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Differential vasodilatory action of 2-octynyladenosine (YT-146), an adenosine A_2 receptor agonist, in the isolated rat femoral artery and vein

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Abstract

The vasodilatory action of 2-octynyladenosine (YT-146), an adenosine A_2 receptor agonist, was investigated in the isolated rat femoral artery and vein. Exposure to YT-146 resulted in preferential vasodilation; the vein was completely dilated at YT-146 concentrations as low as 10^{-7} M; in contrast, a concentration of YT-146 greater than 10^{-4} M was necessary to induce complete relaxation in the femoral artery. 2-[*p*-(2-Carboxyethyl)-phenethylamine]-5′-*N*-ethylcarboxamidoadenosine (CGS 21680) also evoked stronger dilation in the vein than in the artery. The vasodilatory action of N^6-cyclopentyladenosine (CPA) was much weaker in the vein than that of YT-146. YT-146-induced vasodilation in the artery was antagonized by neither 10^{-7} M 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) nor 3×10^{-6} M (*E*)-8-(3,4-dimethoxystylyl)-1,3-dipropyl-7-methylxanthine (KF17837), while the vasodilation in the vein was only antagonized by KF17837, suggesting that the vasodilation may involve adenosine A_2 receptor activation in the vein. However, the present study did not provide evidence of a link between adenosine agonist-induced vasodilation and adenosine A_2 receptor activation in the artery. The addition of 10^{-4} M N^{ω}-nitro-L-arginine partially reversed YT-146-induced vasodilation in the artery, but not in the vein. The reversal of YT-146-induced vasodilation by N^{ω}-nitro-L-arginine in the artery was attenuated by the addition of 10^{-3} M L-arginine. Removal of the endothelium decreased YT-146-induced vasodilation in the artery, but not in the vein. Prior treatment with 10^{-4} M N^{ω}-nitro-L-arginine decreased YT-146-induced vasodilation in the artery, but not in the vein. These results indicate that adenosine A_2 receptor agonists preferentially dilate the femoral vein rather than the femoral artery of rats and that YT-146-induced vasodilation is partially endothelium-dependent in the femoral artery, but not in the vein.

Keywords: Adenosine receptor; Endothelium-dependent relaxation; Femoral artery; Femoral vein; 2-Octynyladenosine; YT-146

1. Introduction

The selective adenosine A_2 receptor agonist, 2-octynyladenosine (YT-146, Fig. 1), has a potent and long-lasting hypotensive effect (Abiru et al., 1991). The antihypertensive effect of YT-146 has been studied in various hypertension models (Kogi et al., 1991; Iwamoto et al., unpublished data) and it has been shown to have a potent coronary vasodilatory effect without showing detrimental effects on the heart (Kogi et al., 1991). Currently, a clinical trial is in progress in Japan to study the effects of YT-146 as an antihypertensive agent. Mechanisms responsible for the vasodilatory effect of YT-146 have been shown to involve the opening of glibenclamide-sensitive K^+ channels (Yoneyama et al., 1992) and an increase in the levels of cAMP and cGMP in segments of coronary arteries (unpublished data). Previous studies have focused predominantly on coronary arterial circulation, and the vasodilatory effects of YT-146 in peripheral blood vessels have not been extensively examined. Furthermore, there have been only a few reports concerning the effect of adenosine receptor agonists on veins. The present study was conducted to examine the vasodilatory effects of adenosine receptor agonists and the vasodilatory mechanism of YT-146 in isolated femoral arteries and veins from the rat.

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2. Materials and methods

2.1. Vascular preparations

Male Wistar rats, 10 weeks old weighing 305–335 g, were purchased from Clea Japan (Tokyo, Japan). The rats were killed, under ether anesthesia, by bleeding from the abdominal aorta, and the right femoral artery and vein were isolated from each rat. The vessels were placed in physiological salt solution (PSS), composed of 118 mM NaCl, 4.7 mM KCl, 1.2 mM $CaCl_2$, 1.2 mM $MgSO_4$, 25 mM $NaHCO_3$, 1.2 mM KH_2PO_4, and 11 mM glucose, and continuously bubbled with 95% O_2-5% CO_2. The vessels were cleaned of loosely adhering connective tissue and cut into rings (5 mm in width) under a dissecting microscope. Special care was taken not to damage the endothelium. In some experiments, the luminal surface of the rings was rubbed gently with a cotton swab to remove the endothelium. Each ring was mounted between two stainless steel hooks and placed in 10-ml organ baths containing PSS at 37° C. The isometric tension of the rings was measured by a force-displacement transducer (TB-611, Nihon-Kohden, Japan) and recorded on a pen recorder (FBR-252A, TOA, Japan). The rings were equilibrated for 60 min at a resting tension of 0.75 g for the femoral artery ring and 0.5 g for the femoral vein ring, the optimal tensions for inducing maximal contraction in each vessel. During the equilibration time, the PSS in the bath was replaced every 20 min.

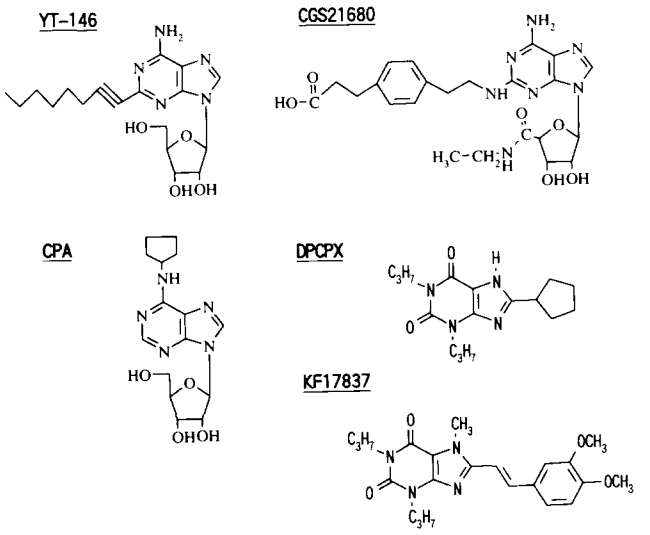

Fig. 1. Chemical structure of adenosine receptor agonists and antagonists: 2-octynyladenosine (YT-146), 2-[*p*-(2-carboxyethyl)-phenethylamine]-5′-*N*-ethylcarboxamidoadenosine (CGS 21680), N^6-cyclopentyladenosine (CPA), 1,3-dipropyl-8-cyclopentylxanthine (DPCPX), and (*E*)-8-(3,4-dimethoxystylyl)-1,3-dipropyl-7-methylxanthine (KF17837).

2.2. Vasodilation study

Following the 1-h equilibration period, the rings were precontracted with 10^{-6} M 5-hydroxytryptamine (5-HT). The addition of 10^{-5} M acetylcholine resulted in greater than 80% vasodilation, confirming the integrity of the ring endothelium. In the endothelium-denuded rings, the addition of acetylcholine did not cause vasodilation. After the contraction induced by 10^{-6} M 5-HT had reached a plateau, the adenosine agonists were added cumulatively to the bath for the vasodilation studies.

To examine the influence of adenosine receptor antagonists on YT-146-induced vasodilation, we used the selective adenosine A_1 receptor antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) (Bruns et al., 1987) and the selective adenosine A_2 receptor antagonist (*E*)-8-(3,4-dimethoxystylyl)-1,3-dipropyl-7-methylxanthine (KF17837) (Shimada et al., 1992). The antagonists were incubated for 20 min prior to the addition of 5-HT.

To investigate the effect of N^{ω}-nitro-L-arginine, a nitric oxide (NO) synthase inhibitor, and L-arginine, a precursor of NO, on YT-146-induced vasodilation, N^{ω}-nitro-L-arginine was added to the bath after the vasodilation had reached a plateau, and L-arginine was later added to the same bath. Additionally, we examined the influence of prior treatment with N^{ω}-nitro-L-arginine on YT-146-induced vasodilation in the femoral artery and vein of rats. N^{ω}-Nitro-L-arginine (10^{-4} M) was added to each bath after 5-HT-induced contraction had reached a plateau.

2.3. Drugs

The receptor agonist YT-146 and antagonist KF17837 were synthesized at the Yamasa Corporation. We obtained 5-HT, N^{ω}-nitro-L-arginine, N^6-cyclopentyladenosine (CPA)(Williams et al., 1986), and L-arginine from Sigma Chemical Co. (St. Louis, MO, USA), acetylcholine hydrochloride from Daiichi Pharmaceuticals (Tokyo, Japan), DPCPX and 2-[*p*-(2-carboxyethyl)-phenethylamine]-5′-*N*-ethylcarboxamido adenosine (CGS21680) (Hutchison et al., 1989) from Research Biochemicals (Natick, MA, USA). We dissolved YT-146, CGS 21680, and CPA in dimethyl sulfoxide (DMSO) at a concentration of 20 mg/ml and stored the solutions at −20° C. KF17837 and DPCPX were freshly dissolved in DMSO at a concentration of 10^{-2} M. Prior to each experiment, an aliquot of each drug was diluted with distilled water to the appropriate concentration. The final concentration of DMSO in the bath was less than 0.2% and this concentration of DMSO did not influence the vascular responses. All of the other drugs were freshly dissolved in distilled water prior to each experiment.

2.4. Data analysis

We expressed vasodilation in response to the drugs as a percentage depression of the 10^{-6} M 5-HT-induced contraction. Data were expressed in the form of means ± S.E. The changes in relative tension within each preparation were evaluated using the paired *t*-test, and differences between groups were assessed using analysis of variance followed by the unpaired *t*-test. EC_{50} values and slope values for the concentration-response curves were calculated using a logistic equation with the program of SAS Proc NLIN (SAS Institute, Cary, NC, USA).

3. Results

5-HT (10^{-7} to 3×10^{-5} M) induced concentration-dependent contractions in the artery and in the vein. Both the artery and vein exhibited similar levels of sensitivity to 5-HT, and the contraction reached a plateau at a concentration of 3×10^{-6} M (Fig. 2). In the vasodilation studies, arterial and venous rings were precontracted with 10^{-6} M 5-HT, which induced contractions with 80% of the intensity of a maximum 5-HT-induced contraction. The contractile response to 5-HT in both the artery and vein was stable during the time period required to construct the concentration-response curve to an adenosine receptor agonist.

The addition of YT-146 induced vasodilation in arterial and venous rings precontracted with 10^{-6} M 5-HT in a concentration-dependent manner (Fig. 3). However, there was a difference in the potency of YT-146-induced vasodilation between the artery and vein. The vein was completely dilated at YT-146 concentrations as low as 10^{-7} M. In contrast, a concentration of YT-146 greater than 10^{-4} M was necessary to induce complete relaxation in the femoral artery.

The results of curve fitting using a logistic equation are shown in Table 1. The slope of the YT-146 concentration-response curve was different between the artery and vein. When the EC_{50} value in the vein was compared with that in the artery, the vasodilatory potency of YT-146 in the vein was over 6000-fold higher than that in the artery. Although the vasodilatory potency of CGS21680 in the vein was more potent than that in the artery, the slope factor of the CGS 21680 concentra-

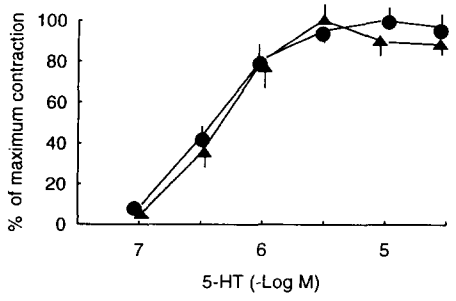

Fig. 2. Concentration-response curves for contraction induced by 5-HT in the rat femoral artery (●) and vein (▲). Each point represents the mean ± S.E. for five rats.

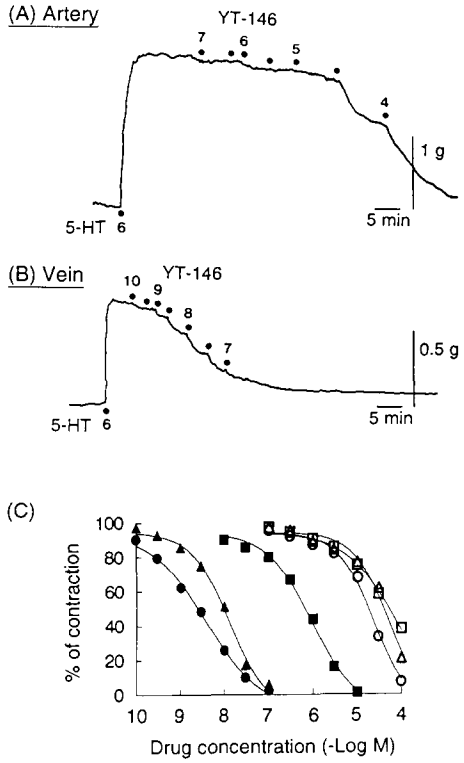

Fig. 3. Vasodilation induced by adenosine agonists in the rat femoral artery and vein. Typical recordings of the vasodilation induced by YT-146 in (A) the artery, and (B) the vein. Drug concentrations are represented as −Log M. (C) Concentration-response curves for vasodilation induced by YT-146 (●,○), CGS 21680 (▲,△), and CPA (■,□) in the femoral vein (closed symbols) and artery (open symbols). Each point represents the mean ± S.E. for six rats.

Table 1
The results of curve fitting for the concentration-response curves using a logistic equation

	Slope value	EC_{50} (M)
YT-146		
Artery	1.07 (0.92–1.22)	2.31×10^{-5} ($1.77–2.84 \times 10^{-5}$)
Vein	0.69 (0.57–0.82)	3.88×10^{-9} ($2.57–5.19 \times 10^{-9}$)
CGS21680		
Artery	1.08 (0.85–1.30)	5.10×10^{-5} ($3.90–6.29 \times 10^{-5}$)
Vein	1.02 (0.82–1.23)	1.29×10^{-8} ($0.97–1.61 \times 10^{-8}$)
CPA		
Artery	0.75 (0.58–0.91)	7.59×10^{-5} ($5.09–10.1 \times 10^{-5}$)
Vein	0.86 (0.69–1.03)	9.31×10^{-7} ($6.78–12.2 \times 10^{-7}$)

Slope values represent the mean for six rats, with 95% confidence limits in parentheses. EC_{50} values represent the geometric mean for six rats, with 95% confidence limits in parentheses. Values were calculated using a logistic equation with the program of SAS Proc NLIN.

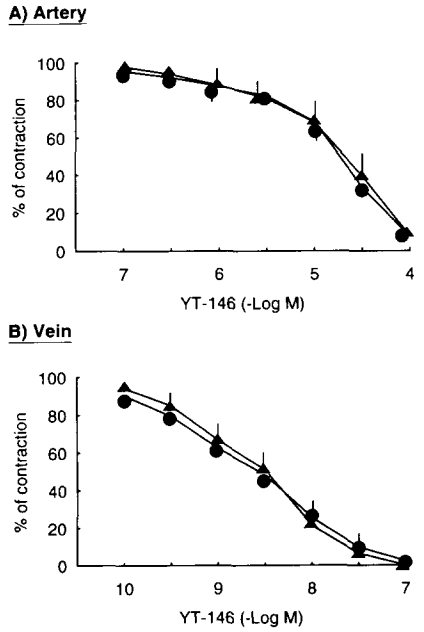

Fig. 4. Effects of 1,3-dipropyl-8-cyclopentylxanthine (DPCPX) on YT-146-induced vasodilation in the rat femoral artery and vein. Concentration-response curves of YT-146-induced vasodilation in (A) the artery, and (B) the vein. Preparations were preincubated with vehicle (●) or 10^{-7} M DPCPX (▲) for 20 min prior to the addition of 5-HT. Each value represents the mean ± S.E. for five rats.

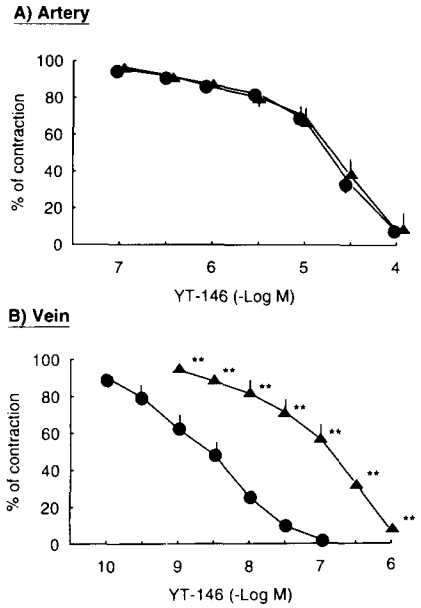

Fig. 5. Effects of (*E*)-8-(3,4-dimethoxystylyl)-1,3-dipropyl-7-methylxanthine (KF17837) on YT-146-induced vasodilation in the rat femoral artery and vein. Concentration-response curves of YT-146-induced vasodilation in (A) the artery, and (B) the vein. Preparations were preincubated with vehicle (●) or 3×10^{-7} M KF17837 (▲) for 20 min prior to the addition of 5-HT. Each value represents the mean ± S.E. for five rats. ** $P < 0.01$ compared with control.

tion-response curve was similar for the artery and vein. The concentration of CPA needed to induce vasodilation in the vein was much higher than that of YT-146 or CGS 21680 and slope values in the artery and vein were less than 1.

Prior treatment with DPCPX (10^{-7} M) did not affect YT-146-induced vasodilation in either the femoral artery or vein (Fig. 4). Prior treatment with 3×10^{-6} M KF17837 markedly shifted the concentration-response curve of YT-146-induced vasodilation in the vein to the right, but not in the artery (Fig. 5).

The removal of endothelium from the artery resulted in a significant decrease in YT-146-induced vasodilation that was not observed in the vein (Fig. 6). The addition of 10^{-4} M N^{ω}-nitro-L-arginine reversed the YT-146-induced vasodilation by 60% in the artery, while the reversal was not observed in the vein (Fig. 7). The increased tension in the artery caused by N^{ω}-nitro-L-arginine was attenuated by the addition of 10^{-3} and 3×10^{-3} M L-arginine. The addition of CGS 21680 at concentrations of 10^{-4} M for the artery and 10^{-7} M for the vein dilated the artery by 75% and the vein by 95%, respectively. The addition of CPA at concentrations of 10^{-4} M for the artery and 10^{-5} M for the vein dilated the artery by 50% and the vein by 95%, respectively. The vasodilations induced by CGS 21680 and CPA were also reversed by the addition of N^{ω}-nitro-L-arginine in the artery, but not in the vein. Prior treat-

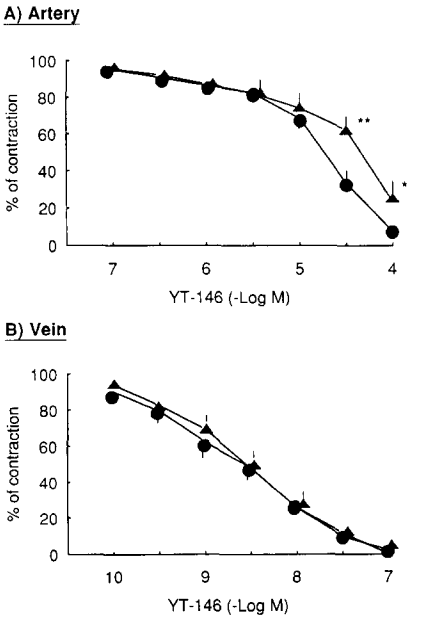

Fig. 6. Influence of endothelium on YT-146-induced vasodilation in the rat femoral artery and vein. Concentration-response curves of YT-146-induced vasodilation in (A) the artery, and (B) the vein with (●) and without (▲) endothelium. Each point represents the mean ± S.E. for six rats. * $P < 0.05$, ** $P < 0.01$ compared with the corresponding rings with endothelium.

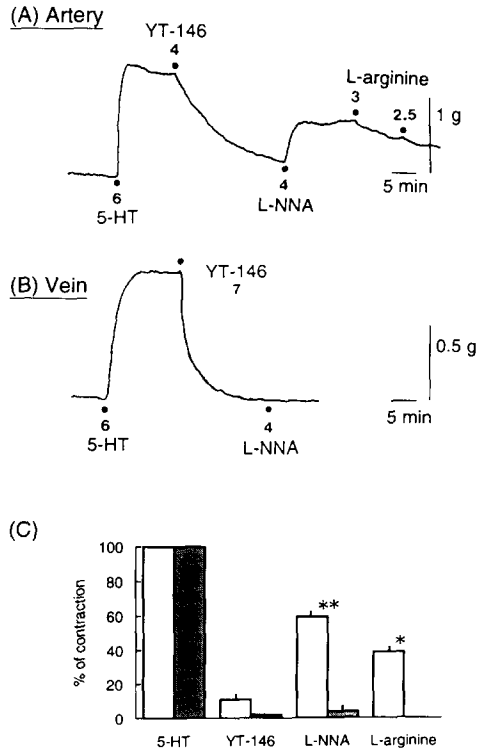

Fig. 7. Effects of N^{ω}-nitro-L-arginine and L-arginine on YT-146-induced vasodilation in the rat femoral artery and vein. Typical recordings of the effects of N^{ω}-nitro-L-arginine (10^{-4} M) and L-arginine (10^{-3} and 3×10^{-3} M) on YT-146-induced vasodilation in (A) the artery, and (B) the vein. Drug concentrations are represented as $-$Log M. (C) Effect of N^{ω}-nitro-L-arginine (10^{-4} M) and L-arginine (10^{-3} M) on YT-146-induced vasodilation in the femoral artery (open columns) and vein (shaded columns). The amount of YT-146 needed to induce vasodilation was 10^{-4} M in the artery and 10^{-7} M in the vein. Each value represents the mean $\pm$ S.E. for five rats. * $P < 0.05$ compared with the N^{ω}-nitro-L-arginine group, and * * $P < 0.01$ compared with the YT-146 group.

ment with 10^{-4} M N^{ω}-nitro-L-arginine resulted in a decrease in YT-146-induced vasodilation in the artery, but not in the vein (Fig. 8). The resting tension of femoral arteries and veins that had not been contracted with 5-HT was not affected by the application of N^{ω}-nitro-L-arginine (data not shown).

4. Discussion

In the present study, we have demonstrated that YT-146 and CGS 21680 preferentially dilate the rat femoral vein over the femoral artery; both compounds are over 6000-fold more potent in the vein. However, CPA was much less potent in inducing vasodilation in the vein than YT-146 and CGS 21680 were. Previously, we reported that the order of decreasing binding affinity was YT-146 > CGS 21680 ≫ CPA for the adenosine A_2 receptor in brain striatal membrane (Matsuda et al., 1991). The binding affinity of the agonists for the brain adenosine A_2 receptor correlated with the vasodilation potency levels in the vein. The link between adenosine-induced vasodilation and the activation of the adenosine A_2 receptor has been commonly accepted (Kusachi et al., 1983). To clarify whether the vasodilation in the femoral vein is mediated through the adenosine A_2 receptor, we examined the influence of adenosine receptor antagonists on YT-146-induced vasodilation. YT-146-induced vasodilation in the vein was antagonized by the adenosine A_2 receptor antagonist KF17837, but not by the adenosine A_1 receptor antagonist DPCPX. These results suggest that the vasodilation induced by adenosine agonists in the femoral vein may be mediated by the activation of the adenosine A_2 receptor. However, the results of curve fitting analysis suggest a complex pharmacology in that the slopes of the YT-146 concentration-response curve were different in the artery and vein. In contrast, the slope of the concentration-response curve for CGS21680, being characterized as an adenosine A_{2A} receptor-selective agonist (Webb et al., 1992), was similar in artery and vein. Therefore, it is possible that the YT-146-induced vasodilation involves another mechanism in addition to the adenosine A_2 receptor activation.

Differences in the potency of vasodilation among the three adenosine agonists were less pronounced in

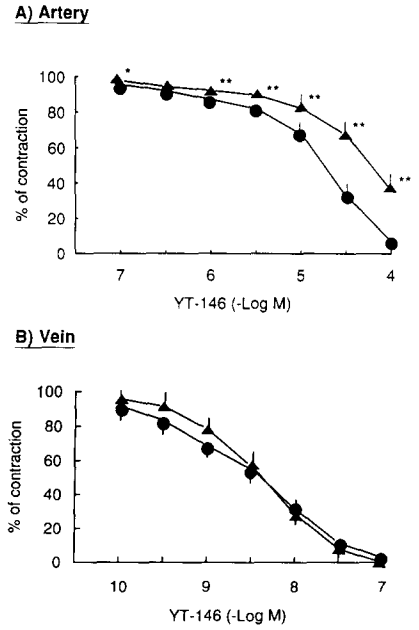

Fig. 8. Influence of prior treatment with N^{ω}-nitro-L-arginine on YT-146-induced vasodilation in the rat femoral artery and vein. Concentration-response curves of YT-146-induced vasodilation in (A) the artery, and (B) the vein. Preparations were preincubated with vehicle (●) or 10^{-4} M N^{ω}-nitro-L-arginine (▲) after the 5-HT-induced contraction had reached a plateau. Each value represents the mean $\pm$ S.E. for five rats. * $P < 0.05$, * * $P < 0.01$ compared with the control.

the artery than in the vein. The vasodilatory potency of the three adenosine agonists in the femoral artery did not correlate with the brain adenosine A_2 receptor binding affinity of the agonists. Furthermore, neither 10^{-7} M DPCPX nor 3×10^{-6} M KF17837 affected YT-146-induced vasodilation in the femoral artery. From these results, the vasodilation induced by adenosine agonists in the femoral artery appears not to be mediated by the activation of the adenosine A_1 and A_2 receptors. However, this issue is not conclusive so far, since we could not examine the effect of higher concentrations of antagonists because of their insolubility and their own vasodilatory action at higher concentrations. In preliminary experiments, we determined the concentration of DPCPX to be 10^{-7} M from the following results. DPCPX (10^{-7} M) did not affect 5-HT-induced contraction and inhibited the negative chronotropic action induced by 3×10^{-7} M CPA in the rat atrium. DPCPX at concentrations higher than 10^{-6} M inhibited 5-HT-induced contraction and showed a relaxant response in the 5-HT-contracted artery and vein. A concentration of KF17837 higher than 10^{-5} M affected the CPA-induced negative chronotropic action in the rat atrium, but 3×10^{-6} M KF17837 did not affect the action.

The present study did not provide evidence of a link between adenosine receptor agonist-induced vasodilation and adenosine A_2 receptor activation in the artery. Currently, the reason for the differences in vasodilatory potency between the vein and artery is unclear. The potency of adenosine agonists has been reported to differ considerably among different species and tissues (Balwierczak et al., 1991). For example, the vasodilatory action of adenosine was more potent in the vein than in artery of canine peripheral blood vessels (De Mey and Vanhoutte, 1982). In contrast, CGS 21680 barely dilated the human saphenous vein, even at a concentration of 10^{-4} M (Makujina et al., 1992). In addition, adenosine preferentially dilates small coronary arteries over large ones (Schnaar and Sparks, 1972; Habazettl et al., 1992). The potency differences among adenosine agonists may be related to a differential distribution and reserve of adenosine receptors in the vascular endothelium and smooth muscle of the artery and vein. The adenosine A_2 receptor has been subdivided into two subtypes, i.e. adenosine A_{2A} receptor and adenosine A_{2B} receptor (Bruns et al., 1986). It has been reported that the receptors in the guinea pig aorta and dog saphenous vein are of the A_{2B} subtype because of the lack of vasodilatory potency of C^2-substituted adenosine analogs such as CGS21680 (Hargreaves et al., 1991; Martin, 1992), which has been characterized as an adenosine A_{2A} receptor agonist (Webb et al., 1992). From these results, it is possible that the adenosine receptor in the rat femoral artery is the A_{2B} subtype. The characterization of the adenosine receptor in femoral artery should be further studied.

There has been controversy over whether or not the vasodilation induced by adenosine agonists is endothelium-dependent in the rat aorta (Yen et al., 1988; Rose'Meyer and Hope, 1990; Moritoki et al., 1990), canine artery and vein (De Mey and Vanhoutte, 1982), and human coronary artery (Sabouni et al., 1989). The present study has shown that YT-146-induced vasodilation in the femoral artery is partially (60%) reversed by N^{ω}-nitro-L-arginine, a NO synthase inhibitor (Palmer et al., 1988), and this reversal is eliminated by L-arginine, a precursor of NO (Palmer et al., 1988). In contrast, YT-146-induced vasodilation in the femoral vein was not reversed by the addition of N^{ω}-nitro-L-arginine. Similar results were obtained with CGS 21680 and CPA, under the same experimental conditions. It is possible that the reversal by N^{ω}-nitro-L-arginine is caused by the inhibition of the 5-HT-stimulated NO synthesis in endothelium of the femoral artery, since 5-HT has been reported to show an endothelium-dependent relaxation in the coronary artery ring (Vanhoutte and Houston, 1985). Even if the reversal involves the inhibition of the 5-HT-stimulated NO synthesis in endothelium of the femoral artery, the 5-HT-induced contraction was augmented only by 20% after the addition of N^{ω}-nitro-L-arginine in both the artery and vein (data not shown) and the reversal of YT-146-induced vasodilation by N^{ω}-nitro-L-arginine was only observed in the femoral artery, and not in the vein. Thus, the reversal of the adenosine agonist-induced vasodilation by N^{ω}-nitro-L-arginine may partially involve the inhibition of NO synthesis in the endothelium. We confirmed the involvement of NO in the adenosine agonist-induced vasodilation in the femoral artery by the results that both the removal of endothelium and the prior treatment of the femoral artery with N^{ω}-nitro-L-arginine resulted in a decrease of YT-146-induced vasodilation. These results suggest that YT-146-induced vasodilation is likely to involve NO and is partially endothelium-dependent in the rat femoral artery.

In summary, adenosine A_2 receptor agonists preferentially dilate the femoral vein rather than the femoral artery of rats. YT-146-induced vasodilation involves A_2 receptor activation in the femoral vein, but not in the femoral artery. YT-146-induced vasodilation is partially endothelium-dependent in the femoral artery, but not in the femoral vein.

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