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Effects of dinucleoside polyphosphates on regulation of coronary vascular tone

Markus van der Giet *, Sven Schmidt, Markus Tölle, Joachim Jankowski, Hartmut Schlüter, Walter Zidek, Martin Tepel

Medizinische Klinik IV, Universitätsklinikum Benjamin Franklin, Freie Universität Berlin, Hindenburgdamm 30, 12200 Berlin, Germany

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Abstract

The aim of the present study was to investigate the effects of Xp_5X and Xp_6X (X = guanosine (G) or adenosine (A); $n = 5$ and 6), which have been identified in human platelets, on coronary vascular tone. The activation of purinoceptors in rat coronary vasculature by Xp_5X and Xp_6X was evaluated by measuring their effects on perfusion pressure in the Langendorff perfused rat. Ap_5X and Ap_6X induced dose-dependent vasodilation that was due to $P2Y_1$ receptor activation, as evidenced by use of the selective $P2Y_1$ receptor antagonist 2′-deoxy-N^6-methyl-adenosine 3′,5′-diphosphate diammonium (MRS2179). Vasodilation was induced by NO release, as evidenced by inhibition of nitric oxide synthases (NO synthases) by N^G-nitro-L-arginine methyl ester (L-NAME). The dose-dependent decrease in coronary perfusion pressure induced by Ap_5X and Ap_6X was converted to a dose-dependent increase in perfusion pressure after inhibition of NO synthases by L-NAME. After endothelium removal, the vasodilation elicited by Ap_5X and Ap_6X was converted to a vasoconstriction which could be inhibited by P2X receptor blockade. Ap_5A, Ap_5G, Ap_6A and Ap_6G are vasodilating or vasoconstricting nucleotides that activate $P2Y_1$ or P2X receptors depending on the status of the coronary vascular endothelium.

Keywords: Dinucleoside polyphosphate; Coronary artery; Isolated; Perfused; P2X receptor; P2Y receptor

1. Introduction

Dinucleoside polyphosphates (Xp_nX) are naturally occurring compounds that are present in the myocardium and platelets (Jovanovic et al., 1998; Luo et al., 1999; Schluter et al., 1994, 1998). Xp_nXs consist of two adenosine molecules (Ap_nA), two guanosine molecules (Gp_nG), or an adenosine molecule and a guanosine molecule (Ap_nG) bridged by up to seven phosphate groups ($n = 2–7$) (Jankowski et al., 1999b; Luo et al., 1999; Schluter et al., 1994, 1998). Several dinucleoside phosphates (Xp_nX) have been isolated from human tissue including platelets. Xp_nXs act as extracellular signaling molecules and neurotransmitters. They alter platelet reactivity, vasomotor tone, and cardiac electrophysiology (Flores et al., 1999; Miras-Portugal et al., 1998).

Dinucleoside phosphates have different actions on the vasculature depending on the number of phosphate groups. Ap_2A, Ap_3A and Ap_4A are potent vasodilators in the mesenteric, renal, and coronary vasculature (Pohl et al., 1991; Ralevic et al., 1995; van der Giet et al., 1997), whereas Ap_5A, Ap_5G, Ap_6A and Ap_6G appear to have potent vasoconstrictor properties in the mesenteric and renal vasculature (Davies et al., 1995; Jankowski et al., 1999b; Ralevic et al., 1995; Schluter et al., 1998; van der Giet et al., 1997, 1998, 1999). In coronary vessels with an intact endothelium, it has been shown that Ap_nAs ($n = 4–6$) cause vasodilation mediated via nitric oxide (NO) and prostanoid release (Stavrou et al., 2001). Dinucleoside phosphates elicit their extracellular effects via P1 and mainly P2 receptors (Flores et al., 1999; Kisselev et al., 1998). However, until now it is not clear which purinoceptors are activated by Xp_5X and Xp_6X (X = A/G) in coronary vessels and whether these substances have an impact on coronary vessels in different disease conditions.

The aim of the present study was to investigate the vasoactive properties of Xp_5X and Xp_6X on rat coronary

* Corresponding author. Tel.: +49-30-8445-3021; fax: +49-30-8445-4235.

E-mail address: vdGiet@zedat.fu-berlin.de (M. van der Giet).

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vessels and to identify the receptors and mechanisms involved in the different effects.

2. Materials and methods

2.1. Perfusion technique

The investigation conformed with German legislation and the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Male Wistar rats (220–380 g) were heparinized (1000 U kg^{-1} intraperitoneally) and anaesthetized with urethane (1.4 g kg^{-1} body weight, intraperitoneally). Following a mid-line thoracotomy, the heart was rapidly excised and placed in ice-cold oxygenated modified Krebs–Henseleit solution (containing (mM): NaCl 118, KCl 4.7, KH_2PO_4 1.2, $MgSO_4$ 1.2, $NaHCO_3$ 25, $CaCl_2$ 2, D-glucose 10 and 2 pyruvate) to stop cardiac contraction. The aortic stump was then cannulated and the heart was perfused retrogradely according to the method of Langendorff (Hopwood and Burnstock, 1987) at a constant flow (6 ml/min) with Krebs–Henseleit solution at 37 °C (gassed with 95%O_2/CO_2) by means of a peristaltic pump (Ismatec BVP, Glattbrug, CH). The pH of the perfusate was maintained at 7.4. Coronary perfusion pressure was measured with a pressure transducer (Statham Transducer P23Gb, Siemens) connected to a sidearm of the perfusion cannula using a bridge amplifier (Hugo Sachs, Freiburg, Germany). Curves were recorded on a polygraph. Drugs were injected as bolus doses (100 μl) close to the aortic inflow cannula. All drugs were heated to 37 °C, gassed with 95%O_2/5%CO_2 and diluted to the appropriate concentration in Krebs–Henseleit buffer prior to application to avoid non-specific vascular effects. Preparations were allowed to equilibrate 30 min before experimentation.

2.2. Experimental protocol

Responses of preparations to dinucleoside phosphates (Xp_nX; X = A/G, $n = 5$ and 6), α,β-methyleneadenosine 5′-triphosphate (α,β-meATP), 2-methylthioadenosine 5′-triphosphate (2-meSATP), 2-chloroadenosine 5′-triphosphate (2-ClATP) were assessed at basal tone. For each substance dose–response curves were made, with 5 min being allowed to elapse between consecutive doses. This procedure allowed dose–response curves for several agonists to be made for the same preparation. Desensitization was not detected when 5 min was allowed to elapse between consecutive doses. Single doses of sodium nitroprusside (10 nmol) and acetylcholine (10 nmol) were used as controls for endothelium independent or endothelium dependent vasodilation mediated via NO.

Some experiments were done after endothelium removal with Triton X-100, to investigate endothelium-independent effects of all the agonists used. The endothelium was removed by perfusion of the isolated heart for 5 s with 0.1% Triton X-100. The lack of response to acetylcholine was used to check endothelium removal. Unaffected contractions to K^+ (130 mM bolus) indicated an intact vascular smooth muscle cell function. In some experiments with endothelium removal, P2X receptors were desensitized by permanent perfusion with α,β-meATP (1 μM) to block P2X-mediated vasoconstriction.

The specific $P2Y_1$ receptor antagonist 2′-deoxy-N^6-methyl-adenosine 3′,5′-diphosphate diammonium (MRS2179, 1 μM), the P2X receptor antagonist pyridoxal-phosphate-6-azophenyl-2;4-disulphonic acid (PPADS, 10 μM), and the nitric oxide (NO) synthase inhibitor N^G-nitro-L-arginine methyl ester (L-NAME, 10 μM) were added to the perfusate 30 min before challenge with mono- or dinucleotides. MRS2179 and PPADS did not significantly influence vascular tone, whereas L-NAME significantly ($P < 0.05$) increased perfusion pressure. Permanent perfusion with α,β-meATP elicited a rapid and completely desensitizing vasoconstriction.

2.3. Materials

All dinucleoside phosphates (Xp_nX; X = A/G, $n = 5$ and 6), monoadenosinephosphates, sodium nitroprusside and acetylcholine were applied as 100 μl bolus into a valve proximal to the preparation. Drug dilutions were prepared daily from stock solutions of 10 mM (concentrates stored frozen in bidistilled water) with Krebs–Henseleit-buffer unless indicated otherwise. Heparin (sodium salt), PPADS, MRS2179, α,β-meATP, 2-meSATP, 2ClATP were from Research Biochemicals, Deisenhofen, Germany. Adenosine(5′)pentaphospho-(5′)adenosine (Ap_5A) and adenosine(5′)hexaphospho-(5′)adenosine (Ap_6A) and Triton X-100 were from Sigma, Deisenhofen, Germany and purified (except for Triton X-100) according to a procedure described earlier (Heidenreich et al., 1995). Adenosine(5′)pentapospho-(5′)guanosine (Ap_5G), guanosine(5′)pentaphospho-(5′)guanosine (Gp_5G), adenosine(5′)hexapospho-(5′)guanosine (Ap_6G) and guanosine(5′)hexaphospho-(5′)guanosine (Gp_6G) were synthesized and purified as described previously (Schluter et al., 1998).

2.4. Statistics

Responses were measured as changes in perfusion pressure (mm Hg) and results are presented as the means ± standstandard error of the mean (S.E.M.). Two-way repeated measures of variance, followed by Bonferroni's multiple comparison test (for changes in coronary perfusion pressure) were used to identify statistically significant differences. The effects of L-NAME, MRS2179, PPADS, and α,β-meATP on coronary perfusion pressure were compared with drug-free control conditions using Mann–Whitney test. All P values presented are two-tailed. P values < 0.05 were considered significant.

3. Results

3.1. Dose–response curves for Xp_nX at basal tone

The mean coronary perfusion pressure as measured in a total of 112 experiments amounted to 62 ± 8 mm Hg.

At baseline perfusion pressure, the nucleotides except for α,β-meATP, Gp_5G, and Gp_6G caused dose-dependent vasodilation (Fig. 1A–C). α,β-meATP induced dose-dependent vasoconstriction, whereas Gp_5G and Gp_6G had no effect on the perfusion pressure. There were no significant differences between the dose–response curves for Ap_5A, Ap_5G, Ap_6A, Ap_6G, 2-meSATP and 2-ClATP.

Table 1
Vasodilator ED_{50} values and maximal responses to 10 nmol doses of mono- and dinucleosides in basal-tone preparation

Compound	ED_{50}	Maximal response to 10 nmol of agonist (mm Hg)
2ClATP	10.90 ± 0.40	− 14.3 ± 2.8
2-meSATP	10.13 ± 0.19	− 12.2 ± 1.2
Ap_5A	8.92 ± 0.27	− 8.6 ± 2.6
Ap_6A	9.09 ± 0.19	− 6.9 ± 1.4
Ap_5G	8.86 ± 0.26	− 4.8 ± 1.8
Ap_6G	9.15 ± 0.29	− 2.9 ± 0.3
Gp_5G	Not calculated	0 ± 0
Gp_6G	Not calculated	0 ± 0

Data are expressed as ED_{50} values (the negative logarithm of the molar dose of an agonist required to produce 50% the maximal response). Values represent the means ± S.E.M. from at least $n = 11$ experiments performed in duplicate.

The dose–response curves were not parallel and the maximal vasodilation induced varied considerably, which makes calculation of potency ratios difficult, but by estimation of concentrations equieffective to 10 nmol Ap_6G the rank order of potency was 2-ClATP ≥ 2-meSATP ≥ $Ap_5A \geq Ap_6A \geq Ap_5G \geq Ap_6G \gg Gp_5G \approx Gp_6G$. Table 1 shows ED_{50} and maximal responses to 10 nmol doses.

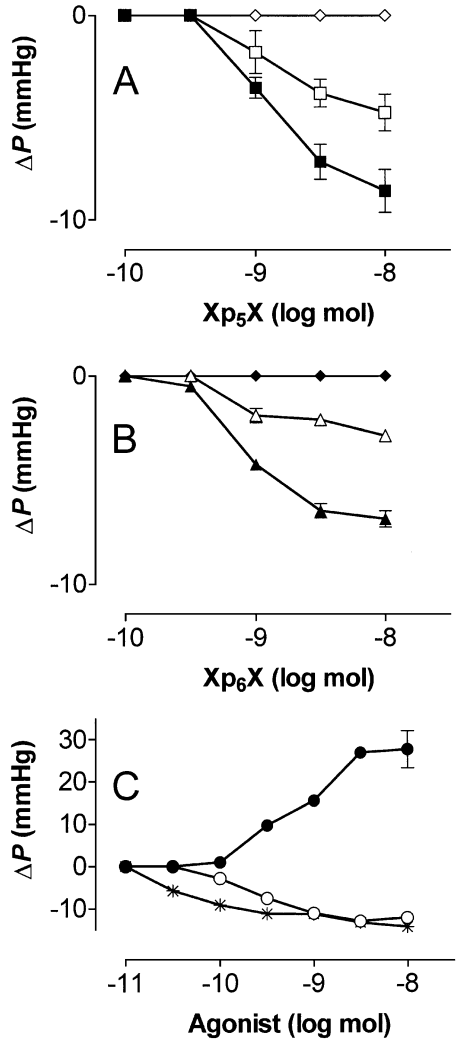

Fig. 1. Changes in perfusion pressure in the isolated perfused rat heart induced by (A) Ap_5A (■), Ap_5G (□), Gp5G (◇), (B) Ap_6A (▲), Ap_6G (△), Gp_6G (◆), (C) α,β-meATP (●), 2-ClATP (○), and 2-meSATP (*). Each point is the mean of at least eight determinations and error bars show S.E.M. Where error bars do not occur, they are within the symbol size. Significant differences ($P < 0.05$) from baseline perfusion pressure 2-meSATP ≥ 30 pmol, 2-ClATP ≥ 100 pmol, α,β-meATP ≥ 300 pmol, Ap_5A, Ap_5G, Ap_6A, $Ap_6G \geq 1$ nmol. For abbreviations see text.

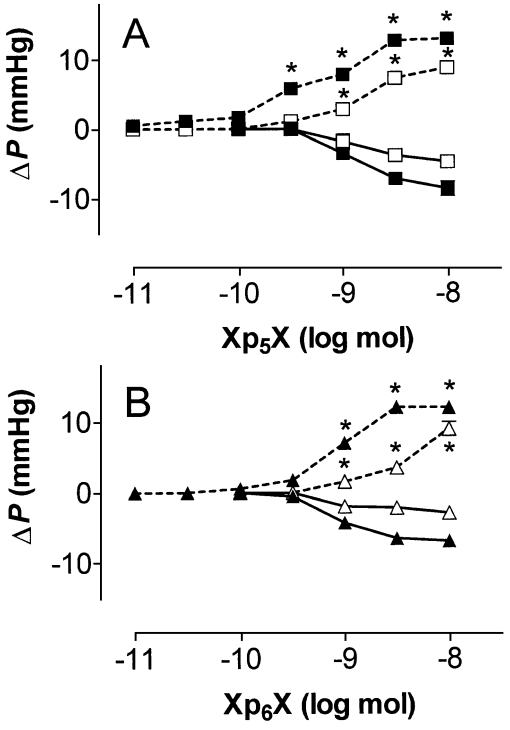

Fig. 2. Changes in perfusion pressure in the isolated rat heart induced by (A) Ap_5A (■), Ap_5G (□), (B) Ap_6A (▲), and Ap_6G (△) in the absence (solid line, control) and presence (dotted line) of L-NAME (10 μM) in the perfusate. Each point is the mean of at least eight determinations and the vertical lines show the S.E.M. Where error bars do not occur, error bars are within the symbol size. * $P < 0.05$ L-NAME vs. control. For abbreviations see text.

Table 2
Vasoconstrictor ED_{50} values and maximal responses to 10 nmol doses of mono- and dinucleosides under permanent perfusion with L-NAME 10 μM

Compound	ED_{50}	Maximal response to 10 nmol of agonist (mm Hg)
α,β-meATP	9.18 ± 0.18	22.8 ± 6.3
Ap_5A	9.22 ± 0.23	13.0 ± 1.7
Ap_6A	9.06 ± 0.09	10.7 ± 1.6
Ap_5G	8.75 ± 0.29	8.8 ± 1.5
Ap_6G	7.34 ± 0.40	9.0 ± 2.6

Data are expressed as ED_{50} values (the negative logarithm of the molar dose of an agonist required to produce 50% the maximal response). Values represent the means ± S.E.M. from at least $n = 10$ experiments performed in duplicate.

3.2. Effects of Xp_nX in the presence of L-NAME

Permanent perfusion with L-NAME (10 μM) significantly ($P < 0.05$) increased the coronary perfusion pressure to 75 ± 8 mm Hg ($n = 16$). Blockade of endothelial NO synthases by L-NAME significantly ($P < 0.05$) reversed the decrease in coronary perfusion pressure induced by bolus application of 1 nmol acetylcholine (control: −9.5 ± 2.3 mm Hg; L-NAME (10 μM): 5.9 ± 2.3 mm Hg). Permanent perfusion with L-NAME neither affected the vasodilator response to bolus application of 10 nmol sodium nitroprusside (control: −19.5 ± 4.2 mm Hg; L-NAME (10 mM): −18.5 ± 4.5 mm Hg) nor the vasoconstrictive response to a 10 nmol bolus of α,β-meATP (control: 22.1 ± 7.4 mm Hg; L-NAME (10 μM): 22.8 ± 6.3 mm Hg). The vasodilator response to a 10-nmol bolus of 2-ClATP and 2-meSATP was converted to a significant ($P < 0.05$) vasoconstrictive response in the presence of L-NAME (2-ClATP: −14.3 ± 2.8 mm Hg, 2-ClATP + L-NAME: 8.2 ± 2.4 mm Hg; 2-meSATP: −12.2 ± 1.2 mm Hg, 2-meSATP + L-NAME: 7.4 ± 2.3 mm Hg [results not shown]). The dose-dependent decrease in coronary perfusion pressure induced by Ap_5A, Ap_5G (Fig. 2A), Ap_6A, and Ap_6G (Fig. 2B) was converted to a dose-dependent increase in perfusion pressure. The dose–response curves were not parallel and the maximal contractions induced varied considerably, which makes calculation of potency ratios difficult. Estimation of the concentration equieffective to 10 nmol Ap_6G in the presence of L-NAME (10 μM) revealed the following order of potency: α,β-meATP ≥ Ap_5A ≥ Ap_6A ≥ Ap_5G ≥ Ap_6G. In Table 2, ED_{50} and max-

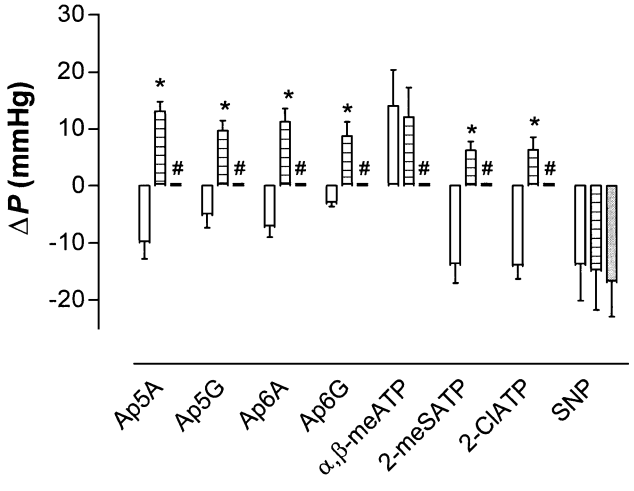

Fig. 3. Changes in perfusion pressure in the isolated perfused rat heart induced by bolus injection of 10 nmol of each agonist before (control, open column) and after endothelium removal (ER) with Triton X-100 (column with grid) and in the presence of α,β-meATP (1 μM, half-tone column) in the perfusate. Each column is the mean of at least eight determinations and error bars show the S.E.M. *$P < 0.05$ ER vs. control; #$P < 0.05$ α,β-meATP/ER vs. ER). For abbreviations see text.

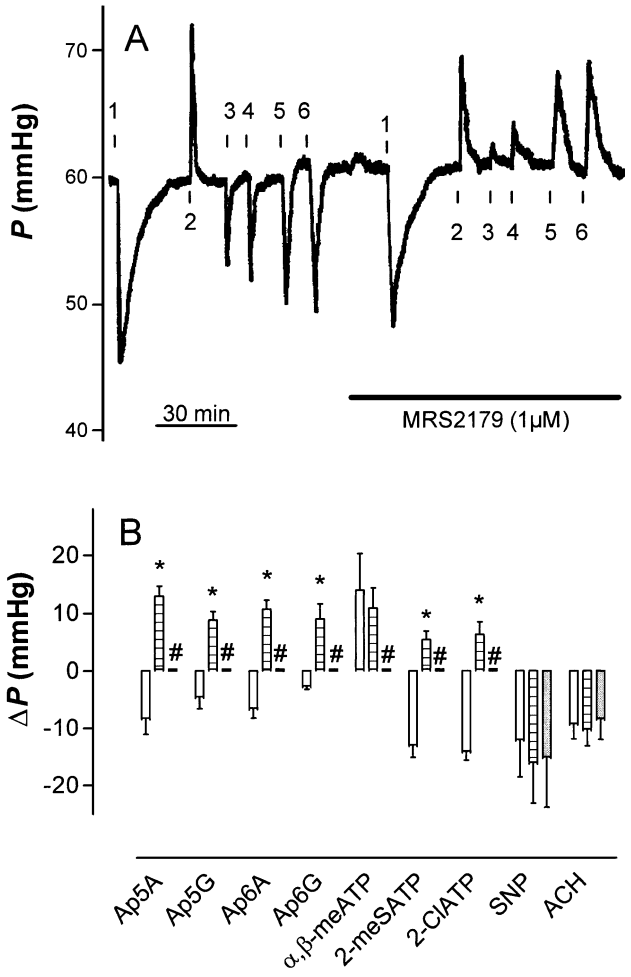

Fig. 4. (A) Original tracing showing the effects of bolus injection of 10 nmol (1) ACH, (2) α,β-meATP, (3) Ap_5A, (4) Ap_5G, (5) Ap_6A, and (6) Ap_6G on the perfusion pressure in the isolated perfused rat heart in the presence and absence of the $P2Y_1$ receptor antagonist MRS2179 (1 μM). (B) Changes in perfusion pressure in the isolated perfused rat heart induced by bolus injection of 10 nmol of each agonist in the absence of any antagonist (control, open column), in the presence of MRS2179 (1 μM, column with grid) and in the presence of both MRS2179 (1 μM) and PPADS (10 μM, half-tone column) in the perfusate. Each column is the mean of at least nine determinations and error bars show the S.E.M. *$P < 0.05$ MRS2179 vs. control; #$P < 0.05$ PPADS/MRS2179 vs. control/MRS2179). For abbreviations see text.

imal responses to 10 nmol doses in the presence of L-NAME (10 μM) are shown.

3.3. Effects of Xp_nX after endothelium removal and P2X receptor desensitisation

After endothelium removal with Triton X-100, vasodilator responses to 10 nmol doses of Ap_5A, Ap_5G, Ap_6A, Ap_6G, 2-meSATP, and 2-ClATP were completely abolished, resulting in a vasoconstriction (Fig. 3, $P<0.05$). The vasodilation induced by 10 nmol doses of sodium nitroprusside and the vasoconstriction induced by 10 nmol α,β-meATP were not significantly affected by endothelium removal. P2X receptor desensitization with α,β-meATP (1 μM) significantly ($P<0.05$) blocked the vasoconstriction induced by 10 nmol doses of Ap_5A, Ap_5G, Ap_6A, Ap_6G, 2-meSATP, 2ClATP, and α,β-meATP.

3.4. Effects of Xp_nX in the presence of the P2Y receptor antagonist MRS2179 and P2X receptor antagonist PPADS

In the presence of MRS2179 (1 μM) vasodilator responses to 10 nmol doses of Ap_5A, Ap_5G, Ap_6A, Ap_6G, 2-meSATP, and 2-ClATP were completely abolished, resulting in a vasoconstriction (Fig. 4A—representative tracing for Ap_5A, Ap_5G, Ap_6A, and Ap_6G; Fig. 4B—bar graph, $P<0.05$). The vasodilation induced by 10 nmol sodium nitroprusside or 1 nmol doses acetylcholine and the vasoconstriction induced by 10 nmol α,β-meATP were not significantly ($P<0.05$) inhibited by MRS2179. Additional perfusion with PPADS (10 μM) significantly blocked the vasoconstriction induced by 10 nmol doses of Ap_5A, Ap_5G, Ap_6A, Ap_6G, 2-meSATP, 2ClATP, and α,β-meATP (Fig. 4B), whereas the vasodilation induced by 10 nmol sodium nitroprusside and 1 nmol acetylcholine was not significantly affected.

4. Discussion

In coronary vessels under basal tone, Ap_5A, Ap_5G, Ap_6A, and Ap_6G induced dose-dependent vasodilation, whereas Gp_5G and Gp_6G had no effect. Stavrou et al. (2001) have shown that Ap_5A and Ap_6A induce dose-dependent vasodilation in coronary vessels in guinea pigs. The Ap_nX (X = A/G; $n=5$ and 6)-induced vasodilation appears to be mediated by $P2Y_1$ receptors, as evidenced by complete blockade with the selective $P2Y_1$ receptor antagonist MRS2179 (Kaiser and Buxton, 2002). It has been shown by Patel et al. (2001) that Ap_5A and Ap_6A can activate $P2Y_1$ receptors stably expressed in 1321N1 cells. Since L-NAME completely abolished the Ap_nX-induced vasodilation, obviously endothelial P2Y receptors are activated, which then induce activation of endothelial NO synthases. It has been earlier shown that P2Y receptors are present in coronary vessels and can be activated by various nucleotides such as ATP or 2-meSATP to induce vasodilation (Hansmann et al., 1998; Korchazhkina et al., 1999). P2Y receptor-mediated vasodilation induced by ATP or 2-meSATP can be inhibited by the blockade of NO synthase with L-NAME (Hansmann et al., 1998). ATP however induces vasodilation not only via P2Y receptors but also via adenosine 2 receptors, due the to rapid degradation of ATP by ectonucleotidases located in the coronary endothelium to adenosine or AMP, which can then activate adenosine 2 receptors (Korchazhkina et al., 1999). In the isolated perfused rat kidney, it has been shown that Ap_5A and Ap_6A do not activate adenosine 2 receptors (van der Giet et al., 1997), although these receptors are present in the renal vasculature. Possible degradation products of dinucleoside polyphosphates, such as ATP or ADP, seem not to be responsible for the vasoactive properties of Ap_nXs (X = A/G, $n=5$ and 6) due to the long half life of dinucleoside polyphosphates (Luthje and Ogilvie, 1988; Schluter et al., 1998). In addition, it has been shown that ATP from platelets at concentrations present during platelet aggregation strongly inhibits the degradation of dinucleoside polyphosphates in whole blood (Luthje and Ogilvie, 1988). The difference in the vasoactive properties of Ap_nX (X = A/G, $n=5/6$) between coronary and renal vessels may be due to a different expression of purinoceptor subtypes. $P2Y_1$ receptors appear to be more important in the coronary vasculature than in the renal vasculature.

After inhibition of NO synthase with L-NAME, the dose-dependent vasodilation induced by Ap_nXs (X = A/G, $n=5$ and 6) was converted to dose-dependent vasoconstriction. Blockade of the $P2Y_1$ receptor by MRS2179 or removal of the endothelium by Triton X-100 converted the vasodilation induced by Ap_nXs (X = A/G, $n=5$ and 6) to vasoconstriction which could be blocked by the P2X receptor antagonist PPADS and by desensitization of the $P2X_1$ receptor subtype with α,β-meATP. It has been shown that Ap_nXs (X = A/G), $n=5$ and 6) can activate $P2X_1$ receptors (Cinkilic et al., 2001; Lewis et al., 2000; Wildman et al., 1999), which are also present in vascular smooth muscle cells of coronary arteries (Kunapuli and Daniel, 1998; Malmsjo et al., 2000). It is very unlikely that the observed vasoconstriction was mediated via $P2Y_2$, $P2Y_4$ or $P2Y_6$ receptors, which have been identified in human coronary arteries (Malmsjo et al., 2000) because these P2Y receptors were not activated by α,β-meATP and the vasoconstriction elicited by Ap_5X and Ap_6X could be blocked by $P2X_1$ receptor desensitization with α,β-meATP.

Ap_nGs showed a weaker vasoactive action than the corresponding Ap_nAs. Since both activate the same receptors, it may be concluded that the presence of two adenosine moeities enhances the chance of receptor binding and activation. This effect has been observed in the isolated perfused rat kidney (van der Giet et al., 2001). Moreover, the number of phosphate groups determines the vasoconstrictive action and, hence, the apparent receptor affinity. The compound containing five phosphate groups had the

most pronounced vasoactive effect. This has already been shown for Ap_nAs (Ralevic et al., 1995; van der Giet et al., 1997). It can be concluded that not only the adenosive moeity is important for P2 receptor activation but also the number of phosphate groups critically changes the apparent receptor affinity.

The effects of dinucleoside polyphosphates on coronary vascular resistance vessels may be of relevance for human pathophysiology for several reasons. Firstly, diadenosine polyphosphates have been found in myocardial tissue. In human myocardium, Ap_2A has been isolated recently (Luo et al., 1999) and Ap_5A has been isolated from guinea pig heart (Jovanovic et al., 1998). Given that sufficient amounts of Ap_nA are produced to affect vascular tone, these nucleotides may be part of autocrine regulation of coronary vessel perfusion.

Ap_nXs have been isolated from human platelets and shown to be released after platelet aggregation (Schluter et al., 1994, 1998). Therefore, the effects of these agents may also be of interest in the context of myocardial ischemia or unstable angina. The release of Ap_nXs from a platelet thrombus might induce changes in local myocardial perfusion. The present findings indicate that these changes in myocardial perfusion depend on the functional status of the coronary endothelium. In a vascular bed with damaged endothelium, which is found in disease conditions like unstable angina (Yeghiazarians et al., 2000), a vasoconstrictive effect of Ap_5X and Ap_6X can be expected, whereas with an intact endothelium vasodilation should be observed.

Last, it has to be examined whether the experimental findings are relevant in vivo. This depends on whether sufficient concentrations of dinucleoside polyphosphates are released on platelet aggregation to affect vascular tone. In earlier studies of platelet dinucleoside polyphosphates, it was estimated that millimolar concentrations of dinucleoside polyphosphates are released from platelets (Jankowski et al., 1999a). Consequently, in the local environment of a platelet thrombus, sufficient concentrations of dinucleoside polyphosphates can be expected to affect vascular tone.

In summary, Ap_5A, Ap_6A, Ap_5G, and Ap_6G are vasodilators in coronary vessels and act by stimulating the endothelial $P2Y_1$ receptor via release of NO. If the coronary endothelium is blocked or removed, Ap_5A, Ap_5G, Ap_6A, and Ap_6G act as vasoconstrictors via the $P2X_1$ receptor. The effects in the coronary vasculature are markedly different from in the renal vasculature. The effects may be relevant for the regulation of coronary perfusion under physiological and pathological conditions. Ap_5X and Ap_6X may be deleterious in coronary vasospastic disorders.

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