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European Journal of Pharmacology 282 (1995) 235–241

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Comparison of responses of canine pulmonary artery and vein to angiotensin II, bradykinin and vasopressin

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Received 27 April 1995; revised 29 May 1995; accepted 2 June 1995

Abstract

Responses to angiotensin II, bradykinin and arginine vasopressin were compared in helical strips of canine pulmonary arteries and veins. Angiotensin II contracted the artery but relaxed the vein strip. The artery contraction was augmented by indomethacin and aspirin and was abolished by losartan. The vein relaxation was not affected by endothelium denudation but was abolished by the cyclooxygenase inhibitors, a prostaglandin I_2 synthase inhibitor and losartan. The bradykinin-induced artery relaxation was inhibited by endothelium denudation, N^G-nitro-L-arginine (L-NA) or indomethacin and abolished by their combined treatment. The vein relaxation produced by bradykinin was endothelium-independent and was abolished by indomethacin. Vasopressin produced a slight relaxation in the arteries, which was abolished by endothelium denudation and L-NA. The vein relaxation produced by vasopressin was abolished by endothelium denudation and combined treatment with L-NA and indomethacin. It may be concluded that (1) activation of angiotensin AT_1 receptor subtype in smooth muscle produces contraction and also relaxation due to prostaglandin I_2 release; the former predominates over the latter in the artery, whereas only the latter is operative in the vein, (2) the bradykinin-induced relaxation is due to nitric oxide (NO) from the endothelium and prostaglandin I_2 from subendothelial tissues in the artery and solely to prostaglandin I_2 in the veins, and (3) the vasopressin-induced relaxation is mediated by endothelial NO in the artery, and NO and prostaglandin I_2 in the vein.

Keywords: Angiotensin II; Bradykinin; Vasopressin; Pulmonary artery; Pulmonary vein; Nitric oxide (NO); Prostaglandin I_2

1. Introduction

Angiotensin II, bradykinin and arginine vasopressin, potent endogenous vasoactive peptides, play important roles in regulating vascular tone. It is generally thought that angiotensin II and vasopressin constrict and bradykinin dilates the peripheral vasculature. However, their effects qualitatively and quantitatively differ in blood vessels from various organs or tissues and from different mammals.

Angiotensin II has been demonstrated to constrict canine mesenteric and femoral arteries but, in contrast, dilate renal and cerebral arteries and mesenteric veins (Toda and Miyazaki, 1978, 1981; Yamazaki and Toda, 1991). The bradykinin-induced vasodilation is reportedly associated with the release of vasodilator prostaglandins such as prostaglandin I_2 and endothelium-derived relaxing factor (EDRF) in the canine renal artery (Toda et al., 1987), endothelium-derived hyperpolarizing factor in the porcine coronary artery (Nagao and Vanhoutte, 1992), and EDRF and the hyperpolarizing factor in the canine coronary artery (Toda et al., 1987).

In addition to the action on the kidney as an antidiuretic, vasopressin has a potent vasoconstrictor property. However, several reports have demonstrated its vasodilator action in the isolated perfused rat lung (Russ and Walker, 1992; Eichinger and Walker, 1994).

Plasma concentrations of these peptides reportedly increase in various clinical settings such as surgical operation, shock status, hypovolemic status, stress (renin-angiotensin system: Oyama et al., 1979; bradykinin: Al-Kaisi et al., 1977; Nagaoka and Katori, 1975; vaso-

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SSDI 0014-2999(95)00343-6

pressin: De Lima et al., 1981; Moran et al., 1964) and during positive pressure ventilation, especially with positive end-expiratory pressure (vasopressin: Kumar et al., 1974). Analyses of the mechanism underlying the action of these peptides in isolated pulmonary vasculature would be useful to our understanding of pulmonary hemodynamics under these conditions.

Little is known about the difference or similarity of responsiveness of pulmonary arteries and veins from the same mammals. Therefore, the present study was aimed to compare the effects of angiotensin II, bradykinin and vasopressin on isolated canine pulmonary arteries and veins and to pharmacologically analyze the underlying mechanisms of action.

2. Materials and methods

2.1. Preparation

Mongrel dogs of either sex, weighing 8–14 kg, were anesthetized with intravenous injection of sodium pentobarbital (30 mg/kg) and killed by bleeding from the common carotid arteries. Lungs were rapidly removed, and second or third branches of pulmonary arteries and accompanying veins were isolated. The arteries and veins were cut helically into strips of approximately 20 mm long. The specimens were fixed vertically between hooks in a 20 ml muscle bath containing modified Ringer-Locke solution maintained at 37.0 ± 0.3°C and aerated with a mixture of 95% O_2 and 5% CO_2. The hook anchoring the upper end of the strip was connected to the lever of a force-displacement transducer (Nihonkohden Kogyo, Tokyo, Japan). The resting tension was adjusted to 1.5 g for artery strips and to 0.7 g for vein strips, which were optimal for inducing maximal contraction.

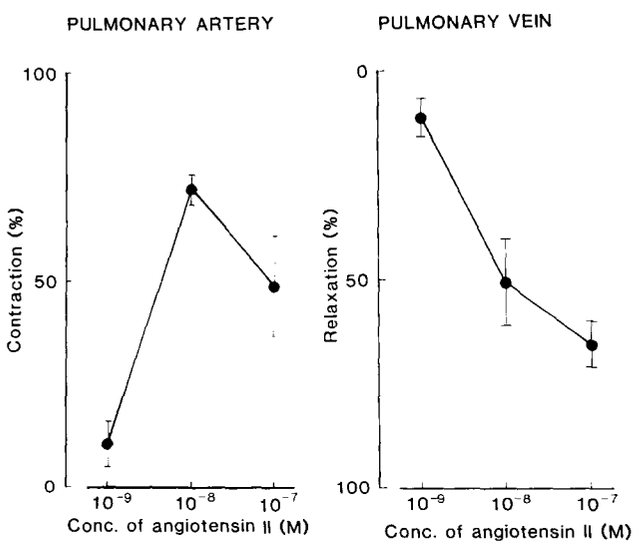

Fig. 1. Concentration-response relationships for angiotensin II in canine pulmonary artery (left, $n = 7$) and vein strips (right, $n = 6$). The veins were partially contracted with prostaglandin $F_{2\alpha}$. Contractions induced by 30 mM KCl were taken as 100% contraction; the mean absolute value was 1167 ± 101 mg in pulmonary arteries. Relaxations induced by 10^{-4} M papaverine were taken as 100% relaxation; mean absolute values at 10^{-9}, 10^{-8} and 10^{-7} M angiotensin II in pulmonary veins were 217 ± 22, 218 ± 17 and 215 ± 12 mg, respectively. Vertical bars represent S.E.M. Conc., concentration.

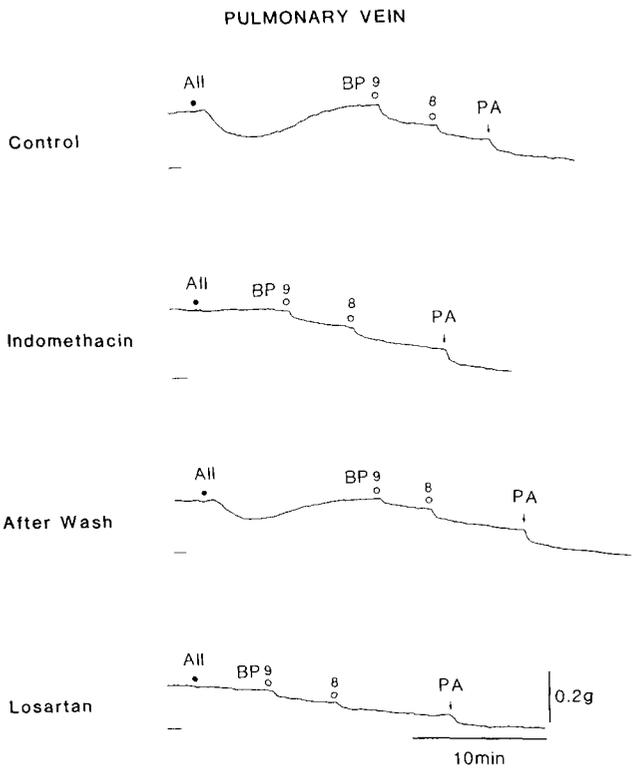

Fig. 2. Typical responses of a canine pulmonary vein strip to 10^{-8} M angiotensin II (AII) and beraprost (BP) before (control and after wash) and after treatment with indomethacin (10^{-6} M) or losartan (10^{-6} M). The strip was partially contracted with prostaglandin $F_{2\alpha}$. The horizontal line just left to each tracing represents the level before addition of prostaglandin $F_{2\alpha}$. PA, 10^{-4} M papaverine. BP 9, 8, 10^{-9}, 10^{-8} M beraprost, respectively.

2.2. Recording of vascular responses

Isometric contractions and relaxations were displayed on an ink-writing oscillograph (Nihonkohden Kogyo Co.). Contractile responses to 30 mM KCl in artery strips and to 5 mM $BaCl_2$ in vein strips were obtained first, and then the preparations were repeat-

Constituents of the solution were as follows (mM): NaCl 120, KCl 5.4, $NaHCO_3$ 25.0, $CaCl_2$ 2.2, $MgCl_2$ 1.0 and dextrose 5.6. The pH of the solution was 7.3–7.4. Before the start of experiments, all strips were allowed to equilibrate for 60–90 min in control media, during which time the solutions were replaced every 10–15 min.

Table 1
Modification by 10^{-6} M indomethacin, 5×10^{-5} M aspirin and 10^{-6} M losartan of the responses to 10^{-8} M angiotensin II in endothelium-intact pulmonary arteries

Treatment	n	Contraction (% control)
Indomethacin	6	234.2 ± 32.0 [a]
Aspirin	6	164.5 ± 27.0 [a]
Losartan	5	7.5 ± 4.4 [b]

Contractions induced by 10^{-8} M angiotensin II before the treatment (C) were taken as 100%; mean absolute values in the strips treated with indomethacin, aspirin and losartan were 669 ± 100, 710 ± 81 and 622 ± 89 mg, respectively. Significantly different from control, [a] $P < 0.05$, [b] $P < 0.01$ (paired t-test). n = number of strips from separate dogs.

edly washed and equilibrated for 30–40 min. Concentration-response relationships for bradykinin and vasopressin were obtained by adding the agents directly to the bathing media in cumulative concentrations. Vasodilating agents were added after the artery and vein strips had been partially contracted with prostaglandin $F_{2\alpha}$ (1×10^{-7} to 3×10^{-6} M); the contraction ranged between 20 and 40% of the contraction induced by 30 mM KCl in artery strips and 25 and 40% of the contraction induced by 5 mM $BaCl_2$ in vein strips. If prostaglandin $F_{2\alpha}$ did not produce sufficient amounts of contraction, serotonin (10^{-9} to 10^{-7} M) was additionally applied. In vein strips, sufficient magnitudes of contraction were obtained with concentrations from 10^{-7} to 2×10^{-6} M prostaglandin $F_{2\alpha}$ alone, whereas in artery strips, these concentrations were not sufficient to produce moderate contractions; thus, serotonin was additionally applied. Precontraction with prostaglandin $F_{2\alpha}$ or prostaglandin $F_{2\alpha}$ plus serotonin did not influence relaxant responses to bradykinin and vasopressin in the artery strips. Papaverine (10^{-4} M) was added at the end of each experimental series to obtain the maximal relaxation. The response to a single concentration of angiotensin II was obtained by adding the agent directly to the bathing medium of artery strips under resting conditions and to vein strips partially contracted with prostaglandin $F_{2\alpha}$.

The agonist-induced relaxation relative to that caused by 10^{-4} M papaverine and the contraction relative to that elicited by 30 mM KCl (artery strips) are presented. The preparations had been treated for 20–30 min with blocking agents before the agonists were added. When the same strips were treated with two drugs, the order of treatment was randomized.

In some strips, the intimal surface of artery and vein strips was gently rubbed with a cotton ball to remove the endothelium; unrubbed strips from the same dog were used for comparison. Endothelium denudation was verified by abolishment of relaxation caused by Ca^{2+} ionophore A23187 (10^{-7} M).

2.3. Statistics and drugs used

The results shown in the text, figures and tables are expressed as mean values ± S.E.M. Statistical analyses were made with the Student's paired and unpaired t-test and the Tukey's method after one-way analysis of variance. A P value less than 0.05 was considered to be significant.

The drugs used were: prostaglandin $F_{2\alpha}$, beraprost sodium (Toray Industries, Tokyo, Japan); indomethacin (Sigma Chemical Co., St. Louis, MO, USA), Ca^{2+} ionophore A23187 (C.H. Boehringer Ingelheim, Elmsford, NY, USA); angiotensin II, bradykinin, arginine vasopressin, N^G-nitro-L-arginine (L-NA; Peptide Institute Co., Minoh, Japan); papaverine hydrochloride (Dainippon Pharmaceutical Co., Osaka, Japan); acetylsalicylic acid (aspirin), tranylcypromine hydrochloride, L-and D-arginine (Nacalai Tesque, Kyoto, Japan); serotonin creatinine sulfate (Merck Pharmaceutical Co., Darmstadt, Germany) and losartan (DUP753; Du Pont Merck Pharmaceutical Co., Wilmington, USA).

3. Results

3.1. Effects of angiotensin II

Angiotensin II (10^{-9} to 10^{-7} M) contracted pulmonary artery strips but did not produce contractions

Table 2
Modification by 10^{-5} M L-NA, 10^{-6} M indomethacin, 5×10^{-5} M aspirin, 10^{-3} M tranylcypromine and 10^{-6} M losartan of the response to 10^{-8} M angiotensin II in endothelium-intact pulmonary veins, partially contracted with prostaglandin $F_{2\alpha}$

Treatment	n	Relaxation (%)
Control	4	41.0 ± 4.6
L-NA		41.9 ± 3.5
Indomethacin		0.0 ± 0.0 [b]
Control	5	37.4 ± 8.1
Aspirin		5.3 ± 2.2 [a]
Control	6	30.1 ± 6.2
Tranylcypromine		0.0 ± 0.0 [b]
Control	5	32.7 ± 5.9
Losartan		0.0 ± 0.0 [b]

The order of treatment with L-NA or indomethacin was randomized. Relaxations induced by 10^{-4} M papaverine were taken as 100%; mean absolute values for control, L-NA- and indomethacin-treated strips were 255 ± 33, 268 ± 36 and 261 ± 34 mg, respectively, those for control and aspirin-treated strips were 178 ± 7 and 201 ± 14 mg, respectively, those for control and tranylcypromine-treated strips were 183 ± 14 and 192 ± 16 mg, respectively and those for control and losartan-treated strips were 220 ± 23 and 191 ± 19 mg, respectively. Significantly different from control, [a] $P < 0.05$, [b] $P < 0.01$ (unpaired t-test). n = number of strips from separate dogs.

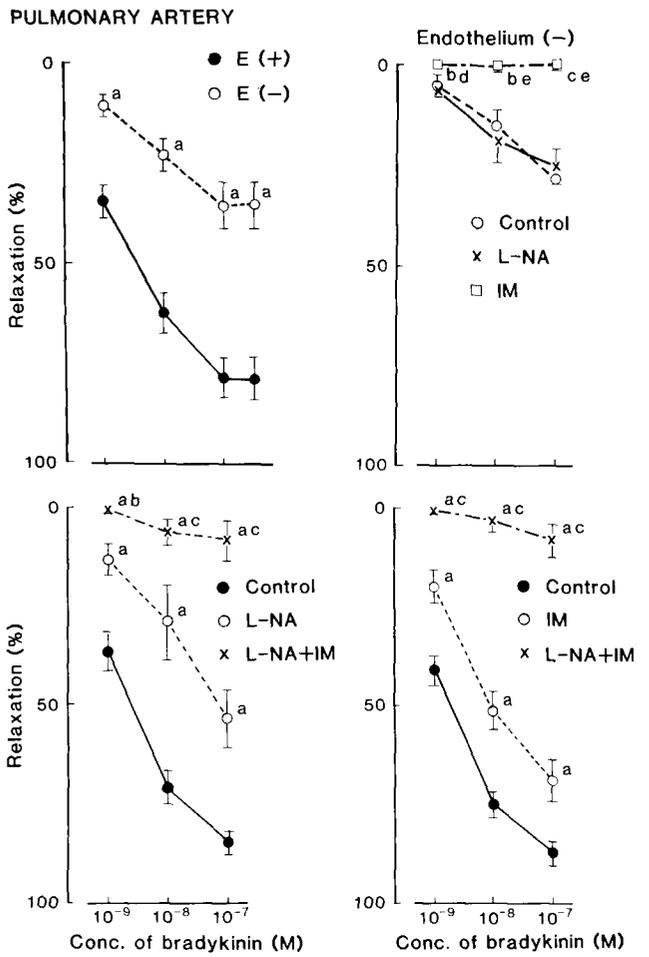

Fig. 3. Modification by endothelium (E) denudation and treatment with L-NA and indomethacin of the response to bradykinin of pulmonary arteries. Effects of L-NA (10^{-5} M) and indomethacin (IM, 10^{-6} M) in the strips with intact endothelium are presented in the lower two panels and those in the strips denuded of the endothelium are shown in the upper right panel. The order of treatment with L-NA or IM was randomized (upper right panel). L-NA and indomethacin were added first in the lower left and right panels, respectively. Relaxations induced by 10^{-4} M papaverine were taken as 100%; mean absolute values for artery strips with or without the endothelium in the upper left panel were 237 ± 17 and 247 ± 25 mg ($n = 11$), respectively, those for control, L-NA-treated and IM-treated strips in the upper right panel were 224 ± 22, 193 ± 16 and 195 ± 15 mg ($n = 7$), respectively, those for control, L-NA-treated and L-NA + IM-treated strips in the lower left panel were 249 ± 23, 239 ± 24 and 209 ± 17 mg ($n = 9$), respectively and those for control, IM-treated and L-NA + IM-treated strips in the lower right panel were 234 ± 22, 218 ± 19 and 213 ± 19 mg ($n = 9$), respectively. Significantly different from values for endothelium-intact or control strips in the upper left panel, [a] $P < 0.001$ (unpaired t-test). Significantly different from control, [b] $P < 0.05$, [c] $P < 0.01$, and from L-NA-treated strips in the upper right panel, [d] $P < 0.05$, [e] $P < 0.01$ (Tukey's method). Significantly different from control, [a] $P < 0.01$. Significantly different from L-NA- or IM-treated strips, [b] $P < 0.05$, [c] $P < 0.01$ (Tukey's method) (lower panels). Vertical bars represent S.E.M. Conc., concentration.

in pulmonary vein strips under resting conditions. When partially contracted with prostaglandin $F_{2\alpha}$, pulmonary veins responded to the peptide with a relaxation. Tachyphylaxis developed with repeated applications, even though a single concentration of 10^{-7} M was used and the strips were repeatedly washed. Therefore, until identical magnitudes of two successive responses to angiotensin II at this concentration were obtained, angiotensin II was repeatedly applied. Then, one of the concentrations (10^{-9} to 10^{-7} M) was applied in each series to obtain the concentration-response relationship. The data obtained from the artery and vein strips are demonstrated in Fig. 1. Angiotensin II at 10^{-8} M elicited the maximal contraction amounting to $72.2 \pm 8.7\%$ relative to the KCl (30 mM)-induced contraction in artery strips ($n = 7$) and a submaximal relaxation of $50.4 \pm 10.4\%$ relative to that caused by 10^{-4} M papaverine in vein strips ($n = 6$). The remainder of this study was carried out with this angiotensin II concentration. The contractile responses to angiotensin II 10^{-8} M did not significantly differ in the endothelium-intact and -denuded artery strips; the mean values were $60.8 \pm 8.6\%$ and $65.0 \pm 7.7\%$ ($n = 10$), respectively. Treatment with 10^{-6} M indomethacin or 5×10^{-5} M aspirin markedly potentiated the contractile response to angiotensin II (Table 1). Contractions caused by prostaglandin $F_{2\alpha}$ (5×10^{-7} to 3×10^{-6} M) did not significantly differ between control strips and

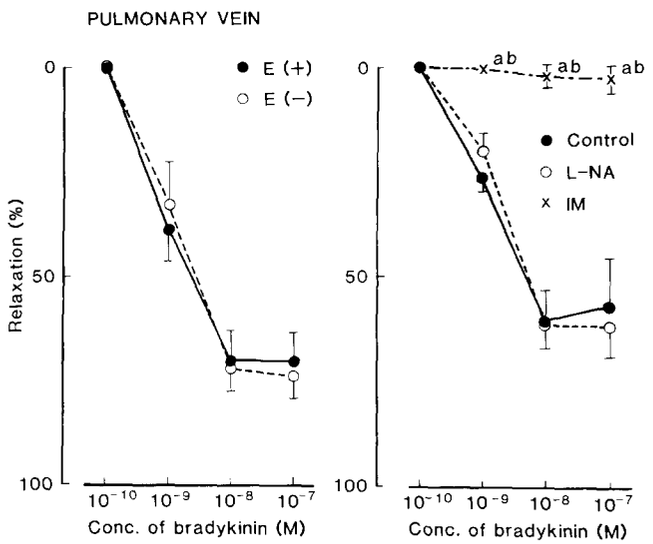

Fig. 4. Concentration-response curves for bradykinin in pulmonary venous strips with (E(+)) or without (E(−)) the endothelium ($n = 5$, left) and those in endothelium-intact strips before and after L-NA (10^{-5} M) or indomethacin (IM, 10^{-6} M) ($n = 6$, right). The order of L-NA or IM was randomized. The strips were partially contracted with prostaglandin $F_{2\alpha}$. Relaxations induced by 10^{-4} M papaverine were taken as 100%; mean absolute values in venous strips with and without the endothelium in the left figure were 193 ± 20 and 176 ± 6 mg, respectively. Those for control, L-NA-treated and IM-treated strips in the right figure were 190 ± 12, 202 ± 15 and 194 ± 17 mg, respectively. Significantly different from control, [a] $P < 0.01$. Significantly different from L-NA-treated strips, [b] $P < 0.01$ (Tukey's method) in the right figure. Vertical bars represent S.E.M. Conc., concentration.

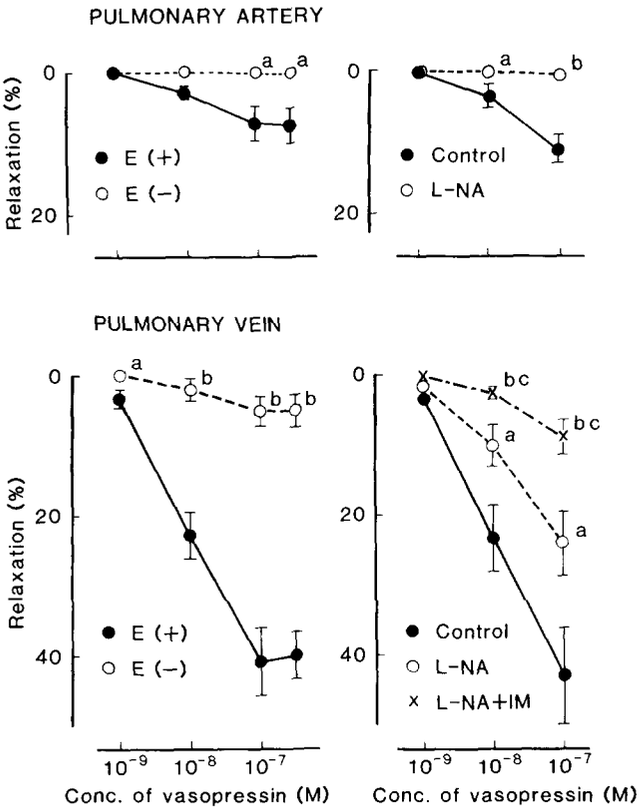

Fig. 5. Modification by endothelium (E) denudation and treatment with L-NA and indomethacin of the response to vasopressin of pulmonary artery (upper two panels) and vein strips (lower panel). Effects of L-NA (10^{-5} M) in the artery strips with intact endothelium are presented in the upper right panel and those of L-NA (10^{-5} M) and indomethacin (IM, 10^{-6} M) in endothelium-intact vein strips are presented in the lower right panel. Relaxations induced by 10^{-4} M papaverine were taken as 100%; mean absolute values for artery strips with and without the endothelium in the upper left panel were 228 ± 17 and 238 ± 16 mg ($n = 16$), respectively, those for control and L-NA-treated strips in the upper right panel were 233 ± 6 and 234 ± 22 mg ($n = 6$), respectively, those for vein strips with and without the endothelium in the lower left panel were 178 ± 9 and 194 ± 20 mg ($n = 10$), respectively and those for control, L-NA-treated and L-NA + IM-treated strips in the lower right panel were 200 ± 12, 191 ± 6 and 186 ± 7 mg ($n = 7$), respectively. Significantly different from values for endothelium-intact or control strips, $^{a}P < 0.05$, $^{b}P < 0.01$ (unpaired t-test, upper left and paired t-test, upper right). Significantly different from values for endothelium-intact strips, $^{a}P < 0.05$, $^{b}P < 0.001$ (unpaired t-test, lower left). Significantly different from control strips, $^{a}P < 0.05$, $^{b}P < 0.01$, and from L-NA-treated strips, $^{c}P < 0.05$ (lower right). Vertical bars represent S.E.M. Conc., concentration.

those treated with aspirin; the mean values were 56.4 ± 5.8% and 56.4 ± 5.2% ($n = 6$), respectively. Losartan (10^{-6} M) abolished the contractile response to angiotensin II (Table 1).

Relaxant responses of vein strips to 10^{-8} M angiotensin II were not influenced by endothelium denudation; the mean values in intact and denuded strips were 58.6 ± 5.1% and 47.9 ± 6.0% ($n = 7$), respectively. Treatment with 10^{-6} M indomethacin, 5×10^{-5} M aspirin or 10^{-3} M tranylcypromine abolished or markedly suppressed the response to the peptide (Table 2). Typical recordings of the angiotensin II-induced relaxation are illustrated in Fig. 2. Treatment with N^{G}-nitro-L-arginine (L-NA) did not significantly reduce the response, whereas losartan (10^{-6} M) completely abolished it (Table 2). Strips treated with indomethacin or losartan responded to beraprost (analog of prostaglandin I_2) with relaxation, as did control strips.

3.2. Effects of bradykinin

Artery strips contracted with prostaglandin $F_{2\alpha}$ responded to bradykinin solely with a relaxation, whereas vein strips responded with a transient, slight contraction followed by a moderate relaxation. Concentration-relaxant response relationships in the arteries are demonstrated in Fig. 3 (upper left). The relaxation was significantly reduced by endothelium denudation. In the denuded artery strips, treatment with 10^{-5} M L-NA did not influence the relaxant response, but indomethacin (10^{-6} M) abolished it (Fig. 3, upper right). In endothelium-intact artery strips, treatment with L-NA or indomethacin partially inhibited the relaxation, and combined treatment with these inhibitors abolished the response (Fig. 3, lower). Concentration-relaxant response relationships in endothelium-intact and -rubbed vein strips did not differ significantly (Fig. 4, left). Treatment with indomethacin abolished the

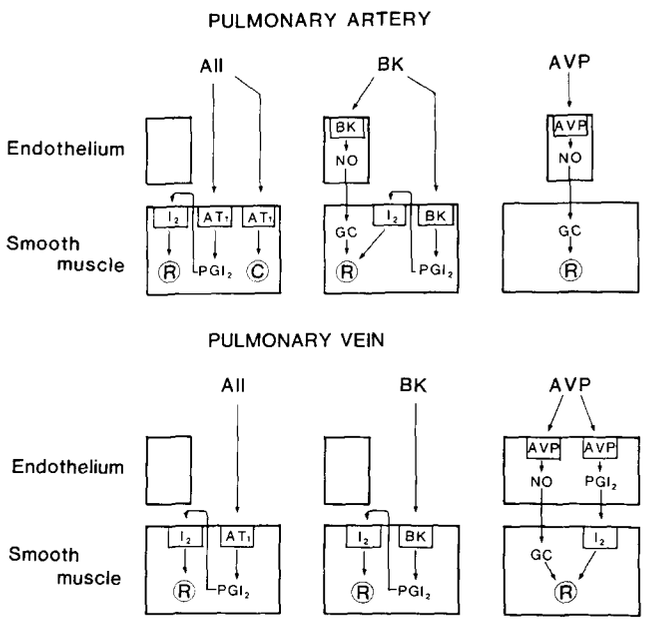

Fig. 6. Possible mechanisms of action of angiotensin II (A II), bradykinin (BK) and vasopressin (AVP) on endothelium and smooth muscle in canine pulmonary artery (upper panels) and vein (lower panels). I_2, prostaglandin I_2 receptor; AT_1, angiotensin AT_1 receptor subtype; BK, bradykinin receptor; AVP, vasopressin receptor; GC, soluble guanylate cyclase; R, relaxation; C, contraction.

response, whereas L-NA was without effect (Fig. 4, right).

3.3. Effects of vasopressin

Artery strips responded to vasopressin (10^{-8} to 3×10^{-7} M) with relaxations in 8 out of 16 strips used, and in the remaining strips no response was obtained; the data are summarized in Fig. 5 (upper left panel). The relaxation was abolished by removal of the endothelium. Treatment with L-NA (10^{-5} M) abolished the relaxation of the strips that responded significantly to the peptide (Fig. 5, upper right). The L-NA-induced inhibition was reversed by L-arginine (3×10^{-3} M, $n = 3$) but not by D-arginine (3×10^{-3} M, $n = 3$).

Vein strips responded to vasopressin consistently with relaxations, which were abolished by removal of the endothelium (Fig. 5, lower left). In the endothelium-intact strips, treatment with 10^{-5} M L-NA partially reduced the response, and the remaining relaxation was almost abolished by additional treatment with 10^{-6} M indomethacin (Fig. 5, lower right).

4. Discussion

Canine pulmonary artery strips responded to angiotensin II with a contraction, whereas vein strips relaxed in response to the peptide. The artery contraction was markedly potentiated by treatment with indomethacin and aspirin, and the vein relaxation was abolished by the cyclooxygenase inhibitors and tranylcypromine, a prostaglandin I_2 synthase inhibitor (Gryglewski et al., 1976; Toda and Miyazaki, 1981). The contraction and relaxation were not influenced by endothelial denudation and treatment with a NO synthase inhibitor, suggesting that EDRF/NO is not involved. These results may indicate that angiotensin II liberates vasodilator prostaglandins, possibly prostaglandin I_2, from subendothelial tissues; the artery contraction elicited by the peptide acting directly on smooth muscle seems to be lessened by the liberated prostaglandin, and the vein relaxation is expected to result exclusively from the prostaglandin release. There are at least two angiotensin II receptor subtypes, AT_1 and AT_2. Most of the well-known responses to angiotensin II, such as vasoconstriction, aldosterone secretion, adrenal catecholamine release and water-drinking, are mediated via the AT_1 subtype (Wong et al., 1990; Tofovic et al., 1991). The functional role of AT_2 receptors remains to be determined. Losartan, a competitive non-peptide angiotensin AT_1 receptor antagonist (Wong et al., 1990), abolished the artery contraction and vein relaxation, suggesting the involvement of the AT_1 subtype also in the relaxation of the pulmonary vein.

Bradykinin produced relaxations in canine pulmonary artery and vein strips. The artery relaxation was partially dependent on the endothelium, and the response was abolished by combined treatment with L-NA and indomethacin. In endothelium-denuded artery strips, the relaxation was abolished by indomethacin alone. These findings suggest that bradykinin releases NO from endothelial cells and vasodilator prostaglandins from subendothelial tissues, although the release of prostaglandin from the endothelium cannot be excluded. In chronically instrumented conscious dogs, L-NA abolishes the pulmonary vasodilator response to bradykinin, which is however unaffected by indomethacin (Nyhan et al., 1987a,b), suggesting that the decreased vascular resistance produced by the peptide is due solely to NO, in contrast to the isolated proximal artery, which responds with relaxation mediated by NO and prostaglandin I_2. In canine pulmonary veins, the bradykinin-induced relaxation was independent of the endothelium and was abolished by indomethacin alone. The vein relaxation seems to be associated with the release of vasodilator prostaglandins from subendothelial tissues. Similar findings were also obtained in canine mesenteric veins, where the peptide produced relaxation possibly by the release of prostaglandin I_2 derived from both endothelial and subendothelial tissues (Toda et al., 1987).

Pulmonary artery relaxations induced by vasopressin, when obtained, were endothelium-dependent and were abolished by L-NA. Studies performed with conscious rats or isolated rat perfused lungs indicate that vasopressin dilates the pulmonary vasculature (Eichinger and Walker, 1994; Russ and Walker, 1992; Walker et al., 1989; Yang et al., 1987). In conscious dogs, intravenous administration of vasopressin causes pulmonary vasoconstriction, which is reversed to vasodilation by treatment with a V_1 receptor antagonist (Nyhan et al., 1987b). The difference from our results might be associated with the fact that vasopressin produces vasoconstriction of pulmonary resistance vessels rather than vasodilation in vivo, whereas relaxation is predominant in isolated proximal arteries. In the vein strips, the peptide consistently produced endothelium-dependent relaxation, L-NA or indomethacin attenuated the response, and the combined treatment abolished it. It may be concluded that the vasopressin-induced vein relaxation is mediated by NO and vasodilator prostaglandins liberated from the endothelium.

In summary, there were quite a few differences in the action and the mechanism of action of peptides in canine pulmonary arteries and veins. Although angiotensin II is expected to release prostaglandin I_2 from subendothelial tissues of both pulmonary arteries and veins, the actual responses were opposite; the artery contraction appears to be ascribed to a predominant contraction over the relaxation, whereas the vein

relaxation may be derived from the vasodilator prostaglandin without a contraction (Fig. 6). Bradykinin and vasopressin dilate pulmonary arteries and veins; similarities and differences between the mechanism underlying their action in these vasculatures are illustrated in Fig. 6. The data obtained in this in vitro study contribute to the further clarification of the role of these peptides in vivo. These peptides physiologically control pulmonary circulation or evoke circulatory disturbances by acting directly on smooth muscle and releasing vasodilator substances including EDRF/NO and prostaglandin I_2.

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