger (2), also abolished the PDGF-induced vasorelaxation (2.5 ± 2.0%; n = 3). Addition of L-NAME, L-NAME + L-arginine, methylene blue, or carboxy-PTIO in the presence of PE (0.5 µM)-induced contraction alone caused little change of contraction in intact aortic rings.

To compare the potency of ACh and PDGF-BB between rat aorta and mesenteric vascular bed, we examined the response to ACh in intact aortic rings from the same batches of rats. Cumulative addition of ACh elicited a vasorelaxation in intact aortic rings precontracted with PE, and its EC50 was ~100 nM (Fig. 5C, Table 3).

Table 2. PDGF-BB-induced hypotensive effect in L-NAME- and PE-infused rats

<table>
<thead>
<tr>
<th>SBP, mmHg</th>
<th>Basal</th>
<th>Test Drug Infusion</th>
<th>PDGF Injection</th>
<th>ΔSBP (PDGF-Test Drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE (6)</td>
<td>137.5 ± 2.6</td>
<td>198.0 ± 5.1</td>
<td>164.2 ± 6.6</td>
<td>−34.3 ± 6.3</td>
</tr>
<tr>
<td>L-NAME (5)</td>
<td>140.8 ± 1.7</td>
<td>195.4 ± 3.3</td>
<td>163.7 ± 2.5</td>
<td>−31.2 ± 1.9</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>102.7 ± 2.6</td>
<td>138.8 ± 2.4</td>
<td>124.3 ± 4.3</td>
<td>−14.5 ± 2.4</td>
</tr>
<tr>
<td>PE</td>
<td>104.6 ± 2.3</td>
<td>142.0 ± 1.4</td>
<td>129.2 ± 1.8</td>
<td>−12.8 ± 1.0</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>436.8 ± 5.9</td>
<td>342.3 ± 19.1</td>
<td>364.2 ± 8.5</td>
<td></td>
</tr>
<tr>
<td>L-NAME</td>
<td>432.4 ± 7.9</td>
<td>323.0 ± 10.5</td>
<td>334.6 ± 12.1</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE. Nos. in parentheses represent nos. of rats. See text for details. PE, phenylephrine.

In vitro experiments: isolated rat mesenteric vascular bed preparation. ACh but not PDGF-BB lowered perfusion pressure markedly in the mesenteric vascular bed, which was contracted submaximally with methoxamine, an α-adrenergic agonist (Fig. 6).

Table 3. EC50 and ED50 for PDGF-BB- and ACh-induced relaxation in rat aorta and mesenteric artery

<table>
<thead>
<tr>
<th>EC50 in Aorta</th>
<th>ED50 (EC50) in MesentericArtery</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF-BB</td>
<td>3 ng/ml (n = 3–9)</td>
</tr>
<tr>
<td>ACh</td>
<td>100 nM (n = 6)</td>
</tr>
</tbody>
</table>

Values for 50% effective concentrations (EC50) were estimated from data in Fig. 5, B and C; 50% effective doses (ED50) were estimated from data in Fig. 6, B and C. ED50 were calculated by calculating the dilution of infusion. n, No. of rats; ACh, acetylcholine.
relaxed both the aortas and mesenteric vascular beds in a similar dose range, whereas PDGF-BB-induced vasorelaxation is more selective to the aortas than to the mesenteric vascular beds.

In vitro experiments: isolated rat heart preparation. After stabilization of preparations, the beat rate in isolated right atrium and the developed tension in isolated papillary muscle were 346 ± 35 beats/min and 188 ± 31 mg, respectively. After treatment, no significant effects of PDGF-BB (10 ng/ml) on the beat rate and the developed tension were detected (beat rate: 347 ± 61 beats/min; developed tension: 179 ± 43 mg; n = 3).

DISCUSSION

PDGF-BB given intravenously caused a transient reduction in SBP as well as in DBP in rats. Reduction in SBP was greater than that in DBP, so PP was reduced. L-NAME markedly reduced the duration of PDGF-BB response, and this reduction was partially recovered by L-arginine as observed in hypotension induced by ACh (1, 23). This effect is not caused by a rise in arterial blood pressure caused by L-NAME, because the duration of PDGF-BB-induced hypotension was not shortened during infusion of PE. These results suggest that the duration of PDGF-BB-induced depressor response was at least in part caused by NO derived from L-arginine. The diminution by L-NAME, methylene blue, and carboxy-PTIO of PDGF-BB-induced relaxation in intact aortic rings in vitro supported this hypothesis.

Among three isoforms of PDGF, only PDGF-BB had effects both in vivo and in vitro. According to current knowledge (9, 16), PDGF is a dimer protein composed of two polypeptide chains, PDGF-A and -B, and each chain of PDGF binds with different affinities to two specific receptors, denoted as the PDGF-α- and β-subtypes. The PDGF α-receptor binds both A and B types of PDGF peptide with high affinity, and the PDGF β-receptor binds only the PDGF-B chain. PDGF receptor dimerization occurs as a result of PDGF binding and appears to be a prerequisite for exerting the biological action of PDGF. Therefore, the effect of PDGF-BB mediated by endothelium-derived NO is initiated by the activation of PDGF ββ-receptor in vitro and in vivo.
This consistency in isoform-specific action of PDGF-BB both in vivo and in vitro may also support the notion that the PDGF-BB-induced depressor response involves NO in vivo.

The magnitude of hypotension elicited by PDGF-BB was affected little by the pretreatment with L-NAME. Similar observations have been reported on the effects of ACh; Aisaka et al. (1) have observed that Nω-nomonethyl-L-arginine (L-NMMA), an inhibitor of NO synthase, does not inhibit the amplitude of ACh-induced hypotension in guinea pigs, and Yamazaki et al. (23) have described a similar action of L-NMMA on ACh-induced hypotension in rats. These data do not fully support the in vitro study, which indicates that the inhibitors of NO synthase attenuate or abolish the amplitudes of relaxations induced by ACh and PDGF-BB (Ref. 18 and present study). The component resistant to NO synthase inhibitors in vivo may be related to prostanoids. However, this possibility is unlikely, because hypotension induced by ACh may not be affected by the pretreatment with indomethacin, a cyclooxygenase inhibitor (1). The second possibility is that the doses of L-NAME and L-NMMA were not sufficient to completely inhibit NO synthase. However, this is also unlikely because the present study demonstrated that the infusion of L-NAME, which elevated blood pressure more than the bolus injection, potentiated the amplitude of hypotension induced by PDGF-BB and because pretreatment with atrapine fails to render the vasodilator response to ACh more sensitive to L-NMMA (12). The third possibility is that the component resistant to NO synthase inhibitors may be mediated by endothelium-derived hyperpolarizing factor (EDHF), which is postulated (13) to mediate the vasodilation induced by ACh in various types of blood vessels. Unfortunately, to date, EDHF has not been identified. The fourth possibility is that PDGF may release NO or related molecules from a preformed pool in vivo (1). Nitrosothiols are thought to be reservoirs of NO, but as yet no definite role has been assigned to them (8).

PDGF-BB lowered SBP more markedly than it lowered DBP, resulting in a decrease of PP. The possible mechanisms for this include 1) a selective dilation of the macrovessel rather than the microvessel, 2) a decrease in venous return, 3) a reduction of cardiac contractility, and 4) an increase in HR. It has been reported that ACh dilates both the large femoral artery and the hindlimb resistance vessels when administered intra-arterially into the hindlimb vasculature of the dog (22) and lowers mean arterial pressure when administered intravenously in the rat, accompanied with increases in renal, mesenteric, and hindquarters vascular conductances (12). In the present study, we showed that ACh relaxed both the aorta and mesenteric artery at a similar dose range, whereas PDGF-BB rather selectively dilated the aorta. Although we did not examine the effect of PDGF-BB on other vascular beds, these observations favor the hypothesis that the reduction of PP induced by PDGF-BB is attributed to a selective dilation of macrovessel rather than microvessel. Mechanisms 3 and 4 as proposed above are unlikely, because no detectable changes in the beat rate of the right atrium preparations nor in the contractilities of papillary muscles were observed in response to PDGF. Further studies are needed to examine mechanism 2.

Although it was considered that PDGF-BB may act only on the endothelial cells of the microvessels but not of the macrovessels (3, 5), recent reports indicate that PDGF-BB may act on the endothelium of macrovessels. Cunningham et al. (10) have demonstrated that PDGF-BB can directly act on macrovessels, which is in good agreement with the present study. In addition, Battegay et al. (4) have found two phenotypes of endothelial cells from bovine aorta in culture. One is an angiogenic endothelial cell type that responds to PDGF-BB, and the other is a nonangiogenic endothelial cell type that is insensitive to PDGF. These findings suggest the possible existence of PDGF-BB receptor on endothelium of specific phenotype in macrovessels.

In isolated aorta, it has been reported (6, 7, 20) that PDGF induces contraction in spite of the presence of endothelium. Furthermore, in denuded aortic rings, Cunningham et al. (10) have described that PDGF-BB initiates contractions at concentrations lower than those required for endothelium-dependent vasorelaxations. However, we could not observe an elevation of blood pressure when PDGF-BB was administered intravenously in basal and PE-induced hypertensive conditions. Thus we conclude that PDGF-BB plays an important role in the hypotensive regulation of systemic blood pressure. However, regional hemodynamic effects of PDGF were not elucidated in the present study, and further evaluations are needed.

Schini and co-workers (11, 21) recently showed that PDGF-BB inhibits NO release from interleukin-1β-stimulated vascular smooth muscle cells. The inhibitory effect of PDGF is thought to be mediated through the inhibition of the transcriptional activation of the inducible NO synthase gene, which requires a lag time for exerting its effect (11). In contrast, the present study showed that the NO release from the endothelium in response to PDGF-BB was very rapid both in vitro and in vivo. These data suggest that there might be different mechanisms involved in the chronic and acute phases in the regulation of vascular tone by PDGF-BB that acts in conjunction with NO.

In summary, we have observed for the first time that PDGF-BB decreased SBP with a reduction in PP in vivo. This hemodynamic change in response to PDGF-BB may be attributed to an increase in aortic compliance mediated through the NO pathway.

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