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Augmented sensory-motor vasodilatation of the rat mesenteric arterial bed after chronic infusion of the P_1-purinoceptor antagonist, DPSPX

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1 The effect of long-term antagonism of P_1-purinoceptors on vascular function was examined in the perfused mesenteric arterial bed isolated from rats which had received constant infusion of either the non-selective P_1-purinoceptor antagonist, 1-3-dipropyl-8-sulphophenylxanthine (DPSPX, 30 $\mu g\ kg^{-1}\ h^{-1}$, i.p.) or saline for seven days. Sympathetic and sensory-motor neurotransmission, smooth muscle and endothelial function were assessed.

2 Basal tone was similar in mesenteric arterial preparations from control and DPSPX-treated rats. Continuous perfusion with methoxamine (7-70 μM) induced similar increases in tone in control and DPSPX-treated preparations. In the presence of guanethidine (5 μM), electrical field stimulation (EFS; 1-12 Hz, 60V, 0.1 ms, 30 s) elicited frequency-dependent vasodilatation due to activation of sensory-motor nerves. In tissues from DPSPX-treated rats the nerve-mediated vasodilator responses were markedly augmented at all frequencies. Maximal relaxation at 8 Hz was $38.34 \pm 4.76\%$ ($n=5$) in controls and $65.92 \pm 3.68\%$ ($n=5$) after DPSPX-treatment ($P<0.01$). Adenosine (3 μM) inhibited the frequency-dependent sensory-motor neurotransmission similarly in preparations from controls and DPSPX-treated rats.

3 In raised-tone preparations calcitonin gene-related peptide (CGRP; 5, 15 and 50 pmol), the principal vasodilator transmitter of sensory-motor nerves in rat mesenteric arteries, produced similar relaxations in control and DPSPX-treated preparations. Vasodilator responses to the sensory neurotoxin capsaicin (50 and 500 pmol) were also similar between the groups.

4 Assay of tissue CGRP levels of the superior mesenteric artery by enzyme-linked immunosorbent assay showed no significant difference in tissue levels of CGRP in controls, 120.25 ± 26.34 pmol g^{-1} tissue ($n=6$) and with DPSPX-treatment, 82.12 ± 24.42 pmol g^{-1} tissue ($n=6$).

5 In raised-tone preparations dose-dependent endothelium-dependent vasodilatation to acetylcholine and ATP, and endothelium-independent vasodilatation to sodium nitroprusside were similar in control and DPSPX-treated preparations.

6 EFS (4-32 Hz, 90V, 1 ms, 30 s) elicited frequency-dependent vasoconstriction due to activation of sympathetic nerves which was similar in controls and in DPSPX-treated preparations. Adenosine (10 and 30 μM) inhibited sympathetic neurotransmission similarly in control and DPSPX-treated preparations. Dose-dependent vasoconstriction to noradrenaline (NA) and ATP, and to KCl (0.15 mmol) was similar between the groups.

7 High performance liquid chromatographic analysis of tissue NA showed no significant difference in NA content of the superior mesenteric artery from DPSPX-treated (1.38 ± 0.09 ng mg^{-1}, $n=6$) and control rats (1.46 ± 0.17 ng mg^{-1}, $n=6$).

8 In conclusion, in rats with hypertension due to 7 days treatment with the P_1-purinoceptor antagonist, DPSPX, there is an increase in sensory-motor vasodilatation of the mesenteric arterial bed. There is no change in sympathetic nerve, endothelial or smooth muscle function. Augmented sensory-motor neurotransmission, which does not involve a change in postjunctional responsiveness to CGRP or in the CGRP content of sensory-motor nerves, could be a compensatory change in response to the DPSPX-induced hypertension.

Keywords: Hypertension; DPSPX; purinoceptor; rat mesenteric arteries; sensory nerves

Introduction

Long-term infusion of the adenosine (P_1) receptor antagonist, 1-3-dipropyl-8-sulphophenylxanthine (DPSPX), produces changes mimicking those occurring in experimental models of hypertension, there being an increase in blood pressure and hyperplasia and hypertrophy of vascular smooth muscle in rats and dogs (Matias *et al.*, 1991; Osswald, 1991; Albino-Teixeira & Osswald, 1993). It has been suggested that the sympathetic nervous system may have a role in these changes via adenosine formed following enzymatic degradation of the sympathetic cotransmitter ATP, since the onset of hypertension caused by DPSPX is delayed by chemical sympathectomy (Albino-Teixeira & Osswald, 1993). Furthermore, the hyperplastic changes observed with chronic (5 days) DPSPX-treatment are similar to those resulting from sympathetic denervation, the latter being prevented by infusion of adenosine or N-ethylcarboxamido-adenosine (Albino-Teixeira *et al.*, 1990). In the tail artery of rats with DPSPX-induced hypertension, sympathetic neurotransmission and tissue levels of noradrenaline (NA) are enhanced (Karoon *et al.*, 1995) and there is an increased sensitivity of prejunctional inhibitory α_2-adrenoceptors (Guimaraes *et al.*, 1994) and facilitatory prejunctional β-adrenoceptors (Guimaraes *et al.*, 1995) on sympathetic nerves. The long-term effects of DPSPX may also involve the renin-angiotensin system in view of the inhibitory effects of adenosine on renin

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release and since DPSPX-induced hypertension and hypertrophy is associated with an increase in plasma renin and can be prevented by treatment with the angiotensin-converting enzyme inhibitor, captopril (Azevedo & Osswald, 1992; Albino-Teixeira & Osswald, 1993).

Mesenteric arterial tone in rats is controlled by a balance between effects mediated by the endothelium, vasoconstrictor actions mediated by noradrenaline (NA) and ATP co-released from sympathetic nerves (Burnstock, 1990; Sjöblom-Widefeldt *et al.*, 1990), and vasodilatation mediated by calcitonin gene-related peptide (CGRP) released from sensory-motor nerves (Kawasaki *et al.*, 1988). In spontaneously hypertensive rats (SHR) changes in perivascular nerves and endothelial cells in mesenteric arteries have been described: sympathetic transmission may be augmented (Longhurst *et al.*, 1986; Head, 1989) and sensory-motor transmission reduced (Kawasaki *et al.*, 1990b,c); prejunctional neuromodulation by the A_1 subtype of P_1-purinoceptor found on sympathetic nerves may be impaired (Jackson, 1987); abnormalities in endothelial cell structure and function have also been described (Diederich *et al.*, 1990). Limited evidence documenting the functional consequences of DPSPX-induced hypertension include reports of enhanced sympathetic neurotransmission in the rat tail artery without a change in postjunctional responses to NA (Guimaraes *et al.*, 1994; Karoon *et al.*, 1995) and reduced cardiac sympathetic neurotransmission occurring at the postjunctional level (Rubino & Burnstock, 1995).

The aim of the present study was to characterize the functional consequences of DPSPX-induced hypertension in rat mesenteric arteries. Specifically, we aimed to investigate the function of sympathetic and sensory-motor nerves, smooth muscle and endothelium. Tissue content of the sympathetic transmitter, NA and the sensory-motor transmitter, CGRP was evaluated biochemically. Adenosine-mediated modulation of sympathetic and sensory-motor neurotransmission was also examined. Preliminary results were presented at the Winter Meeting of the British Pharmacological Society (Ralevic *et al.*, 1995b).

Methods

In vivo *infusion of 1-3-dipropyl-8-sulphophenylxanthine*

Long-term infusion of DPSPX (30 $\mu g\ kg^{-1}\ h^{-1}$) or saline was achieved with Alzet osmotic minipumps (model 2ML1) implanted into the abdominal cavity of male Wistar rats (200–250 g) under halothane anaesthesia (Matias *et al.*, 1991). Blood pressure was monitored daily by the tail-cuff occlusion technique (Blood pressure recorder: Ugo Basile, Cernobio, Italy). Rats were killed by sodium pentobarbitone overdose (i.p.) on day 7 after implantation and the mesenteric arterial beds isolated and perfused as described below.

Isolated mesenteric arterial bed preparation

Mesenteric beds were isolated and set up for perfusion as described previously (Ralevic *et al.*, 1995a). The abdomen was opened and the superior mesenteric artery exposed and cannulated with a hypodermic needle. The superior mesenteric vein was severed, the gut dissected away and the preparation mounted on a stainless steel grid (7 × 5 cm) in a humid chamber (custom made at University College London). The preparation was perfused at a constant flow rate of 5 ml min^{-1} using a peristaltic pump (model 7554-30, Cole-Parmer Instrument Co., Chicago Illinois, U.S.A.). The perfusate was Krebs solution of the following composition (mM): NaCl 133, KCl 4.7, NaH_2PO_4 1.35, $NaHCO_3$ 16.3, $MgSO_4$ 0.61, $CaCl_2$ 2.52 and glucose 7.8, gassed with 95% O_2–5% CO_2 and maintained at 37°C. Responses were measured as changes in perfusion pressure (mmHg) with a pressure transducer (model P23XL, Viggo-Spectramed, Oxnard, CA, U.S.A.) on a side arm of the perfusion cannula, and recorded on a polygraph (model 7D, Grass Instrument Co., Quincy, Mass, U.S.A.). Preparations were allowed to equilibrate for 30 min prior to experimentation.

In five control and five DPSPX-treated preparations vasoconstrictor responses to electrical field stimulation (EFS) were examined by construction of frequency-response curves at 4–32 Hz, 90V, 1 ms, duration 30 s. After a 10 min recovery period preparations were electrically stimulated repeatedly at 32 Hz (90V, 1 ms, 5 s) at 2 min intervals. The inhibitory effect of two separate perfusions with adenosine (10 and 30 μM for 8 min) on the constrictor responses was examined. After a further recovery period during which time adenosine was washed out, vasoconstrictor responses of preparations to increasing doses of NA and ATP were assessed. Individual doses were applied as 50 μl bolus injections at intervals of at least 2 min; 10–15 min was allowed between consecutive dose-response curves. The tone of the preparations was then raised with methoxamine (7–70 μM) and dose-response curves to acetylcholine (ACh), ATP and sodium nitroprusside (SNP) were established. Responses to a single dose of KCl (0.15 μmol) were tested at the end of each experiment after washout of methoxamine and a return of tone to baseline.

In a separate group of control and DPSPX-treated preparations, guanethidine (5 μM) was added to the perfusate to block sympathetic transmission 20 min before raising the tone of the preparations with methoxamine. After preparations had equilibrated for approximately 10 min at raised tone, EFS was applied at 8 Hz (60V, 0.1 ms, 30 s). Thereafter, a frequency-response curve was constructed to EFS at 1, 2, 4, 8 and 12 Hz (60V, 0.1 ms, 30 s). The effect of adenosine (3 μM) on the frequency-response curves was then assessed. After washout of adenosine, responses to doses of exogenous CGRP (5, 15 and 50 pmol) and capsaicin (50 and 500 pmol) were established.

Noradrenaline assay

The superior mesenteric artery was dissected out and two adjacent segments, each approximately 1 cm in length, were taken from the centre of the vessels, rapidly frozen and stored in liquid nitrogen until assay. The proximal segment was used for NA assay and the distal segment for CGRP assay (see below). After measurements of the vessel weight and length, NA levels were measured by high-performance liquid chromatography with electrochemical detection as described previously (Ralevic *et al.*, 1995a).

Calcitonin gene-related peptide assay

Distal segments of mesenteric artery (approximately 1 cm in length) were rapidly frozen and stored in liquid nitrogen until peptide extraction. After measurement of the weight and length, peptides were extracted into 0.5 M acetic acid in polypropylene tubes in a boiling water bath for 15 min. The samples were homogenized, centrifuged for 30 min at 3500 *g*, and lyophilized. CGRP was quantified by an inhibition enzyme-linked immunosorbent assay as described previously (Belai *et al.*, 1988).

Drugs used

All drugs were applied as 50 μl bolus injections into a rubber septum proximal to the preparation. Drug dilutions were made up daily from stock solutions of 10 or 100 mM (concentrations stored frozen) in distilled water, except for NA which was made up daily as a stock solution in 0.1 mM ascorbic acid and diluted in distilled water. The following drugs were obtained from Sigma: acetylcholine chloride, adenosine 5′-triphosphate (disodium salt), capsaicin (8 methyl-N-vanillyl-6-nonenamide), 1-3-dipropyl-8-sulphophenylxanthine (DPSPX), methoxamine (hydrochloride), noradrenaline bitartrate and sodium nitroprusside. Calcitonin gene-related peptide was from Cambridge Research Biochemicals. Antiserum raised in rabbits to synthetic CGRP was from UCB-Bioproducts, Belgium. Goat-antirabbit immunoglobulin conjugated to alkaline phosphatase was from Sigma.

Data analysis

All data are presented as means ± s.e.mean. Vasodilator responses at raised tone are expressed as a percentage of the methoxamine-induced tone. Response-curves were compared by analysis of variance with repeated measures with post hoc analysis using Student's t test. Other statistical comparisons between groups were by Student's t test. A probability (P) of 0.05 was taken as the level of statistical significance.

Results

DPSPX-induced hypertension

There was no significant difference in the body weight of control rats, 293.1 ± 6.2 g (n = 11) and rats treated with DPSPX, 281.4 ± 6.7 g (n = 11). The blood pressure of DPSPX-treated rats, 163.3 ± 2.6 mmHg (n = 9) was significantly greater than that of control rats, 140.4 ± 1.8 mmHg (n = 11).

Electrical field stimulation at raised tone: sensory-motor neurotransmission

There was no significant difference in methoxamine-induced tone in control and DPSPX-treated preparations; 53.6 ± 4.22 mmHg (n = 5) and 53.4 ± 5.54 mmHg (n = 5) respectively. EFS at raised tone in the presence of guanethidine (5 μM) elicited frequency-dependent relaxations which were significantly greater in preparations from DPSPX-treated rats (Figure 1, 2).

Effect of adenosine on sensory-motor neurotransmission

At raised tone, adenosine (3 μM) had no significant effect on tone of the preparations. Bolus injections of adenosine (50 and 500 nmol) elicited weak vasodilator responses which were not different with and without DPSPX treatment. Adenosine (3 μM) attenuated vasodilator responses to EFS (1–12 Hz, 60V, 0.1 ms, 30 s) in a manner that was proportionately greater at lower frequencies of stimulation. There was no significant difference between the two groups of preparations with respect to percentage inhibition by adenosine (Figure 3).

Vasodilatation to calcitonin gene-related peptide and capsaicin

In raised tone preparations CGRP (5, 15 and 50 pmol) and capsaicin (50 and 500 pmol) elicited dose-dependent vasodilatation which was similar in preparations from control and DPSPX-treated rats (Figure 4).

Vasodilatation to acetylcholine, ATP and sodium nitroprusside

There was no significant difference in methoxamine-induced tone: 50.36 ± 10.83 mmHg (n = 5) in control and 69.87 ± 6.51 mmHg (n = 5) in DPSPX-treated preparations. In raised-tone preparations, ACh, ATP and SNP elicited dose-dependent relaxations which were not significantly different between control and DPSPX-treated preparations (data not illustrated).

Electrical field stimulation at basal tone: sympathetic neurotransmission

There was no significant difference in the basal perfusion pressure of mesenteric arterial beds from control and DPSPX-

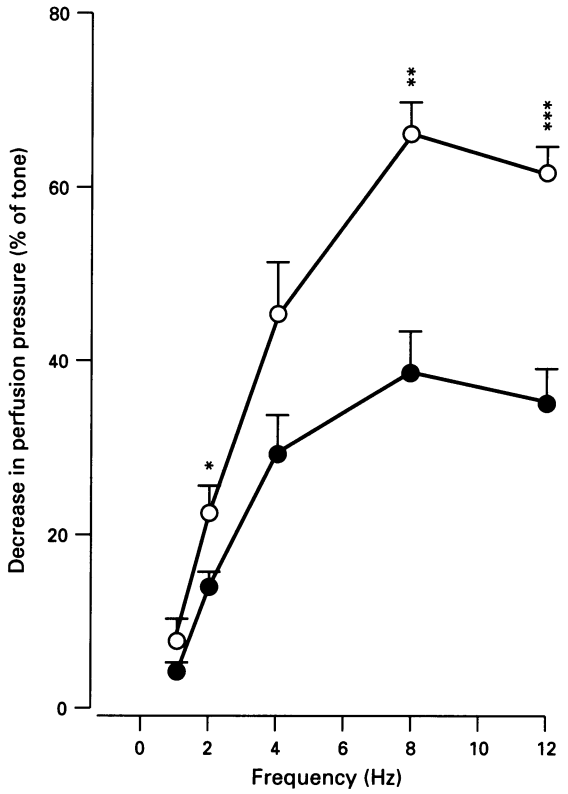

Figure 2 Frequency-dependent vasodilatation to electrical field stimulation (1–12 Hz, 60V, 0.1 ms, 30 s) of mesenteric arterial preparations from control (●, n = 5) and DPSPX-treated (○, n = 5) rats. Statistically significant difference from control is denoted by *(P < 0.05), **(P < 0.01) and ***(P < 0.001). Values are means with s.e.mean.

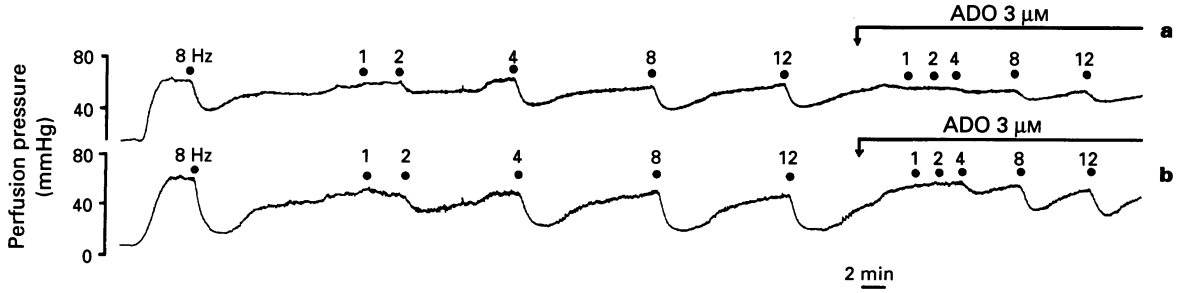

Figure 1 Representative traces showing frequency-dependent vasodilatation to electrical field stimulation (1–12 Hz, 0.1 ms, 60V, 30 s) of sensory-motor nerves in isolated perfused mesenteric arterial beds from a control rat (a) and a 1-3-dipropyl-8-sulphophenylxanthine (DPSPX)-treated rat (b). Tone of the preparations was raised with methoxamine (20 μM) and guanethidine (5 μM) was present in the perfusate throughout to block sympathetic transmission. The response curves were repeated in the presence of 3 μM adenosine (ADO) which inhibited the responses.

treated rats: 34.4±1.69 mmHg ($n=5$) and 31.9±1.94 mmHg ($n=5$) respectively. EFS (4–32 Hz, 90V, 1 ms, 30 s) at basal tone elicited frequency-dependent vasoconstrictor responses due to activation of sympathetic nerves. Responses were similar in control and DPSPX-treated preparations (Figure 5a).

Effect of adenosine on sympathetic neurotransmission

Adenosine (10 and 30 μM) attenuated vasoconstrictor responses to EFS in a concentration-dependent manner which was not significantly different between the groups (data not illustrated). Adenosine at 10 μM inhibited responses to sympathetic nerve stimulation by 6.04±1.69% ($n=5$) in controls and by 6.2±2.03% ($n=5$) in preparations with DPSPX-treatment. Adenosine at 30 μM inhibited constrictor responses by 19.82±3.45% ($n=5$) in controls and by 23.2±2.98% ($n=5$) in preparations with DPSPX-treatment.

Vasoconstriction to noradrenaline, ATP and potassium chloride

NA and ATP elicited dose-dependent vasoconstrictions of the mesenteric arterial preparations in a similar manner in controls and with DPSPX-treatment (Figure 5b,c). Responses to KCl at 102±19.38 mmHg ($n=5$) in controls and 94.6±11.68 mmHg ($n=5$) with DPSPX-treatment were not significantly different.

Noradrenaline and calcitonin gene-related peptide content of the superior mesenteric artery

There was no significant difference in the NA content of the superior mesenteric artery from controls, 1.46±0.17 ng mg^{-1} tissue ($n=6$), and with DPSPX-treatment, 1.38±0.09 ng mg^{-1} tissue ($n=6$).

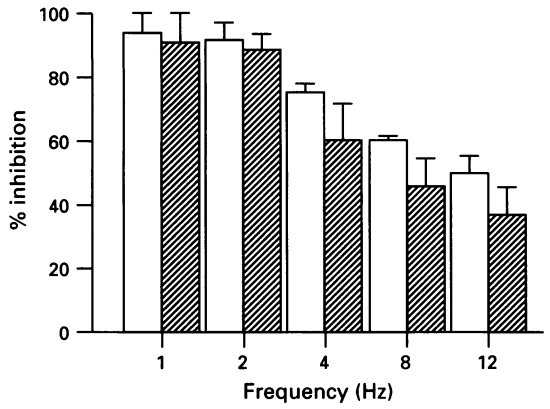

Figure 3 Percentage inhibition by adenosine (3 μM) of decrease in perfusion pressure to electrical field stimulation (1–12 Hz, 60V, 0.1 ms, 30 s) of rat mesenteric arterial preparations. Open columns, controls ($n=5$); hatched columns, DPSPX-treated ($n=5$). Columns show means with s.e.mean.

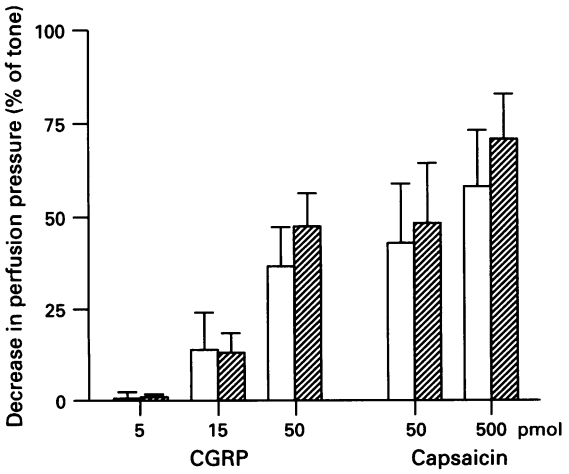

Figure 4 Vasodilator responses to calcitonin gene-related peptide (CGRP; 5, 15 and 50 pmol) and capsaicin (50 and 500 pmol) in mesenteric arterial preparations from control (open columns, $n=5$) and DPSPX-treated (hatched columns, $n=5$) rats. Columns show mean with s.e.mean.

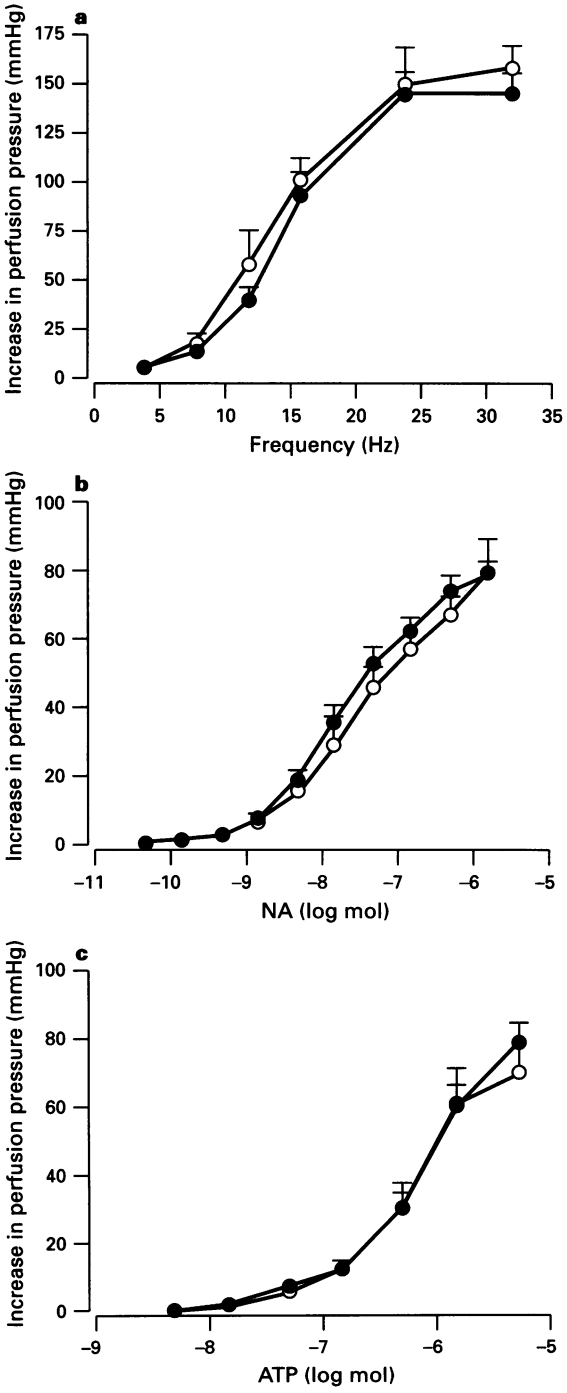

Figure 5 Vasoconstrictor responses of mesenteric arterial beds from control rats (●, $n=5$) and rats treated for 7 days with DPSPX (○, $n=5$). (a) Frequency-dependent vasoconstriction to electrical field stimulation (4–32 Hz, 90V, 1 ms, 30 s); (b) dose-dependent vasoconstrictor responses to noradrenaline (NA; 0.05–1500 nmol); (c) dose-dependent vasoconstrictor responses to adenosine 5′-triphosphate (ATP; 5–5000 nmol). Values are mean with s.e.mean.

There was no significant difference in the CGRP content of the superior mesenteric artery from controls, 120.25 ± 26.34 pmol g^{-1} tissue ($n=6$), and with DPSPX-treatment, 82.12 ± 24.42 pmol g^{-1} tissue ($n=6$).

Discussion

The present results show that there is a marked increase in sensory-motor nerve-mediated vasodilatation of the rat mesenteric arterial bed after long-term (7 days) treatment with the non-selective P_1-purinoceptor antagonist, DPSPX. This does not appear to be due to changes in postjunctional mechanisms involving CGRP, the principal vasodilator transmitter of rat mesenteric arterial sensory nerves (Kawasaki *et al.*, 1988; Han *et al.*, 1990) since responses to applied CGRP were similar in control and DPSPX-treated preparations. This is in contrast to SHR where a decrease in mesenteric arterial sensory-motor neurotransmission relative to normotensive rats has been reported (Kawasaki *et al.*, 1990b,c).

The possibility that there was an increase in the number of sensory-nerve fibres and/or in their transmitter content was tested pharmacologically using capsaicin and by immunoassay of tissue CGRP content of the superior mesenteric artery. Applied acutely, capsaicin causes mesenteric arterial vasodilatation in rats due to the release of transmitters from sensory-motor nerves. The lack of difference in capsaicin-induced relaxation between control and DPSPX-treated preparations suggests that levels of CGRP in sensory-motor nerves are similar in these preparations. On the other hand, these negative findings are not unequivocal since EFS and capsaicin excite sensory nerves by different mechanisms: EFS mimics the action potential by a mechanism which is blocked by ω-conotoxin, suggesting an involvement of L-type calcium channels, whereas capsaicin acts on specific receptors to open non-specific ion channels (Maggi & Meli, 1988). However, our results showing no significant difference in tissue CGRP content in the superior mesenteric artery of control and DPSPX-treated rats are consistent with those obtained with capsaicin, suggesting a similar number and transmitter content of sensory-motor nerves in mesenteric arteries from the two groups. While CGRP is the principal vasodilator transmitter of sensory-motor nerves in rat mesenteric arteries, a number of other co-transmitters are likely to be present and we cannot exclude the possibility that levels of these are altered with long-term DPSPX-treatment.

Hypertrophy and hyperplasia of the mesenteric arteriolar smooth muscle of rats has been described after chronic (7 days) adenosine receptor antagonism (Matias *et al.*, 1991). We did not study the morphology of the mesenteric arteries and therefore do not know if such hyperplastic changes occurred under the conditions of the present study. However, if such changes did occur these do not appear to be responsible for the increase in sensory-motor neurotransmission since direct relaxant responses to CGRP and SNP were unchanged. Furthermore, constrictor responses to EFS, NA, ATP and KCl were also unchanged, consistent with a lack of alteration in smooth muscle function.

The lack of change in tissue NA content of the superior mesenteric artery is consistent with the similar contractile responses to EFS with and without DPSPX-treatment and suggests that there is no underlying enhancement of sympathetic responses which is masked by augmented sensory-motor vasodilatation. These findings are in contrast to the enhanced tissue NA and enhanced sympathetic constrictor responses to EFS observed in tail arteries in the same DPSPX model of hypertension (Karoon *et al.*, 1995). In the mesenteric vasculature of SHR there are conflicting reports of no change in the release of endogenous NA (Cline & Yamamoto, 1987) and elevated tissue NA and NPY content and augmented sympathetic neurotransmission (Scott & Pang, 1989; Longhurst *et al.*, 1986; Lee *et al.*, 1988; Heat, 1989; Mangiarua & Lee, 1989). Augmented sympathetic activity is a feature of other experimental models of hypertension and elevated plasma levels of NA have been reported in some patients with essential hypertension (De Champlain, 1990).

Endothelial function of the mesenteric arteries was unaltered in DPSPX-induced hypertension as shown by unchanged relaxations to ACh and ATP. This is in contrast to the attenuated endothelium-dependent vasodilatation of rat mesenteric arteries which have been described in SHR (Diederich *et al.*, 1990).

Sensory-motor nerves are under prejunctional inhibitory modulation by adenosine via P_1-purinoceptors of the A_1 subtype (Rubino *et al.*, 1994). The DPSPX-induced increase in sensory-motor neurotransmission does not appear to be due to long-term changes in these A_1 receptors since modulation of sensory-motor neurotransmission by applied adenosine was similar with and without DPSPX treatment. There was also no change in adenosine modulation of sympathetic transmission. Defective prejunctional modulation by A_1-purinoceptors on sympathetic terminals in SHR has been described (Jackson, 1987; Ungerer *et al.*, 1992). In the rat tail artery of DPSPX-hypertensive rats, an increase in the sensitivity of inhibitory prejunctional α_2-adrenoceptors (Guimaraes *et al.*, 1994) and facilitatory β-adrenoceptors (Guimaraes *et al.*, 1995) on sympathetic terminals has been described. Prejunctional inhibitory α_2-adrenoceptors are present on sensory-motor nerves of rat mesenteric arteries (Kawasaki *et al.*, 1990a) and it is possible that these may be changed in DPSPX-induced hypertension, facilitating release of sensory transmitter.

Adenosine is a potent and physiologically important regulator of renin release and increased levels of renin and a role for the renin-angiotensin system in DPSPX-induced hypertension has been suggested (Azevedo & Osswald, 1992; Albino-Teixeira & Osswald, 1993). There is some evidence for a link between the renin-angiotensin system and the sympathetic nervous system. Angiotensin II (AII) can facilitate NA release through activation of prejunctional AII receptors (Zimmerman, 1981; Westfall *et al.*, 1985). In SHR enhanced β-adrenoceptor-mediated facilitation of adrenergic neurotransmission is dependent, at least in part, on activation of the renin-angiotensin system (Kawasaki *et al.*, 1984). AII was able to potentiate constrictor responses of the rat mesentery to EFS but this was not altered by DPSPX treatment *in situ* (Holycross & Jackson, 1989). A functional tissue renin-angiotensin system has been described in the rat mesenteric vasculature and is closely related to blood pressure (Weishaar *et al.*, 1991). Whether there is a relationship between P_1-purinoceptors, the tissue renin-angiotensin system and sensory-motor neurotransmission in mesenteric arteries remains to be determined.

In conclusion, the present study shows that there is an increase in sensory-motor vasodilatation of rat mesenteric arteries after chronic (7 days) antagonism of P_1-purinoceptors with DPSPX *in vivo*. There was no change in sympathetic responses and in this respect this model differs from other models of hypertension. The increase in sensory-motor neurotransmission does not involve an increase in the number and/or density of sensory-motor nerves and does not involve changes in prejunctional modulation by P_1-purinoceptors. Augmented sensory-motor transmission may represent a compensatory mechanism to counter the increase in systemic blood pressure occurring in DPSPX-induced hypertension.

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