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Effect of antiproliferative agents on vascular function in normal and in vitro balloon-injured porcine coronary arteries

Simon Kennedy*, Roger M. Wadsworth, Cherry L. Wainwright

Department of Physiology and Pharmacology, Strathclyde Institute of Biological Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, Scotland, UK

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Abstract

Local infusion of antiproliferative agents following coronary balloon angioplasty is used in vivo. This study examined the effects of the antiproliferative agents paclitaxel (5-β, 20-Epoxy-1,2-α,4,7-β,10-β,13-α-Hexahydroxy-Tax-11-en-9-one 4,10-Diacetate 2_Benzoate 13-Ester with (2*R*,3*S*)-*N*-Benzoyl-3-Phenylisoserine; 10 and 50 μM), farnesyl protein transferase inhibitor III (FPT III, (*E*,*E*)-2-[2-Oxo-2-[(3,7,11-trimethyl-2,6,10-dodecatrienyl) oxy] amino] ethyl] phosphonic acid, (2,2-dimethyl-1-oxopropoxy) methyl ester, sodium); 10 and 25 μM), perillyl alcohol (4-isopropenyl-cyclohexenecarbinol; 1 and 2 mM) and Van 10/4 (Decahydro-1,1,4,7-tetramethyl-1*H*-cycloprop[*e*]azulen-4-*o*-[2-(3-methylpent-2-enoyl)-fucopyranoside]; 10 and 25 μM) on normal and in vitro balloon-injured porcine coronary arteries. Short-term (30 min) incubation had no effect on contraction or relaxation. Overnight incubation with 25 μM Van 10/4-attenuated contraction while perillyl alcohol abolished contractility completely. Endothelium-dependent relaxation was significantly attenuated by the higher concentration of paclitaxel, FPT III and Van 10/4. Stretch injury significantly enhanced sensitivity to 3-morpholinosydnonimine (SIN-1) while attenuating relaxation to calcimycin. Drug incubation (15 min) had no effect on these responses. In conclusion, paclitaxel, FPT III and Van 10/4 have no detrimental effects on vascular function after short-term administration to normal or stretch-injured arteries.

Keywords: Vascular contraction; Vascular relaxation; Balloon injury; Antiproliferative; Restenosis

1. Introduction

Balloon angioplasty is a commonly used technique to widen arteries narrowed by atherosclerotic disease. The principal problem associated with balloon angioplasty is that of restenosis, complicating an estimated 30% of procedures (De Feyter et al., 1999). Restenosis is a complex process that is primarily caused by a combination of arterial remodelling and smooth muscle cell migration and proliferation to form a fibrocellular neointima (Newby, 2000). Introduction of stent technology has had a beneficial effect on the incidence of restenosis, however, stenting is not suitable in all cases, and around 25% of all patients still undergo simple balloon angioplasty (Timmis, 1999). The importance of smooth muscle cell proliferation in restenosis has resulted in interest in using antiproliferative agents to limit development of neointima. Such drugs can be delivered locally to the site of balloon injury, and published studies have shown this approach to be effective in reducing neointimal formation in the pig coronary (Work et al., 2001) and carotid arteries (Herdeg et al., 2000) and the carotid arteries of rabbits (Oberhoff et al., 2000) and rats (Signore et al., 2001). Antiproliferative agents have also been effective in reducing restenosis when delivered via implanted stents in pig coronary arteries (Heldman et al., 2001; Hong et al., 2001) and rabbit iliac arteries (Drachman et al., 2000). However, it is unclear what effect local drug delivery of antiproliferative agents has on vascular reactivity.

Another important determinant of restenosis is arterial remodelling (Pasterkamp et al., 2000). A contributory factor in remodelling may be changes in vascular reactivity, which have been shown to occur early after injury (Wilensky et al., 1995; Merhi et al., 1995). Local administration of drugs to the coronary artery immediately after injury may influence vessel reactivity initially and ultimately modify the response to injury which culminates in restenosis. Hence, the vascular effects of agents delivered to the coronary artery are of

* Corresponding author. Tel.: +44-141-548-2505; fax: +44-141-552-2562.
E-mail address: simon.kennedy@strath.ac.uk (S. Kennedy).

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crucial importance. In a previous study, arteries removed 28 days after injury and local drug delivery of a farnesyl protein transferase inhibitor (FPT III, (*E*,*E*)-2-[2-Oxo-2-[(3,7,11-trimethyl-2,6,10-dodecatrienyl) oxy] amino] ethyl] phosphonic acid, (2,2-dimethyl-1-oxopropoxy) methyl ester, sodium) showed no deterioration in vascular contraction and relaxation (Work et al., 2001). However, other studies using paclitaxel (5-β, 20-Epoxy-1,2-α,4,7-β,10-β,13-α-Hexahydroxy-Tax-11-en-9-one 4,10-Diacetate 2_Benzoate 13-Ester with (2*R*,3*S*)-*N*-Benzoyl-3-Phenylisoserine) have shown vessel enlargement and major impairment of vessel contractility (Axel et al., 1997; Herdeg et al., 2000).

In vitro studies using the microtubule-stabilising drug paclitaxel have shown reduced vessel contractility in rat aorta (Sauro et al., 1995) and enhanced contractility in human arteries and veins (Gomez-Alvis et al., 2000), while another study using rat aorta found no change in contractility (Zhang et al., 2000). The in vitro vascular effects of the three other antiproliferative agents used in the current study do not appear to have been tested. FPT III prevents membrane adherence of the G-protein $p21^{ras}$, an essential step in the activation of mitogen-activated protein kinase (MAP-kinase). Although FPT III inhibits vascular smooth muscle cell proliferation and migration in vitro (Kouchi et al., 1999; Cohen et al., 1999), its effects on vessel function are unknown. Perillyl alcohol (4-isopropenyl-cyclohexene-carbinol), which inhibits the enzyme geranylgeranyl transferase at mM concentrations, induces apoptosis of human vascular smooth muscle cells (Unlu et al., 2000) and reduces intimal hyperplasia of vein grafts in rabbits (Fulton et al., 1997). The vascular effects of Van 10/4 (Decahydro-1,1,4,7-tetramethyl-1*H*-cycloprop[*e*]azulen-4-*o*-[2-(3-methylpent-2-enoyl)-fucopyranoside]), a compound isolated from *Calendula officinalis*, were also studied. This compound has been shown to reduce [^{3}H]-thymidine incorporation in porcine coronary artery smooth muscle cells (Kennedy et al., 2002a), but its effects on vascular function are unknown.

Due to the importance of vascular function early after injury and the current trend in using local drug delivery experimentally to reduce restenosis, the aim of this study was to measure the effect of antiproliferative agents on vascular contractility and relaxation in porcine coronary arteries. In addition, to mimic the effects of local infusion in vivo, antiproliferative agents were added to coronary arteries immediately following in vitro balloon injury and the effect on vascular function measured.

2. Materials and methods

2.1. Coronary artery preparation

Porcine hearts were obtained from a local abbatoir. The left anterior descending (LAD) coronary artery and, in experiments involving in vitro balloon injury, the left circumflex (LCx) artery were rapidly dissected and placed in aerated Krebs solution. Arteries were cleaned of surrounding fat and connective tissue and cut into rings of 3–4 mm diameter. The proximal portion of each artery was used, with the first 0.5 cm length of artery discarded. Arteries used in all experiments were placed in calcium-free Krebs solution and stored overnight at 4 °C. For functional experiments, artery rings were suspended between two parallel stainless-steel wires, one fixed and the other connected to an isometric transducer (FT03 Grass Instrument Division, RI, USA), in a 10-ml organ bath containing Krebs solution (37 °C) of the following composition (mM): NaCl 118.3, $NaHCO_3$ 25, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO4 1.2 and glucose 11.1. Coronary artery rings were placed under an optimum resting force of 4 g, determined by increasing the resting force on the artery and performing a dose–response study to KCl (Work et al., 2001), and were allowed to equilibrate for 1 h. All rings were subjected to repeated exposure to 40 mM KCl to ensure adequate contractility before commencing the experimental protocol. In all experimental protocols, arteries were contracted with either 5-hydroxytryptamine (5-HT, 10^{-6} M), or the thromboxane mimetic 9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin $F_{2\alpha}$ (U46619; 5×10^{-7} M). These concentrations of contractile agents were chosen on the basis of previous studies using 5-HT (Work et al., 2001) and U46619 (Ren et al., 2001) in the pig coronary artery. Once the level of contraction had stabilised, relaxation to cumulative addition of the endothelium-dependent vasodilator calcimycin (10^{-9} to 10^{-5} M) and the endothelium-independent vasodilator 3-morpholinosydnonimine (SIN-1; 10^{-9} to 10^{-5} M) was measured. We have previously demonstrated the endothelium dependence of calcimycin in endothelium denuded and N^{ω}-nitro-L-arginine treated arteries (unpublished data).

2.2. Drug incubation

The effect of short-term (30 min) and long-term (overnight) drug incubation was tested. For short-term incubation, left anterior descending coronary artery rings were mounted in organ baths, equilibrated and sensitised by two additions of 40 mM KCl. Drug was then added for 30 min prior to contraction of the ring with 5-HT (10^{-6} M). Once the contraction had stabilised, endothelium-dependent relaxation was measured by cumulative addition of calcimycin (10^{-9} to 10^{-6} M). Concentrations of drugs used in all experiments were those that were shown to significantly reduce [^{3}H]-thymidine incorporation in cultured porcine coronary artery smooth muscle cells (Work et al., 2001; Kennedy et al., 2002a). In experiments involving overnight drug incubation, fresh left anterior descending coronary artery rings were dissected and placed in individual wells of a 12-well culture plate with each well containing 5 ml of Krebs solution with or without drug. The plate was stored at 4 °C overnight and rings used the next day. Rings were then mounted as normal and the requisite concentration of drug

Table 1
Effect of 30-min drug incubation on endothelium-dependent relaxation to calcimycin in porcine LAD coronary artery

	Control (% maximum relaxation)	+Drug (% maximum relaxation)	
		Low concentration	High concentration
Paclitaxel	77.9 ± 6.1	86.4 ± 7.4	87.7 ± 5.7
FPT III	94.6 ± 4.1	102.4 ± 1.2	100.1 ± 2.7
Van 10/4	104.7 ± 2.9	98.6 ± 6.4	95.7 ± 7.8
Perillyl alcohol	104.5 ± 2.6	102.9 ± 3.7	96.6 ± 5.9

Figures shown are maximum relaxation induced by cumulative addition of calcimycin. Low concentration of drug was 10 μM for paclitaxel, FPT III and Van 10/4 and 1 mM for perillyl alcohol. High concentration was 50 μM for paclitaxel, 25 μM for FPT III and Van 10/4 and 2 mM for perillyl alcohol. $n=6$ for all groups; no differences in relaxation compared to control were found.

was maintained throughout the measurement of contraction and endothelium-dependent relaxation.

2.3. In vitro injury

Roughly dissected left anterior descending and left circumflex arteries which had been stored overnight at 4 °C were cleaned of surrounding fat and connective tissue and pinned to the surface of a Sylgard-coated petri dish containing Krebs solution. A 3.5-mm balloon angioplasty catheter was advanced down the length of the left anterior descending artery to injure the target section of the artery (0.5 cm distant from the bifurcation point). Stretch injury was induced by inflating the balloon three times to a pressure of 10 atm for 30 s with 1 min between inflations. The left anterior descending artery and non-injured left circumflex artery were immediately sectioned into rings and mounted in 10-ml organ baths. A resting force of 4 g was applied, and drug was added to non-injured and injured rings for 15 min. After 15 min, all rings were washed to remove drug, equilibrated for a further 45 min, sensitised using 40 mM KCl and contracted with 5×10^{-7} M U46619. Relaxation to calcimycin and SIN-1 was measured in both drug-treated and non-drug-treated left circumflex artery rings and in drug-treated and non-drug-treated left anterior descending artery rings. This allowed the effects of both in vitro injury alone and injury combined with drug incubation on vascular contraction and relaxation to be studied. An incubation period of 15 min was chosen since this is the infusion time employed when these drugs have been administered locally to the coronary artery after balloon injury in vivo (Work et al., 2001; Kennedy et al., 2002b).

2.4. Drugs

The following drugs were used in this study: FPT III was used at concentrations of 10 and 25 μM, paclitaxel was used at concentrations of 10 and 50 μM, Van 10/4 was used at 10 and 25 μM and perillyl alcohol was used at 1 and 2 mM. All drugs were prepared as a stock solution in dimethyl sulphoxide (DMSO) (10^{-2} M for paclitaxel, FPT III and Van10/4 and 1 M for perillyl alcohol) and added directly to the tissue. In all experiments, an equivalent volume of DMSO was added to control rings.

2.5. Materials

Calcimycin, U46619 and (*S*)-(−)-perillyl alcohol were obtained from Sigma-Aldrich, Poole, Dorset, UK. Paclitaxel was from ICN Pharmaceuticals, Basingstoke, UK. FPT III and SIN-1 were both obtained from CN Biosciences, Nottingham, UK. Van 10/4 was synthesized by Dextra Laboratories, Reading, Berkshire.

2.6. Statistics

All results are shown as mean ± S.E.M., where n is the number of hearts used. Data on vascular contraction is presented as absolute values (g) and data for relaxations to calcimycin and SIN-1 are presented as percentage loss of the initial contractile force induced by 5-HT or U46619. Two-way analysis of variance (ANOVA) was used to compare relaxation curves in control and drug-treated arteries and non-injured left circumflex coronary arteries vs. left anterior descending coronary arteries injured in vitro. Contractions in control vs. drug-treated arteries were compared using a Student's paired t test. EC_{50} values were obtained by fitting the Hill equation to the mean curve and maximum relaxation was taken from

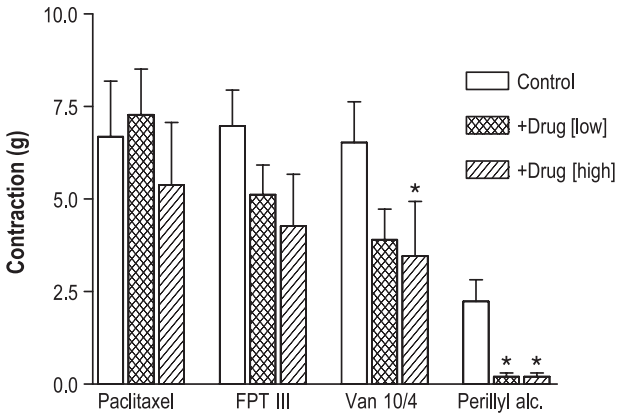

Fig. 1. Effect of overnight drug incubation of porcine coronary artery rings on vascular contractility to 5×10^{-7} M U46619 (for paclitaxel, FPT III and Van 10/4) or 10^{-6} M 5-HT (for perillyl alcohol). Drugs were added at low concentration (10 μM for paclitaxel, FPT III and Van 10/4 and 1 mM for perillyl alcohol) and high concentration (50 μM for paclitaxel, 25 μM for FPT III and Van 10/4 and 2 mM for perillyl alcohol). Perillyl alcohol totally abolished the contraction to 5-HT at both concentrations. $n=5$ for all drugs; $^*P<0.05$ compared to control value.

the mean curve. In all cases, a P value <0.05 was taken to indicate statistical significance.

3. Results

3.1. Short-term drug incubation

Short-term (30 min) incubation with paclitaxel (10 and 50 μM), FPT III (10 and 25 μM) and Van 10/4 (10 and 25 μM) had very little effect on vascular function. Neither concentration of any of the three drugs significantly affected contraction to 5-HT compared to control (data not shown). However, both concentrations of perillyl alcohol (1 and 2 mM) totally abolished contraction to 5-HT. Extensive washing of the artery rings with Krebs solution to remove the perillyl alcohol only resulted in a partial restoration of the contraction. Endothelium-dependent relaxation to calcimycin was not significantly affected following 30 min of drug incubation with paclitaxel, FPT III or Van 10/4 (Table 1). After washing to remove perillyl alcohol, the artery was relaxed by cumulative addition of calcimycin to the same extent as control arteries (Table 1).

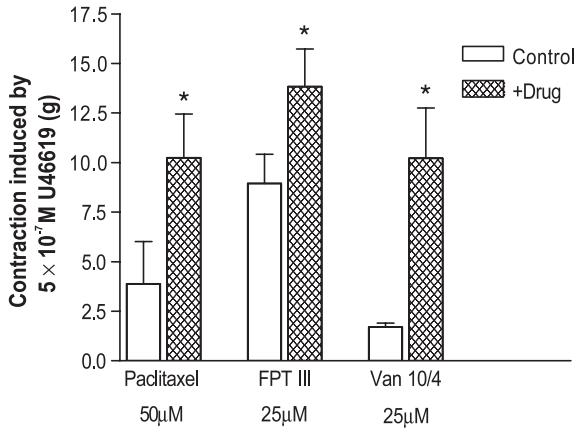

Fig. 3. Enhanced contraction induced by in vitro injury in porcine LAD rings was unaffected by incubation with drugs. Control value represents contraction to U46619 in non-injured LCx artery. The LAD was injured by balloon inflation and incubated with drug at the indicated concentration for 15 min. $n=6$ for all drugs; $^{*}P<0.05$ vs. corresponding control value.

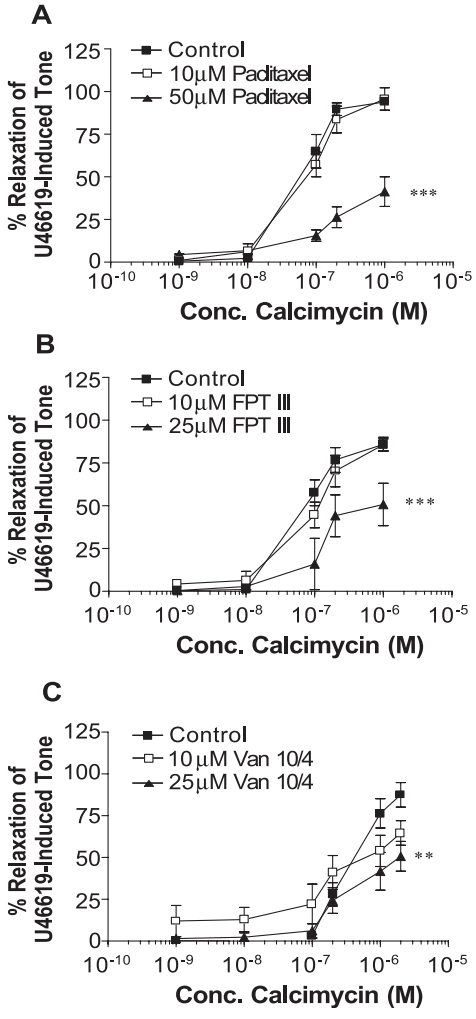

Fig. 2. Endothelium-dependent relaxation to calcimycin in control LAD rings and rings incubated overnight with paclitaxel (A), FPT III (B) and Van 10/4(C). Data presented as % loss of U46619-induced tone. $n=5$ for all drugs; $^{**}P=0.03$, $^{***}P=0.0002$ vs. control curve in absence of drug.

3.2. Long-term drug incubation

Overnight incubation with paclitaxel and FPT III had no effect on U46619-induced contraction (Fig. 1), while the higher concentration of Van 10/4 (25 μM) significantly reduced vascular contractility. Compared to control vessels contracted with 5-HT, vessels incubated overnight with either 1 or 2 mM perillyl alcohol could not be contracted by addition of 5-HT, KCl or U46619 (Fig. 1). The lower concentration of paclitaxel, FPT III and Van 10/4 had no significant effect on endothelium-dependent relaxation (Fig. 2A–C), but the higher concentration of all three drugs significantly attenuated relaxation to calcimycin (Fig. 2A–C). Since no contraction could be elicited in rings treated

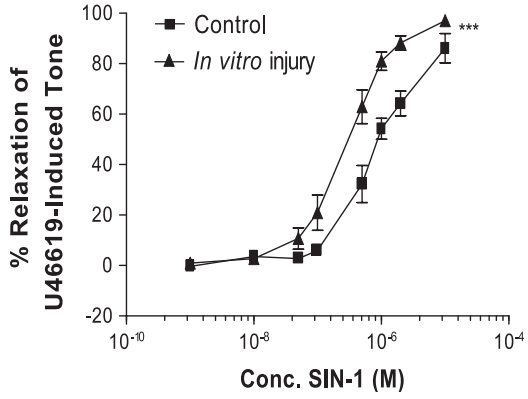

Fig. 4. Increased sensitivity to relaxation induced by SIN-1 after in vitro balloon injury. Control represents relaxation in the LCx artery, in vitro injury was performed in the LAD artery. $^{***}P<0.0001$ vs. control curve.

Table 2
Relaxation to SIN-1 in control porcine LCx and LAD coronary artery rings subjected to in vitro stretch injury

	LCx		LAD	
	% Maximum relaxation	EC_{50}	% Maximum relaxation	EC_{50}
Control (no drug)	86.2 ± 5.8	1.245	97.0 ± 1.5	1.036
Paclitaxel (50 μM)	74.4 ± 10.9	1.272	92.6 ± 3.8	1.093
FPT III (25 μM)	67.6 ± 6.8	1.393	92.9 ± 2.2	1.069
Van 10/4 (25 μM)	50.5 ± 8.8	1.516	66.8 ± 7.6	1.484

Figures are maximum relaxation to cumulative addition of SIN-1 and the log EC_{50} value for the dose–response curve. $n = 6$ for all groups.

overnight with perillyl alcohol, endothelium-dependent relaxation could not be measured.

3.3. In vitro injury

Left anterior descending coronary rings subjected to stretch injury in vitro without drug incubation demonstrated a significantly enhanced contraction to U46619 compared to non-injured left circumflex coronary rings (contraction was 7.4 ± 1.9 g in LCx vs. 13.6 ± 1.4 g in LAD; $n = 6$; $P < 0.05$). To rule out an effect of differences in contractility between left anterior descending and left circumflex coronary rings, the contraction in injured LAD rings was compared to non-injured rings from the same artery and contraction to U46619 was still significantly enhanced (5.7 ± 2.3 g in control LAD vs. 10.9 ± 2.5 g in injured LAD; $n = 6$; $P < 0.05$). Incubation of the injured artery with paclitaxel (50 μM), FPT III (25 μM) or Van 10/4 (25 μM) for 15 min immediately after stretch injury did not affect the enhanced contraction to U46619 (Fig. 3). Stretch injury attenuated endothelium-dependent relaxation to calcimycin compared to non-injured left circumflex coronary rings (maximum relaxation was 96.6 ± 1.8% in LCx rings vs. 61.5 ± 6.2% in injured rings; $n = 6$; $P < 0.05$). In rings treated with drug for 15 min after injury, the relaxation response to calcimycin remained significantly attenuated (maximum relaxation was 32.3 ± 14.1% with paclitaxel treatment, 21.2 ± 8.8% after FPT III treatment and 25.6 ± 12.3% after Van 10/4 treatment; $n = 6$, $P < 0.05$ compared to respective LCx ring from each group). In contrast, relaxation to the endothelium-independent vasodilator SIN-1 was enhanced in artery rings that had undergone stretch injury. Maximal relaxation to SIN-1 was unchanged, but the concentration–response curve was shifted to the left in injured vessels (Fig. 4). Incubation of the injured artery with paclitaxel, FPT III or Van 10/4 did not influence the increase in sensitivity of the injured vessel to SIN-1 (Table 2).

4. Discussion

In this study, the effect of four different antiproliferative agents on vascular function was tested. In addition, the changes induced following in vitro stretch injury and the influence of incubation with the four antiproliferative agents was studied. The use of antiproliferative agents to combat the problem of restenosis is currently being tested clinically and drug-coated stents have recently received European marketing approval. However, not all coronary lesions are suitable for stent deployment and hence local infusion of antiproliferative agents after balloon angioplasty offers an alternative method of drug delivery. The effect of these compounds on vascular function is therefore of great importance, and, to date, little work has been performed in this area.

4.1. Short-term drug incubation

Short-term incubation of porcine coronary arteries had little effect on contractility to 5-HT or endothelium-dependent relaxation to calcimycin. During local drug delivery to an injured artery segment in vivo, there is likely to be significant overspill of drug to non-injured proximal and distal sections of artery and so the effect of these drugs on normal arteries is also important. A previous study, using precontracted porcine coronary arteries also found no effect of paclitaxel (22 μM incubated for 30 min) on isometric force (Paul et al., 2000). A similar study in rat aorta also found that paclitaxel (10 μM incubated for 90 min) had no effect on contraction to phenylephrine (Zhang et al., 2000). In spontaneously hypertensive rats (SHR), however, 10 μM paclitaxel incubated for only 10 min attenuated contraction to phenylephrine. This attenuation of contractility may be specific to arteries from SHR rats, since no comparison with normotensive rats was performed. Very little is known about the vascular effects of the other three drugs used in the present study. In arteries infused with FPT III for 15 min at the time of balloon injury, an attenuation of contraction was observed compared to non-treated, injured arteries when assessed 4 weeks later (Work et al., 2001). In agreement with the present study, however, FPT III did not seem to have an effect on endothelial dependent relaxation. Comparison of these results with the present study is difficult as Work et al., examined arteries injured 4 weeks previously and containing regenerated endothelium, which is known to be dysfunctional in the porcine coronary artery (Shimokawa et al., 1989). Incubation with perillyl alcohol abolished contraction to 5-HT, an effect which was only partly reversible. In a previous study in vivo (Fulton et al., 1997), oral perillyl alcohol induced hypersensitivity to 5-HT in vein grafts in rabbits 28 days after injury. Again, comparison with the present study is difficult as the vein graft had an increased medial thickness, which may have caused the increased contractile responses.

The concentration of perillyl alcohol used in the present study was chosen on the basis of published data (Unlu et al., 2000), and high concentrations are routinely used in oncology studies (Belanger, 1998). Due to its lipophilic nature, significant incorporation into the artery would be anticipat-

ed, and this may underlie its inhibitory effect on vascular contractility (Baumbach et al., 1999). Very little information is available on Van 10/4. Its mechanism of action is currently being studied in our laboratory, but it effectively inhibits thymidine uptake by porcine vascular smooth muscle cells at a similar concentration to that observed with paclitaxel and FPT III (Kennedy et al., 2002a).

4.2. Overnight drug incubation

With more prolonged drug incubation, effects on artery contraction and endothelium-dependent relaxation were observed. For these experiments, U46619 was used as the contractile agonist as it was found to produce more stable contractions of a greater magnitude compared to 5-HT. This may be due to the differential effect of 5-HT in inducing contraction on the smooth muscle but relaxation via release of nitric oxide (NO) from the endothelium (Yang et al., 2001). The attenuation of contraction by the higher concentration of Van 10/4 may be relevant in vivo at sites of vascular injury. Platelet aggregation following vascular injury may generate thromboxane, which could contract adjacent segments of non-injured artery (Merhi et al., 1995). An attenuation of this contraction by a locally infused drug would represent a beneficial effect by reducing the likelihood of vasospasm in the injured artery (Vanhoutte and Shimokawa, 1989). Overnight incubation with the higher concentration of paclitaxel, Van 10/4 and FPT III significantly reduced endothelium-dependent relaxation to calcimycin. This was not due to deterioration of the endothelium caused by storage since control arteries and those treated with the lower concentration of each drug showed normal relaxation to calcimycin. An effect on the endothelium would seem likely as contractility was unaffected. Lipophilic drugs such as paclitaxel readily transfer into the arterial wall after local delivery (Baumbach et al., 1999), and, hence, the artery may be exposed to high concentrations over a prolonged period in vivo. A reduced endothelium-dependent relaxation would represent an undesirable effect, though whether these drug concentrations would be maintained for fully 24 h in the artery is unclear.

4.3. In vitro balloon injury

Stretch injury of the porcine left anterior descending coronary artery caused a significant reduction in endothelium-dependent relaxation to calcimycin but increased the sensitivity of the artery to SIN-1 compared to the non-injured left circumflex coronary artery. The reduction in calcimycin-induced relaxation is not unexpected as significant endothelial trauma would be anticipated following balloon inflation. Total denudation of the endothelium was not achieved as the injured artery still maintained some relaxation to calcimycin. Balloon injury in vivo results in rapid denudation of the rabbit subclavian artery and restoration of endothelial function occurs around 1 week after injury (Hadoke et al., 1995). Not surprisingly, none of the three drugs tested could restore endothelium-dependent relaxation, although they did not appear to induce any further deterioration in function when added after injury. The sensitivity of the injured artery to relaxation by SIN-1 was increased following injury, and drug treatment had no effect on this. The mechanism of this increased sensitivity is likely to be due to partial denudation of the endothelium by balloon inflation. Such an effect has been observed in both human and porcine arteries and veins (Luscher et al., 1989) and dog basilar arteries (Katusic and Vanhoutte, 1989). The fact that drug incubation did not modify this response would imply that the ability of the artery to relax to spontaneously added nitric oxide is unaffected by exposure to the drug or the presence of drug retained in the artery wall after washing.

4.4. Conclusions

This study demonstrates that the antiproliferative drugs paclitaxel, FPT III and Van 10/4 have no detrimental effects on endothelium-dependent relaxation or vascular contraction in the porcine coronary artery when applied for short periods or at low concentrations. In arteries injured in vitro, short-term incubation with these compounds does not modify the changes in vessel contractility or endothelium-dependent and -independent relaxations, which are induced by injury. This suggests that use of effective antiproliferative concentrations in vivo should not induce short-term vascular dysfunction. In contrast, perillyl alcohol had a marked inhibitory effect on contraction at concentrations required to induce antiproliferative effects in smooth muscle cells.

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