

Erratum

Erratum to: “On the suitability of adenosine 3′-phosphate 5′-phosphosulphate as a selective P_{2Y} receptor antagonist in intact tissues”[Eur. J. Pharmacol. 351 (1998) 209–215]¹Ralph Bültmann^{*}, Florin Tuluc, Klaus Starke*Pharmakologisches Institut, Hermann-Herder-Strasse 5, D-79104 Freiburg i. Br., Germany*

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Abstract

Agonist and antagonist effects of the putative P2Y₁ receptor antagonist adenosine 3′-phosphate 5′-phosphosulphate (PAPS) were studied in intact tissues. In the carbachol-precontracted guinea-pig taenia coli, PAPS caused prominent relaxation (EC₅₀ 3.3 μM). The response was attenuated by the P2 receptor antagonists 4,4′-diisothiocyanatostilbene-2,2′-disulphonate (DIDS) and reactive red 2 with apparent K_d values (0.27 and 0.29 μM) indicating that PAPS acts through the non-P_{2Y} receptor, which is the site of action of α,β-methylene ATP (α,β-MeATP) in the taenia coli. Incubation with PAPS (10–100 μM) attenuated the P_{2Y} receptor-mediated relaxation caused by adenosine 5′-O-(2-thiodiphosphate) (ADPβS); PAPS (100 μM) also attenuated the relaxation caused by α,β-MeATP, as well as the α₁-adrenoceptor-mediated response to noradrenaline. In the noradrenaline-precontracted rat aorta, PAPS caused minor relaxation (EC₅₀ 24.7 μM), which was reduced by the P2 receptor antagonist pyridoxalphosphate-6-azophenyl-2′,5′-disulphonate (iso-PPADS; 1 μM), indicating that PAPS activates endothelial P_{2Y} receptors. Incubation with PAPS (10 and 100 μM) attenuated the P_{2Y} receptor-mediated relaxation caused by ADPβS; PAPS (100 μM) also attenuated the P_{2U} receptor-mediated relaxation caused by UTP and the muscarine receptor-mediated response to acetylcholine. In rat vas deferens, PAPS (100 μM) attenuated the P_{2X} receptor-mediated contraction elicited by α,β-MeATP but did not alter the α₁-adrenoceptor-mediated response to noradrenaline. The results indicate that PAPS attenuates P_{2Y} receptor-mediated relaxation in intact tissues. However, due to its limited subtype selectivity and non-P2 receptor effects, the nucleotide is not a suitable antagonist for this subtype. © 1998 Elsevier Science B.V. All rights reserved.

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1. Introduction

During the past few years, the coding sequences of several membrane receptors for extracellular nucleotides have been identified. On the basis of their different molecular structure, two receptor families are currently discerned: P2X receptors (P2X_{1–7}), which form ligand-gated ion channels, and G-protein-coupled P2Y receptors

(P2Y_{1–7}; for review, see Fredholm et al., 1997). Upon heterologous expression, the cloned P2Y receptor subtypes can be discriminated by means of agonist potency series, provided care is taken to avoid degradation or interconversion of the nucleotides employed (see Harden et al., 1997). The recombinant P2Y₁ receptor, for example, is particularly sensitive to 2-methylthio ATP (MeSATP) but insensitive to UTP; it is thought to represent the ‘classical’ P_{2Y} receptors² previously identified pharmacologically in the

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² The terms P_{2Y} and P_{2X} are used here to designate native receptors that have been defined pharmacologically (see Fredholm et al., 1994), whereas P2X_n and P2Y_n refer to the molecularly defined receptor subtypes (see Fredholm et al., 1997).

guinea-pig taenia coli and in vascular endothelium (see Burnstock and Kennedy, 1985; O'Connor et al., 1991; Fredholm et al., 1994).

P₂ receptor research is impeded by the lack of specific and subtype-selective antagonists. For this reason, the recent introduction of adenosine 3'-phosphate 5'-phosphosulphate (PAPS; known as a sulphate donor in biotransformation reactions) and adenosine 3'-phosphate 5'-phosphate as selective P₂Y₁ receptor antagonists might be an important step ahead. Both compounds behaved as weak partial agonists at the P₂Y receptor of turkey erythrocytes (P₂Y₁; apparent antagonist K_d values 0.35 and 2.2 μ M, respectively), were competitive antagonists devoid of agonist activity at the recombinant human P₂Y₁ receptor expressed in 1321N1 human astrocytoma cells, and displayed no agonist or antagonist activity at recombinant P₂Y₂, P₂Y₄ and P₂Y₆ subtypes equally expressed in these cells. They did not block the turkey erythrocyte β -adrenoceptor which, like the P₂Y₁ receptor, couples to the phospholipase C cascade (Boyer et al., 1996).

The present experiments were performed in order to test the suitability of PAPS as a selective P₂Y receptor antagonist in intact tissues. Possible agonist and antagonist effects were assessed in three model tissues previously characterized in our laboratory: the guinea-pig taenia coli, the rat aorta and the rat vas deferens. In the carbachol-precontracted guinea-pig taenia coli, nucleotides cause relaxation either by activation of a P₂Y receptor, which is the site of action of adenosine 5'-O-(2-thiodiphosphate) (ADP β S), or through a receptor distinct from P₂Y and selectively activated by α,β -methylene ATP (α,β -MeATP; Dudeck et al., 1995; Windscheif et al., 1995; Bültmann et al., 1996; Lambrecht et al., 1996). In the noradrenaline-precontracted rat aorta, the endothelium-dependent relaxation caused by ADP β S is again mediated by a P₂Y receptor; UTP selectively acts on a P₂U receptor to elicit relaxation (Dainty et al., 1991; Hansmann et al., 1997). In rat vas deferens, α,β -MeATP causes contraction by activation of a P₂X receptor (Bültmann and Starke, 1994; Khakh et al., 1994, 1995); the existence of two additional contraction-mediating receptors for ATP, distinct from P₂X, has been proposed (Bültmann and Starke, 1994).

Of these native P₂ receptors, only the P₂X receptor of rat vas deferens has been cloned (P₂X₁; Valera et al., 1994). The P₂Y receptors of the guinea-pig taenia coli and rat aortic endothelium—both 'classical' P₂Y (see above)—resemble the native turkey erythrocyte and the recombinant human P₂Y₁ receptor in terms of agonist potency orders (cf. Schachter et al., 1996), but differ from each other in terms of antagonist sensitivity (see Hansmann et al., 1997). It would have been of interest to study the effects of PAPS also in a tissue with molecularly identified functional P₂Y₁ receptors. However, no such tissue is known; although a P₂Y₁ receptor has been cloned from rat ileal myocytes, a functional role of this receptor remains to be defined (Pacaud et al., 1996).

2. Materials and methods

2.1. General

Methods were those of Bültmann and Starke (1995), Dudeck et al. (1995) and Hansmann et al. (1997). Briefly, relaxations of strips of the guinea-pig taenia coli, precontracted with carbachol (50–90 nM), were elicited by PAPS, ADP β S, α,β -MeATP or noradrenaline. Relaxations of rings of the rat aorta, precontracted with noradrenaline (1 μ M), were elicited by PAPS, ADP β S, UTP or acetylcholine. Contractions of prostatic portions of the rat vas deferens were elicited by PAPS, α,β -MeATP or noradrenaline. Agents causing relaxation (taenia coli and aorta) or contraction (vas deferens) were washed out after responses had peaked. Unless stated otherwise, two or three concentration–relaxation curves (taenia coli, aorta) or concentration–contraction curves (vas deferens) were determined in each experiment. Antagonists or solvent were added after the first, or after the first and the second, curve.

Logistic curves were fitted to the weighted mean relaxation or contraction values by means of equation 25 of Waud (1976) and nonlinear regression. The calculation yielded the maximal agonist effect and the EC₅₀, i.e., the concentration producing 50% of the maximum of that curve. The shift of the second or third curve with respect to the first curve in the presence of an antagonist ('agonist concentration ratio') was read at the level of the EC₅₀ and corrected for the mean shift occurring in solvent controls. Apparent antagonist K_d values in guinea-pig taenia coli were calculated using equation 4 of Furchgott (1972).

2.2. Statistics

Data are expressed as either the arithmetic mean \pm S.E.M. or, in the case of EC₅₀ values and maximal effects, the S.E. as defined by Waud (1976). Fitted curves were tested for a significant difference according to p. 371 of Motulsky and Ransnas (1987). $P < 0.05$ was taken as the limit of statistical significance.

2.3. Materials

Reactive red 2 was synthesized in our laboratory as previously described; the identity and purity of the product was confirmed by thin layer chromatography, ¹H-nuclear magnetic resonance and infrared spectroscopy (Bültmann and Starke, 1995). Other drugs used were pyridoxalphosphate-6-azophenyl-2',5'-disulphonate tetrasodium (*iso*-PPADS; Cookson, Southampton, UK); acetylcholine chloride, adenosine 3'-phosphate 5'-phosphosulphate (PAPS), adenosine 5'-O-(2-thiodiphosphate) trilithium (ADP β S), carbachol chloride, 4,4'-diisothiocyanatostilbene-2,2'-disulphonate disodium (DIDS), α,β -methylene ATP dilitium (α,β -MeATP), (–)-noradrenaline hydrogen-(+)-

tartrate, UTP trisodium (Sigma). Compounds were dissolved in distilled water or medium.

3. Results

3.1. Relaxation of guinea-pig taenia coli

When added during the plateau of the contraction elicited by carbachol (50–90 nM; force of contraction 74 mN on average), PAPS elicited rapid, transient relaxation of the guinea-pig taenia coli (EC_{50} $3.3 \pm 0.1 \mu\text{M}$; maximal relaxation $101 \pm 1\%$; $n = 14$; empty circles in Fig. 1). In order to characterize the relaxation-mediating receptor, interactions of 4,4'-diisothiocyanatostilbene-2,2'-disulphonate (DIDS; Dudeck et al., 1995) and reactive red 2 (Bültmann and Starke, 1995) with PAPS were assessed. A second concentration–relaxation curve of PAPS, after ad-

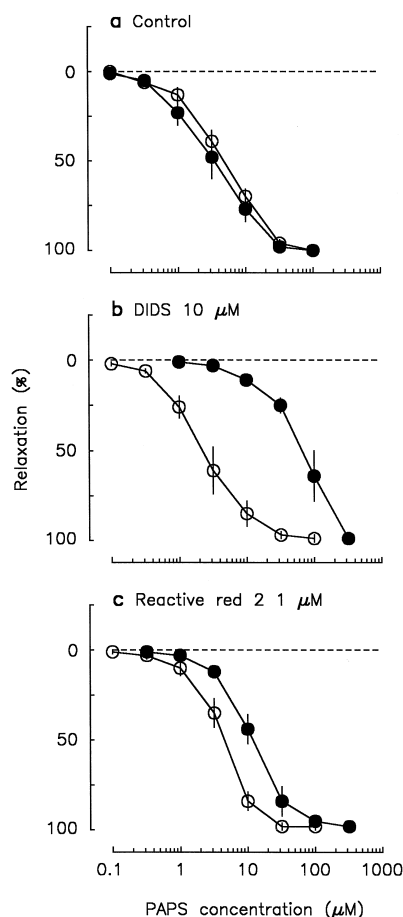


Fig. 1. Guinea-pig taenia coli: relaxation by PAPS and interaction with DIDS and reactive red 2. Carbachol was added every 15 min. Increasing concentrations of PAPS were added with each successive carbachol dose. Two concentration–response curves were determined in each tissue. Solvent (a), DIDS (10 μM ; (b)) or reactive red 2 (1 μM ; (c)) was added after completion of the first curve (○) and the second curve (●) was determined 60 min later. Abscissae show concentration of PAPS; ordinates show relaxation as a percentage of the respective response to carbachol. Means \pm S.E.M. from four experiments.

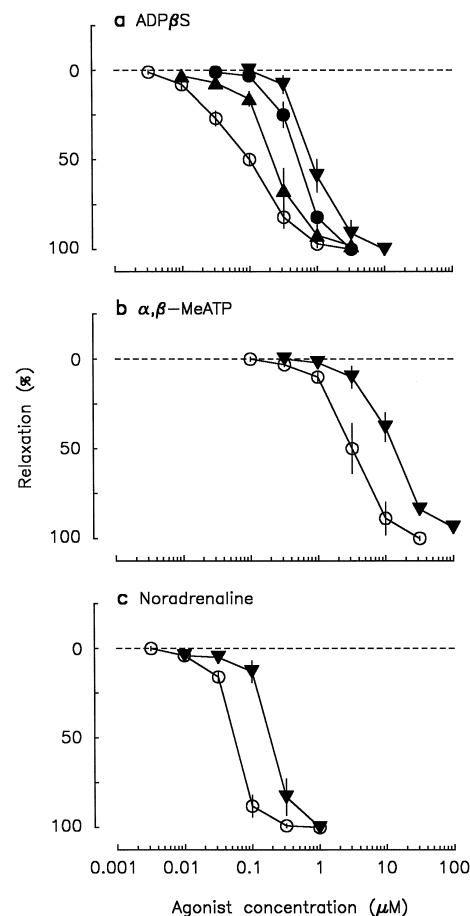


Fig. 2. Guinea-pig taenia coli: effect of PAPS on nucleotide- and noradrenaline-evoked relaxations. Carbachol was added every 15 min. Increasing concentrations of ADP β S (a), α,β -MeATP (b) or noradrenaline (c) were added with each successive carbachol dose. Two concentration–response curves were determined in each tissue. Solvent (○) or PAPS (10 μM \blacktriangle ; 32 μM \bullet ; 100 μM \blacktriangledown) was added after completion of the first curve and the second curve was determined 60 min later. Abscissae show agonist concentration; ordinates show relaxation in second concentration–response curves as a percentage of the respective response to carbachol. Means \pm S.E.M. from three to eight experiments.

dition of solvent (water), was close to the first (Fig. 1a). DIDS (10 μM) and reactive red 2 (1 μM) shifted the curve to the right without changing the maximum (Fig. 1b and c), yielding apparent antagonist K_d values of 0.27 and 0.29 μM , respectively. DIDS (100 μM) abolished the relaxation caused by PAPS over the entire range of concentrations studied ($n = 2$; not shown).

In order to test a possible antagonist effect of PAPS, two concentration–relaxation curves of ADP β S (acting through P_{2Y} receptors), α,β -MeATP (acting through the separate α,β -MeATP-receptors) or noradrenaline (acting through α_1 -adrenoceptors; Den Hertog et al., 1984) were determined in each taenia coli strip (cf. Bültmann and Starke, 1995). In the first curve, the EC_{50} (and maximal percentage relaxation) values were 103 ± 17 nM ($101 \pm 3\%$) for ADP β S ($n = 20$), $2.2 \pm 0.3 \mu\text{M}$ ($104 \pm 4\%$) for α,β -MeATP ($n = 7$) and 45 ± 1 nM ($100 \pm 1\%$) for nor-

Table 1

Potency of adenosine 3'-phosphate 5'-phosphosulphate (PAPS) at antagonizing effects of various agonists

Tissue	Agonist	Response	Receptor	Agonist concentration ratio in experiments with PAPS		
				10 μ M	32 μ M	100 μ M
Guinea-pig taenia coli	ADP β S	Relaxation	P _{2Y} receptor	3.2	4.8	9.6
	α , β -MeATP	Relaxation	α , β -MeATP receptor			4.8
	Noradrenaline	Relaxation	α_1 -adrenoceptor			3.7
Rat aorta	ADP β S	Relaxation	P _{2Y} receptor	3.5 ^a		3.9 ^a
	UTP	Relaxation	P _{2U} receptor	0.9		4.2
	Acetylcholine	Relaxation	Muscarine receptor	1.6		2.7 ^a
Rat vas deferens	α , β -MeATP	Contraction	P _{2X} receptor	1.3		3.8 ^a
	Noradrenaline	Contraction	α_1 -adrenoceptor			1.2

The potency of PAPS is expressed in terms of the agonist concentration ratio, i.e., the ratio of the agonist EC₅₀ in the presence of the concentration of PAPS indicated over the EC₅₀ in the absence of PAPS. From the experiments of Fig. 2, Fig. 4 and Fig. 5 and from the noradrenaline experiments in rat vas deferens mentioned in the text.

^aMaximum of concentration–response curve reduced in presence of PAPS.

adrenaline ($n = 7$). For either agonist, a second curve, after addition of solvent (water), was close to the first ($n = 3$ to 8; not shown).

PAPS (10, 32 or 100 μ M), when added after completion of the first concentration–response curve of ADP β S, α , β -MeATP or noradrenaline, did not change the tension of the (non-precontracted) taenia coli and also did not change subsequent contractions elicited by carbachol. PAPS (10, 32 and 100 μ M) shifted the concentration–relaxation curve of ADP β S progressively to the right without changing the maximum (Fig. 2a). The degree of the shift—i.e., the ADP β S concentration ratio—increased with the concentration of PAPS (Table 1). The increase was less, however, than expected from the relationship between antagonist concentration and agonist concentration ratio for the case of competitive antagonism (equation 3 of Furchgott, 1972). In consequence, the apparent antagonist K_d values calculated from the shift increased with the concentration of PAPS (4.6, 8.4 and 11.6 μ M, respectively), indicating deviation from competitive kinetics, as in the case of many P2 antagonists (see Bültmann et al., 1996). PAPS (100 μ M) also shifted the concentration–relaxation curve of α , β -MeATP and noradrenaline to the right (Fig. 2b and c). As shown by the ensuing concentration ratios, its potency against α , β -MeATP and noradrenaline was hardly less than against ADP β S (Table 1).

3.2. Relaxation of rat aorta

When added during the plateau of the contraction elicited by noradrenaline (1 μ M; force of contraction 5.0 mN on average), PAPS elicited weak relaxation of the rat aorta (EC₅₀ 24.7 \pm 4.0 μ M; maximal relaxation 36 \pm 2%; $n = 7$; empty circles in Fig. 3). In order to characterize the receptor involved, the interaction of pyridoxalphosphate-6-azophenyl-2',5'-disulphonate (*iso*-PPADS; Hansmann et al., 1997) with PAPS was examined. A second concentra-

tion-relaxation curve of PAPS, after addition of solvent (water), was close to the first (Fig. 3a). *iso*-PPADS (1 μ M) greatly reduced the relaxation caused by PAPS (Fig. 3b).

In order to test a possible antagonist effect of PAPS, three concentration–relaxation curves of ADP β S (acting through P_{2Y} receptors), UTP (acting through P_{2U} receptors) or acetylcholine (acting through muscarine receptors)

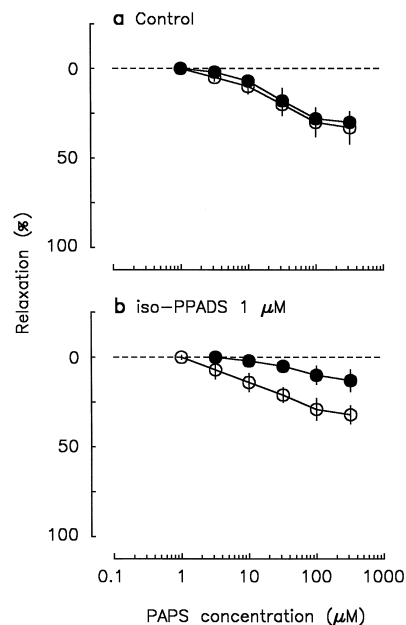


Fig. 3. Rat aorta: relaxation by PAPS and interaction with *iso*-PPADS. Noradrenaline (1 μ M) was added to the medium twice, interval 60 min. PAPS was administered in a cumulative fashion during the plateau of each response to noradrenaline. Solvent (a) or *iso*-PPADS (1 μ M; (b)) was added immediately after the first PAPS concentration–relaxation curve, i.e., about 50 min before the second concentration–relaxation curve. Abscissae show concentration of PAPS; ordinates show relaxation in first (○) and second (●) curves as a percentage of the respective response to noradrenaline. Means \pm S.E.M. from four experiments.

were determined in each aortic ring (cf. Hansmann et al., 1997). In the first curve, the EC_{50} (and maximal percentage relaxation) values were $0.48 \pm 0.02 \mu\text{M}$ ($87 \pm 1\%$) for ADP βS ($n = 12$), $1.2 \pm 0.2 \mu\text{M}$ ($70 \pm 4\%$) for UTP ($n = 10$) and $36 \pm 2 \text{ nM}$ ($97 \pm 1\%$) for acetylcholine ($n = 11$). For either agonist, a second and third curve, after addition of solvent (water), was close to the first ($n = 5$ to 7; not shown).

PAPS (10 or 100 μM), when added after completion of the first concentration–response curve of ADP βS , UTP or acetylcholine, did not change the tension of the (non-pre-contracted) aorta and also did not change subsequent contractions elicited by noradrenaline. PAPS (10 and 100 μM) shifted the concentration–relaxation curve of ADP βS to the right and progressively decreased the maximum (Fig. 4a; Table 1). PAPS (10 μM) did not alter the

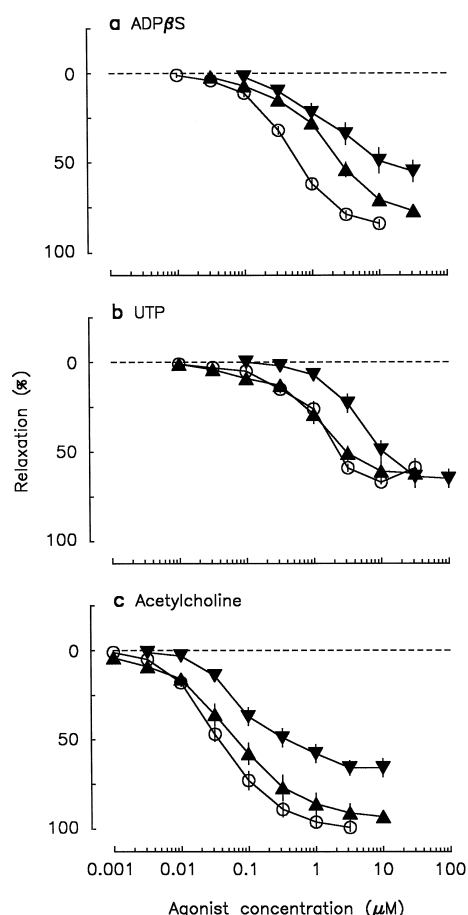


Fig. 4. Rat aorta: effect of PAPS on nucleotide- and acetylcholine-evoked relaxations. Noradrenaline (1 μM) was added to the medium three times, interval 60 min. ADP βS (a), UTP (b) or acetylcholine (c) was administered in a cumulative fashion during the plateau of each response to noradrenaline. PAPS was added at two increasing concentrations immediately after the first and second nucleotide or acetylcholine concentration–relaxation curve, i.e., about 50 min before the second and third concentration–relaxation curve. Abscissae show agonist concentration; ordinates show relaxation in first curves (○), and second and third curves in the presence of PAPS (10 μM ▲; 100 μM ▼), as a percentage of the respective response to noradrenaline. Means \pm S.E.M. from four to seven experiments.

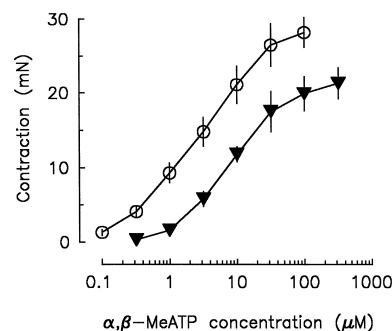


Fig. 5. Rat vas deferens: effect of PAPS on α,β -MeATP-evoked contractions. Increasing concentrations of α,β -MeATP were added every 15 min and washed out immediately after the contraction had peaked. Two concentration–response curves were determined in each tissue. Solvent (○) or PAPS (100 μM ▼) was added after completion of the first curve and the second curve was determined 120 min later. Abscissae, concentration of α,β -MeATP. Ordinates show contraction (mN) in second curves. Means \pm S.E.M. from three to five experiments.

concentration–relaxation curves of UTP (Fig. 4b) and acetylcholine (Fig. 4c) but PAPS (100 μM) shifted either curve to the right and, in the case of acetylcholine, also decreased the maximum (Fig. 4b and c). As in the guinea-pig taenia coli, the concentration ratios indicate that PAPS did not differentiate well between UTP, acetylcholine and ADP βS (Table 1).

3.3. Contraction of rat vas deferens

PAPS (100 μM) elicited small, transient contractions of the rat vas deferens ($0.6 \pm 0.3 \text{ mN}$; $n = 3$); lower concentrations were without effect. Because of its small size, the response was not investigated further.

In order to test a possible antagonist effect of PAPS, two concentration–contraction curves of α,β -MeATP (acting through P_{2X} receptors) and noradrenaline (acting through α_1 -adrenoceptors) were determined in each vas deferens (cf. Bültmann and Starke, 1995). In the first curve, the EC_{50} value (and maximal contraction) was $2.9 \pm 0.7 \mu\text{M}$ ($24.9 \pm 1.4 \text{ mN}$) for α,β -MeATP ($n = 12$) and $4.9 \pm 0.8 \mu\text{M}$ ($23.3 \pm 0.9 \text{ mN}$) for noradrenaline ($n = 6$). For either agonist, a second curve, after addition of solvent (water), was close to the first ($n = 5$ and 3; not shown).

PAPS (10 μM) did not alter the concentration–contraction curve of α,β -MeATP ($n = 3$; not shown). PAPS (100 μM) shifted the curve to the right and decreased the maximum (Fig. 5; Table 1). PAPS (100 μM) did not alter contractions elicited by noradrenaline ($n = 3$; not shown).

4. Discussion

4.1. Guinea-pig taenia coli

In the guinea-pig taenia coli, PAPS elicited prominent relaxation that was attenuated by the P_2 receptor antago-

nists DIDS and reactive red 2 (Fig. 1). The apparent K_d value of DIDS against PAPS (0.27 μM) is close to its K_d against α, β -MeATP (0.7 μM) but much lower than its K_d against ADP β S in the taenia coli (70.1 μM ; Dudeck et al., 1995). The apparent K_d of reactive red 2 against PAPS (0.29 μM) also is close to its K_d against α, β -MeATP (1.6 μM) in the taenia but, in this case, considerably higher than the K_d against ADP β S (0.028 μM ; Bültmann and Starke, 1995). Apparently, PAPS activates the P2 receptor which is also the site of action of α, β -MeATP to cause relaxation of the taenia coli (cf. Bültmann and Starke, 1995; Dudeck et al., 1995; Windscheif et al., 1995; Bültmann et al., 1996). There is no evidence for an agonist action at the P_{2Y} receptor, the site of action of ADP β S.

When tested as an antagonist, PAPS attenuated relaxations of the taenia coli caused by ADP β S (mediated by P_{2Y} receptors), α, β -MeATP (mediated by the separate α, β -MeATP receptors) or noradrenaline (mediated by α_1 -adrenoceptors; Fig. 2; Table 1). PAPS, hence, displays little, if any, P_{2Y} selectivity in the guinea-pig taenia coli. The noncompetitive (Fig. 2a; Table 1) inhibitory effect against ADP β S may result from P_{2Y} receptor blockade (see Introduction) but may also be due to heterologous desensitization following activation of the separate α, β -MeATP receptor. The apparent antagonism against α, β -MeATP and noradrenaline possibly results from homologous and heterologous desensitization, respectively. In fact, α, β -MeATP itself attenuates the hyperpolarization of the taenia coli produced by noradrenaline (Den Hertog and van den Akker, 1986).

4.2. Rat aorta

In rat aorta, PAPS elicited weak relaxation that was attenuated by the P2 antagonist *iso*-PPADS (Fig. 3). *iso*-PPADS, at a concentration of 1 μM , antagonizes the P_{2Y} receptor-mediated relaxation of the rat aorta caused by ADP β S (and MeSATP) but does not alter the P_{2U} receptor-mediated relaxation caused by UTP (and ATP; Hansmann et al., 1997). Apparently, PAPS activates the (endothelial) P_{2Y} receptors to cause relaxation of rat aorta. Compared to ADP β S (Fig. 4a), PAPS behaves as a partial agonist at this receptor.

When tested as an antagonist, PAPS attenuated relaxations of the aorta caused by ADP β S (mediated by P_{2Y} receptors), UTP (mediated by P_{2U} receptors) or acetylcholine (mediated by muscarine receptors; Fig. 4; Table 1). PAPS, hence, displays little, if any, P_{2Y} selectivity in the rat aorta. The noncompetitive (Fig. 4a) effect against ADP β S is probably due to the partial agonist action of PAPS at the P_{2Y} receptor, resulting in either blockade or homologous desensitization. The mechanism underlying the apparent antagonism against UTP and acetylcholine is uncertain. It is not due to heterologous desensitization, as preincubation with MeSATP, an agonist with high intrinsic

activity at the P_{2Y} receptor, does not alter the relaxation of the rat aorta caused by UTP (Dainty et al., 1991; Hansmann et al., 1997) and acetylcholine (G. Hansmann and R. Bültmann, unpublished observation).

4.3. Rat vas deferens

In rat vas deferens, PAPS elicited very small contractions. Its mechanism of action was not investigated in detail.

When tested as an antagonist, PAPS attenuated contractions of the vas deferens elicited by α, β -MeATP (mediated by P_{2X} receptors; Fig. 5) but did not alter the response to noradrenaline (mediated by α_1 -adrenoceptors). PAPS, hence, displays a certain degree of selectivity for the P_{2X} receptor in rat vas deferens (Table 1). The noncompetitive (Fig. 5) effect against α, β -MeATP may result from blockade of the P_{2X} receptor, but also from homologous desensitization if one assumes that the small contraction caused by PAPS was due to P_{2X} receptor activation. As shown by the concentration ratios obtained in the presence of 100 μM PAPS (Table 1), PAPS was about as effective against α, β -MeATP in rat vas deferens as it was against relaxation-producing agonists in guinea-pig taenia coli and rat aorta.

5. Conclusion

Although evidence was obtained for a possible partial agonist or antagonist activity of PAPS at native P_{2Y} receptors, the nucleotide is at best slightly selective for this subtype. Most prominently, it acts as an agonist at the P2 receptor activated by α, β -MeATP in the guinea-pig taenia coli. In addition, it blocks (or desensitizes) the P_{2X} receptor of rat vas deferens and blocks non-P2 receptor effects in guinea-pig taenia coli and rat aorta. Taken together, these findings question the suitability of PAPS as a P_{2Y} receptor antagonist in intact tissues.

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