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Role for adenosine A_1 and A_2 receptors in femoral vasodilatation induced by intra-arterial adenosine in rabbits

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Abstract

The vasodilator effects of adenosine injected into the femoral artery (i.a.) of rabbits were analyzed. Single bolus i.a. doses of adenosine (0.3–10 μg) and 5′-(*N*-cyclopropyl)-carboxamidoadenosine (CPCA) (0.03–1 μg), an adenosine A_2-receptor agonist, produced dose-dependent increases in femoral blood flow and decreases in resistance, almost without affecting blood pressure, heart rate, left ventricular (LV) pressure, and LV$dP/dt$ max, even though CPCA elicited slight decreases in arterial blood pressure and LV pressure. On the other hand, bolus i.a. injections of N^6-cyclopentyladenosine (CPA) (1–30 μg), an adenosine A_1 receptor agonist, caused a relatively weak increase in blood flow, but markedly affected cardiac parameters, especially heart rate and LV$dP/dt$ max. I.v. treatment with 3,7-dimethyl-1-propargylxanthine (DMPX)(2 mg kg^{-1}), an antagonist of adenosine A_2 receptors, or 8-phenyltheophylline (1 mg kg^{-1}), an antagonist of adenosine A_1 receptors, significantly attenuated the vasodilator response to adenosine, but not that to acetylcholine. Decreases in blood pressure, heart rate, LV pressure, LV$dP/dt$ max and femoral vascular resistance, and increases in the blood flow elicited by CPA were not significantly modified by the DMPX treatment, but when this was combined with 8-phenyltheophylline, the responses to CPA were completely abolished. The present results indicate that the adenosine-induced femoral vasodilatation in rabbits may be mediated throughout activation of both adenosine A_1 and A_2 receptors.

Keywords: Adenosine, intra-arterial; Vasodilatation; Femoral; Adenosine A_1 receptor; Adenosine A_2 receptor; (Rabbit)

1. Introduction

It has been widely accepted that adenosine, a metabolite of adenine nucleotides, is a biological substance found in every cell of the human body, and that it plays an important physiological role in the cardiovascular system (Hori and Kitakaze, 1991; Mubagwa et al., 1996). Based on its pharmacological actions, adenosine receptors are classified into two subtypes: the adenosine A_1 receptor subtype, responsible for negative chronotropic, inotropic and dromotropic responses in the heart (Leung et al., 1986; Clemo et al., 1987; Webb et al., 1990; Merkel et al., 1993), and the adenosine A_2 receptor subtype, which when stimulated, induces vasodilatation (Mustafa and Askar, 1985; Webb et al., 1990; Furukawa et al., 1993). Recently, we investigated the vasodepressor response to adenosine in anesthetized rats, and found a possible contribution of the adenosine A_2 receptor subtype (Saito and Sakai, 1998a,b). On the other hand, there have been several reports that the adenosine A_1 receptor subtype is also responsible for vasodilatation (Merkel et al., 1992; Randall et al., 1994; Cox et al., 1997; Danialou et al., 1997). Thus, it seems that the distribution of the adenosine receptor subtypes is different in various species or organs. The aim of the present study was to find if either of the adenosine A_1 or A_2 receptor subtypes play a role in the adenosine-induced vasodilatation in the femoral vascular bed of the rabbit.

2. Materials and methods

2.1. Chemicals

The agents used were as follows: adenosine free base (Sigma Chemical, St. Louis, MO, USA), N^6-cyclopentyladenosine (CPA), 5′-(*N*-cyclopropyl)-carboxamidoadenosine (CPCA), 3,7-dimethyl-1-propargylxanthine (DMPX), 1,3-dimethyl-8-phenylxanthine (8-phenyltheophylline) and acetylcholine chloride (all RBI, Natick, MA, USA). CPA and CPCA were dissolved in 0.01 M HCl at a

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concentration of 1 mg ml^{-1}. 8-Phenylxanthine was dissolved in 0.01 M NaOH at a concentration of 5 mg ml^{-1}. These solutions were diluted with 0.9% saline solution to the desired concentrations, just before the experiment. Other compounds were dissolved in and diluted with 0.9% saline solution.

2.2. Animal preparations

All experiments were performed according to the regulations of the 'Animal Research Committee of the Chugai Pharmaceutical', Tokyo, Japan. Male Japanese white rabbits (Kitayama Rabes, Minowa, Nagano, Japan) weighing 3.0–3.5 kg were utilized to analyze vasodilator responses to adenosine injected into the femoral artery. The rabbits were anesthetized with urethane (1.2 g kg^{-1} s.c.), 60 min prior to the experiment, and just before the experiment 20 mg kg^{-1} of pentobarbital sodium was injected i.v. The animals were tracheotomized, and cannulated with a tube, through which the animal ventilated spontaneously. To inject agents intra-arterially (i.a.), a 30-mm, 27-gauge needle with a polyethylene tube (PE 10) was inserted by direct puncture of the vessel wall of the right femoral artery and fixed there with biotissue adhesive (Aron Alpha®, Sankyo). For i.a. injection, 0.1 ml of the drug solutions was given over a period of approximately 10 s, and flushed with 0.9% saline. A miniaturized VF-1 Pulsed Doppler Flow Probe (Crystal Biotech, Hopkinton, MA, USA) was sutured around the right femoral artery, and connected to 20 MHz High Velocity Pulsed Doppler Module (model HVPD-20, Crystal Biotech, Northborough, MA, USA). Even though the Doppler method has the disadvantages that the calibration factor is sensitive to changes in vessel diameter, velocity profile, and any flow disturbances, the changes in blood flow velocity (kHz), measured as Doppler shifts, are directly proportional to volume flows (ml min^{-1}) (Haywood et al., 1981). Femoral vascular resistance (mmHg ml^{-1} min^{-1}) determined from mean arterial blood pressure and the mean femoral blood flow were calculated with a Nihon Kohden analog multiplier (EO-601G). The left femoral artery and the right jugular vein were cannulated for arterial blood pressure measurement and for i.v. injection of agents, respectively. Arterial blood pressure and heart rate were measured by means of a Nihon Kohden pressure transducer (DX-360, Tokyo, Japan) and a Nihon Kohden heart rate counter (AT-601G), respectively. To measure left ventricular (LV) pressure, a microtip pressure manometer (model SPR-524; Millar Instruments,

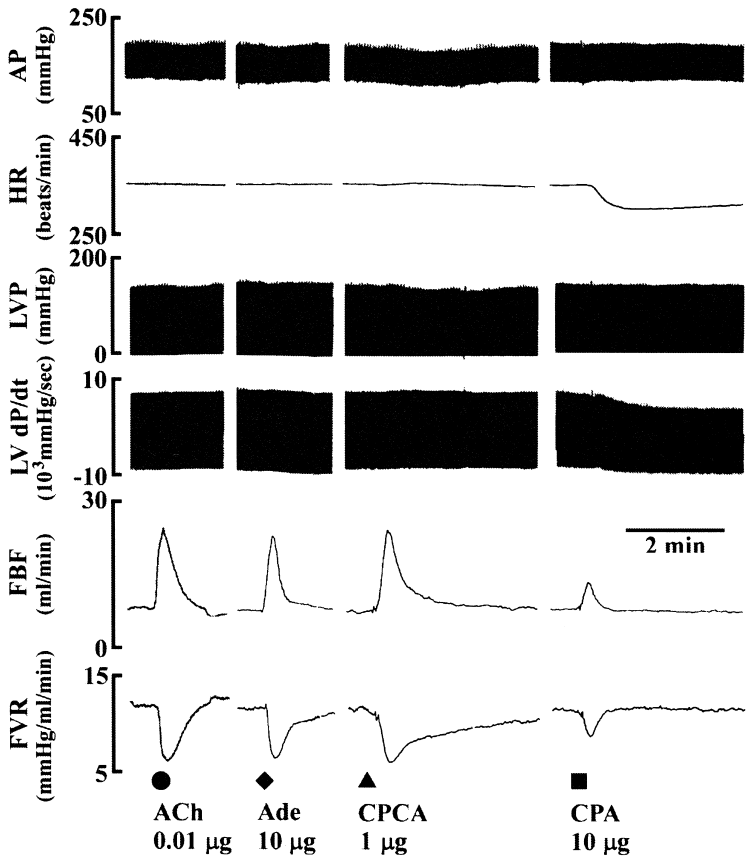


Fig. 1. Effects of acetylcholine (ACh), adenosine (Ade), CPCA and CPA injected into the femoral artery on arterial blood pressure (AP), heart rate (HR), left ventricular pressure (LVP), LV$dP/dt$ max, femoral blood flow (FBF) and femoral vascular resistance (FVR). Note that the figures are based on individual preparations (see experimental protocols in Section 2).

Houston, TX, USA) was introduced into the left ventricle via the right carotid artery. The first derivative (LV$dP/dt$ max) of the LV pressure was obtained using a pressure processor (Nihon Kohden, EQ-601G). All data were recorded on a Graphtec Linearcorder (WR-3101, Tokyo, Japan). Following surgery, a period of at least 30 min was allowed for stabilization of preparations.

2.3. Experimental protocols

Twenty-five rabbits were divided into five groups (each $n = 5$) as follows: in groups I, II and III, cardiovascular responses to bolus i.a. acetylcholine (0.01 μg), adenosine (0.3–10 μg) and CPCA (0.03–1 μg), an adenosine A_2 receptor agonist (Bruns et al., 1986), were examined before and after 0.9% saline, 8-phenyltheophylline (1 mg kg^{-1} i.v. over 1 min, 1 ml kg^{-1} as the drug solution), an antagonist of adenosine A_1 receptors (Bruns et al., 1986), and DMPX (2 mg kg^{-1} i.v. over 3 min, 2 ml kg^{-1} as the drug solution), an antagonist of adenosine A_2 receptors (Seale et al., 1988; Sebastiao and Ribeiro, 1989), respectively. In group III, after the experiment was finished, 8-phenyltheophylline (1 mg kg^{-1}), in the presence of DMPX (2 mg kg^{-1}), was administered i.v., and the responses to acetylcholine, adenosine and CPCA, as described above, were examined in that order; in group IV, the dose–response curve to bolus CPA (1–30 μg i.a.), an adenosine A_1 receptor agonist (Williams et al., 1986), for cardiovascular parameters was recorded; and in group V, cardiovascular responses to bolus CPA (10 μg i.a.), following bolus i.a administration of acetylcholine (0.01 μg), were examined before and after i.v. injection of DMPX, and then 8-phenyltheophylline was given i.v. and about 10–15 min later the effects of acetylcholine and CPA were examined again in that order. The doses of DMPX (2 mg kg^{-1}) and 8-phenyltheophylline (1 mg kg^{-1}) were so selected that they produced no non-specific effects, because larger ones of both antagonists inhibited the femoral vascular response to acetylcholine (0.01 μg i.a.).

2.4. Statistical analysis

Values in the text are presented as means ± S.E.M. The peak responses to the agents are expressed as changes from preadministration levels. The doses of adenosine and CPCA required to cause a 7-ml min^{-1} increase in mean femoral blood flow before and after i.v. treatment with DMPX or/and 8-phenyltheophylline were calculated from individual dose–response curves for adenosine and CPCA. Differences between paired or unpaired mean values were analyzed with Student's *t*-test. Analysis of variance (ANOVA) was used for the statistical analysis of multiple comparisons of data. When multiple comparisons were made with a single control, Dunnett's test was used to

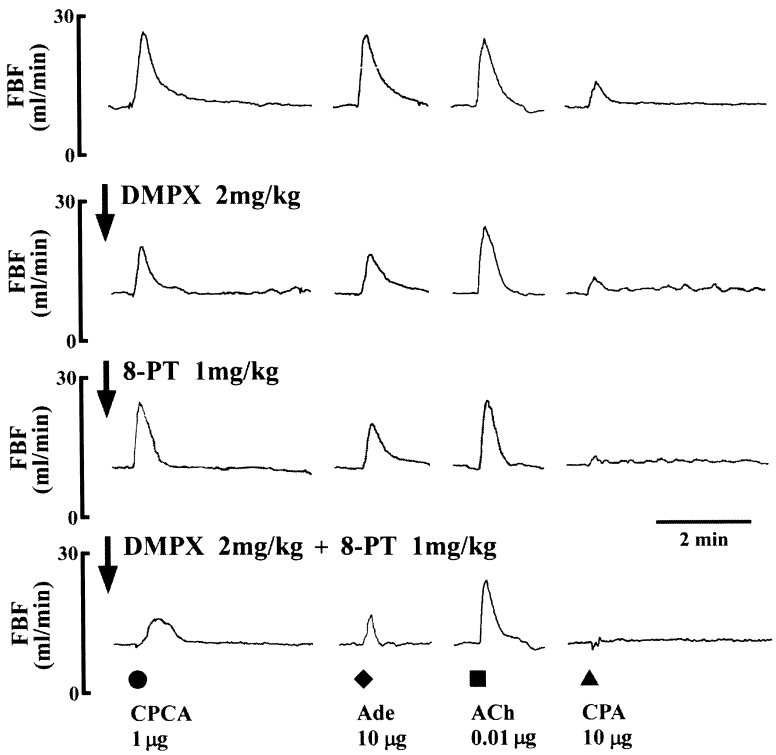
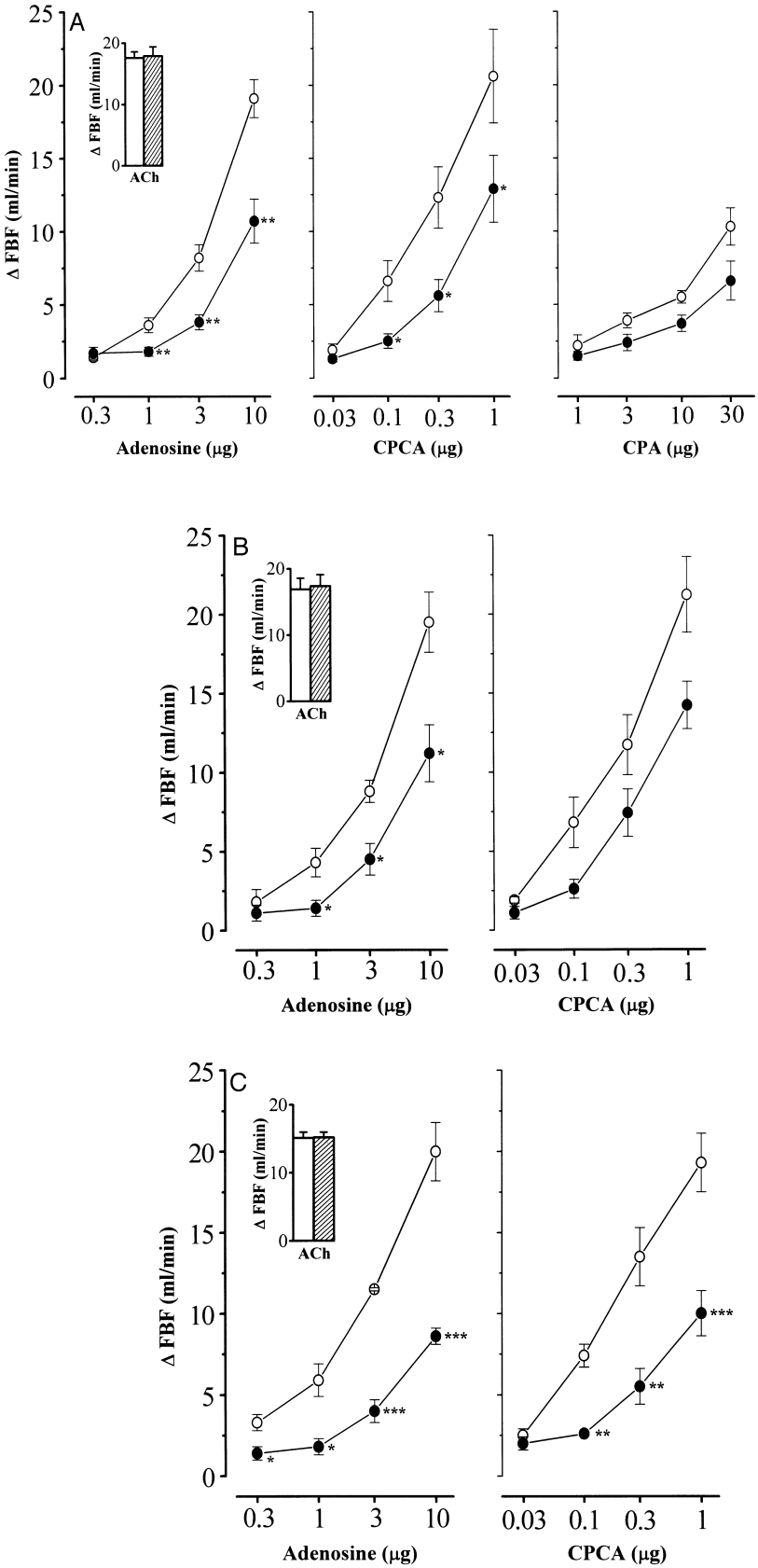


Fig. 2. Effects of CPCA, adenosine (Ade), acetylcholine (ACh) and CPA injected into the femoral artery on femoral blood flow (FBF) in the absence (upper part) or presence of i.v. injection of either DMPX, 8-phenyltheophylline (8-PT) alone (middle part), or the combination of DMPX with 8-PT (lower part).


A
B
C
Δ FBF (ml/min)
ACh
Adenosine (μg)
CPCA (μg)
CPA (μg)
0.3
1
3
10
0.03
0.1
0.3
1
1
3
10
30

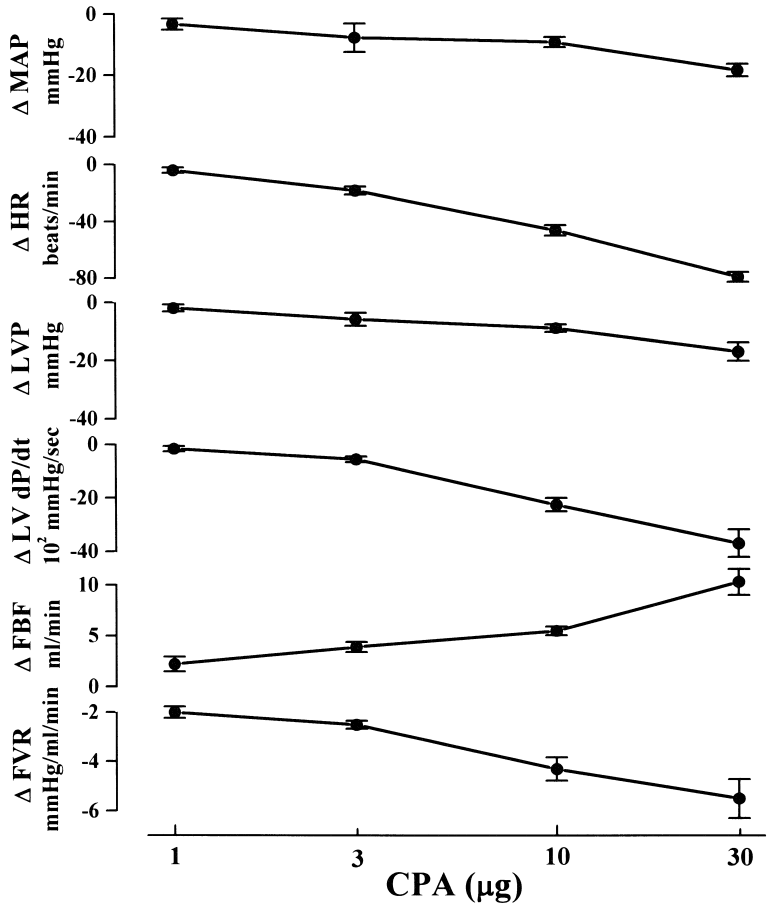


Fig. 4. Dose–response curves for CPA injected into the femoral artery for peak changes in mean arterial blood pressure (MAP), heart rate (HR), left ventricular pressure (LVP), LV$dP/dt$ max, femoral blood flow (FBF) and femoral vascular resistance (FVR). Data are expressed as means ± S.E.M. from five observations.

determine the level of statistical significance. A P value less than 0.05 was considered to be statistically significant.

3. Results

Baseline values of mean arterial blood pressure (mmHg), heart rate (beats per minute), LV pressure (mmHg), LV$dP/dt$ max (mmHg s^{-1}), femoral blood flow (ml min^{-1}) and femoral vascular resistance (mmHg ml^{-1} min^{-1}) in 25 rabbits tested were as follows: 107.8 ± 4.6, 348.0 ± 14.0, 111.2 ± 5.0, 7089 ± 762, 11.4 ± 1.4 and 10.1 ± 0.7; respectively, just before the first bolus injection of agents; 101.7 ± 5.6, 338.3 ± 11.1, 110.1 ± 4.6, 6522 ± 553, 11.1 ± 1.4 and 9.9 ± 0.8; respectively, just before the first bolus injection of agents following i.v. treatment with DMPX (2 mg kg^{-1}) or 8-phenyltheophylline (1 mg kg^{-1}). No significant differences were observed over time for the respective values. Thus, the preparations remained stable throughout the experimental period.

Single bolus doses of adenosine (0.3–10 μg), CPCA (0.03–1 μg), and acetylcholine (0.01 μg) were injected into the femoral artery. Adenosine as well as CPCA in the doses tested induced dose-dependent increases in femoral blood flow, almost without affecting cardiovascular parameters, except that CPCA (e.g., 1 μg) induced slight decreases in arterial blood pressure (less than 16%) and LV pressure (less than 13%) (Figs. 1–3). I.v. treatment with DMPX (2 mg kg^{-1}) or 8-phenyltheophylline (1 mg kg^{-1}), which did not affect basal cardiovascular parameters, significantly attenuated the femoral vascular responses to adenosine, but not those to acetylcholine (Figs. 2 and 3).

Fig. 3. Dose–response curves for adenosine, CPCA and CPA injected into the femoral artery on peak increases in femoral blood flow (FBF) before (control, ○) and after (●) i.v. treatment with (A) DMPX (2 mg kg^{-1}), (B) 8-phenyltheophylline (8-PT, 1 mg kg^{-1}) or (C) the combination of DMPX (2 mg kg^{-1}) and 8-PT (1 mg kg^{-1}). Inset: before (open columns) and after (hatched columns) the treatment with DMPX, 8-PT or the combination, the peak increase in FBF caused by intra-arterial injection of acetylcholine (ACh) (0.01 μg) was illustrated. Data are expressed as means ± S.E.M from five observations. $*\ P < 0.05$, $**\ P < 0.01$, $***\ P < 0.001$, compared with the corresponding values from the control group.

The dose–response curves for adenosine and CPCA before and 10–15 min after i.v. treatment with either DMPX or 8-phenyltheophylline were recorded, as depicted in Fig. 3A,B.

The vasodilator responses to adenosine and CPCA remained unaltered before and after i.v. treatment with 0.9% saline solution. The doses of adenosine and CPCA required to cause a 7-ml min^{-1} increase in mean femoral blood flow before (control) and after i.v. injection of 0.9% saline (2 ml kg^{-1} over 3 min) were calculated as follows (each $n = 5$): before, 1.58 ± 0.20 μg; after, 1.25 ± 0.32 μg; for adenosine (n.s. vs. before): before, 0.09 ± 0.03 μg; after, 0.06 ± 0.01 μg; for CPCA (n.s. vs. before). The doses of adenosine and CPCA required to cause a 7-ml min^{-1} increase in the blood flow before and after i.v. injection of DMPX were (each $n = 5$): before, 3.03 ± 0.50 μg; after, 5.64 ± 0.45 μg; for adenosine ($P < 0.01$ vs. before): before, 0.23 ± 0.03 μg; after, 0.40 ± 0.07 μg; for CPCA ($P < 0.05$ vs. before). The values for adenosine and CPCA were around 1.8- and 1.7-fold, respectively, greater than those for the control, when they were calculated based on the doses required to cause a 7-ml min^{-1} increase in the flow. The doses of adenosine required to cause a 7-ml min^{-1} increase in mean femoral blood flow before (control) and after the i.v. injection of 8-phenyltheophylline, which were around 2.1-fold greater than those for the control, were calculated to be (each $n = 5$): before, 2.13 ± 0.36 μg; after 4.52 ± 0.40 μg; for adenosine ($P < 0.01$ vs. before): before, 0.15 ± 0.04 μg; after, 0.35 ± 0.11 μg; for CPCA (n.s. vs. before). It was noted that the dose ratios of adenosine in the absence and presence of DMPX or 8-phenyltheophylline were of similar magnitude.

CPA administered into the femoral artery in increasing doses (1–30 μg) caused a relatively weak dose-related increase in femoral blood flow (Figs. 1–3A). As demonstrated in Figs. 1 and 4, the increase in flow was accompanied by dose-dependent changes in the cardiovascular parameters tested: decreases in heart rate and LV$dP/dt$ were especially prominent. The effects of CPA on these parameters, in spite of i.a. injection, were long-lasting, e.g., persisted over 20 min at 10 μg i.a. of CPA. It was confirmed that 8-phenyltheophylline (1 mg kg^{-1} i.v.) markedly prevented the responses to CPA (10 μg i.a.) (Fig. 2). As shown in Figs. 2, 3A (right part) and Fig. 5, i.v. treatment with DMPX (2 mg kg^{-1}) did not significantly attenuate the cardiovascular responses to bolus injection of CPA into the femoral artery. When 8-phenyltheophylline (1 mg kg^{-1}) was given i.v. in the presence of DMPX (2 mg kg^{-1}), the cardiovascular responses to CPA were markedly inhibited, similarly to the vascular ones to CPCA and adenosine (Figs. 2, 3C and Fig. 5). The doses of adenosine required to cause a 7-ml min^{-1} increase in

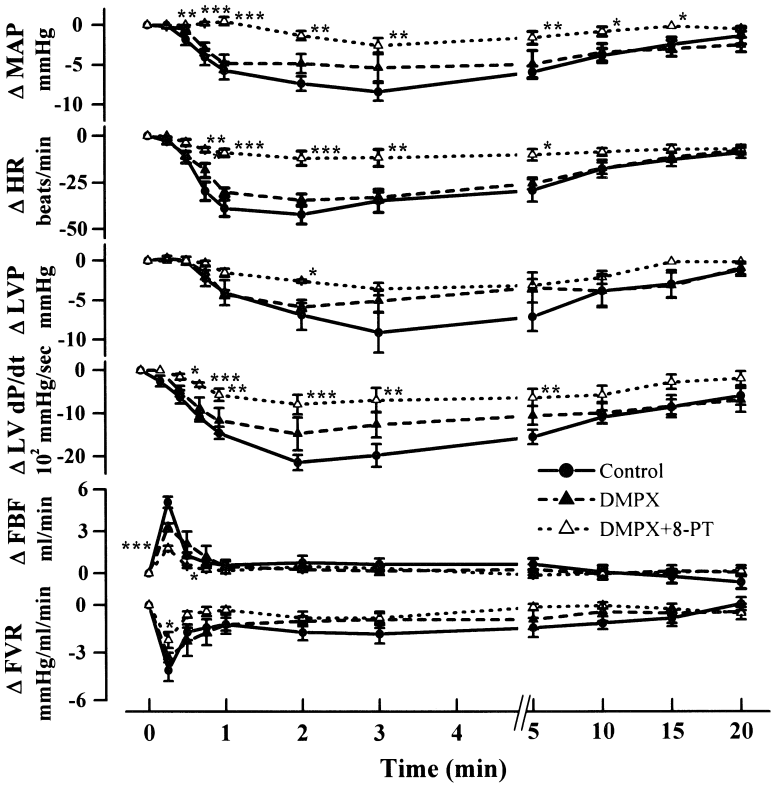


Fig. 5. Cardiovascular effects of CPA (10 μg) injected into the femoral artery on mean arterial blood pressure (MAP), heart rate (HR), left ventricular pressure (LVP), LV$dP/dt$ max, femoral blood flow (FBF) and femoral vascular resistance (FVR), before (●, control) and after i.v. treatment with DMPX (2 mg kg^{-1}) alone (▲) or in combination with 8-phenyltheophylline (8-PT) (1 mg kg^{-1}) (△). Data are expressed as means ± S.E.M from five observations. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, compared with the corresponding values from the control group.

mean femoral blood blow before (control) and after combined i.v. injection of DMPX (2 mg kg^{-1}) and 8-phenyltheophylline (1 mg kg^{-1}) were calculated as follows (each $n = 5$): before, 1.38 ± 0.22 μg; after, 7.48 ± 0.86 μg; for adenosine ($P < 0.001$ vs. before): before, 0.11 ± 0.02 μg; after, 0.40 ± 0.11 μg; for CPCA ($P < 0.05$ vs. before). The values for adenosine and CPCA after the combined injection of DMPX and 8-phenyltheophylline were around 5.4- and 3.6-fold, respectively, greater than those for the control.

4. Discussion

The present results revealed that single bolus doses of adenosine and CPCA injected into the femoral artery of the rabbit elicited dose-dependent increases in femoral blood flow, almost without affecting cardiac parameters, except for slight changes in arterial blood pressure and LV pressure caused by large doses of CPCA, whereas CPA induced pronounced changes in the parameters, especially in heart rate and LVdP/dt max, preceded by transient increases in femoral blood flow. Thus, the pharmacological profile of adenosine is similar to that of CPCA, but not to that of CPA.

It has been generally accepted that adenosine is non-selective for adenosine A_1 and A_2 receptors (Londos et al., 1980), and that adenosine A_1 receptor activation produces cardiac effects (Leung et al., 1986; Clemo et al., 1987; Webb et al., 1990), whereas adenosine A_2 receptor activation is commonly associated with vasodilatation (Mustafa and Askar, 1985; Webb et al., 1990; Furukawa et al., 1993). Indeed, we also found that vasodepression caused by adenosine given i.v. to rats is mediated partly through adenosine A_2 receptors, which are coupled with K_{ATP} channels (Saito and Sakai, 1998b). On the other hand, Merkel et al. (1992) reported that adenosine A_1, but not adenosine A_2, receptor agonists produce glibenclamide-sensitive vasorelaxation in porcine coronary vessels, and suggested that K^+ channels are implicated in adenosine A_1 receptor agonist-induced relaxation in the vascular smooth muscle. Similar findings, leading to the same conclusion, have been obtained in work with rabbit ear arteries (Randall et al., 1994), rat diaphragmatic arterioles (Danialou et al., 1997), streptozotocin-treated rats (Cox et al., 1997). Thus, there have been a number of reports that adenosine A_1 receptors are also associated with vasodilatation or vasodepression, partly through K_{ATP} channels, in some animal species and organs.

In the present experiments, the femoral vasodilatation caused by adenosine as well as CPCA, an adenosine A_2 receptor agonist (Bruns et al., 1986) was partially but significantly attenuated to a similar extent by treatment with DMPX, an antagonist of adenosine A_2 receptors (Seale et al., 1988; Sebastiao and Ribeiro, 1989), indicating that CPCA is not more selective than adenosine for adenosine A_2 receptors. Additionally, treatment with 8-phenyltheophylline, an antagonist of adenosine A_1 receptors (Bruns et al., 1986), also significantly reduced the femoral vasodilatation caused by adenosine and CPA, an adenosine A_1 receptor agonist (Williams et al., 1986), but not that caused by CPCA and acetylcholine. Interestingly, inhibitory effects of the adenosine A_1 or A_2 receptor antagonist on the adenosine-induced vasodepression were of a similar magnitude. It was further noted that not only the brief and weak increase in femoral blood flow, but also changes in cardiac parameters, caused by bolus i.a. injections of CPA, were not significantly inhibited by DMPX alone, but were completely abolished by the combined administration of DMPX and 8-phenyltheophylline. In addition, the dose–response curves to adenosine and CPCA for femoral blood flow increase were more markedly shifted rightwards by the combined administration of DMPX and 8-phenyltheophylline, than by the respective adenosine receptor antagonists alone. Together, these facts suggest that femoral vasodilatation in the rabbit is mediated by both adenosine A_1 and A_2 receptors in the vasculature.

Studies of the affinities of adenosine receptor agonists and antagonists for inhibition of adenosine A_1 and A_2 receptor binding in rat brain membranes by Bruns et al. (1986) and Seale et al. (1988), yielded K_i ratios (A_2/A_1) for CPA, CPCA, 8-phenyltheophylline (Bruns et al., 1986) and DMPX (Seale et al., 1988) of 784, 2.08, 9.85 and 0.24, respectively. Thus, these substances seem to have selectivity for the respective adenosine receptors in rat brain membranes. However, Williams et al. (1986) found that, despite the selectivity of CPA for adenosine A_1 receptors, some binding to adenosine A_2 receptors could not be excluded, suggesting that CPA has some adenosine A_2 receptor agonist-like properties. In the present study, we found that the femoral vasodilatation induced by CPA and CPCA was partially attenuated by DMPX and 8-phenyltheophylline, respectively, even though the effects of the antagonists were not significant. We also found that the vasodilatation induced by CPA and CPCA was significantly and markedly blocked by the combined administration of DMPX and 8-phenyltheophylline (see Fig. 2). Furthermore, it should be noted that the cardiovascular effects of CPA (10 μg) injected into the femoral artery were slightly, but not significantly, attenuated by DMPX, whereas after the treatment with 8-phenyltheophylline, the residual changes in CPA-induced cardiovascular parameters were almost completely prevented. The findings seem to indicate that these adenosine receptor agonists and antagonists might not necessarily be selective for the respective adenosine receptors in the femoral vasculature of the rabbit. In the present experiments, the doses of the antagonists used were such that they did not significantly prevent the acetylcholine (0.01 μg)-induced femoral vasodilatation.

In summary, we have shown that in anesthetized rabbits (1) adenosine injected into the femoral artery elicited a dose-dependent increase in femoral blood flow, almost without influencing cardiac parameters, and the increases in blood flow were significantly inhibited by i.v. DMPX and 8-phenyltheophylline, respectively, to a similar extent; and (2) the combined i.v. administration of DMPX and 8-phenyltheophylline caused a more marked rightward shift of the dose–response curve for adenosine. Taken together, these results led us to conclude that both adenosine A_1 and A_2 receptors may contribute to the adenosine-induced vasodilatation in the femoral vascular beds of rabbits.

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