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Vascular actions of octreotide in the portal hypertensive rat

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1 We have investigated the actions of the somatostatin analogue octreotide in the portal hypertensive Wistar rat *in vivo* and in rat small mesenteric artery and aorta *in vitro*.

2 In small mesenteric artery, octreotide (0.1–0.3 μM) failed to produce any direct contraction, nor did it affect contractions to noradrenaline (NA, 10 μM) or endothelium-dependent relaxations to acetylcholine.

3 In rat aorta, octreotide (0.3 μM) and somatostatin (1 μM) failed to affect contractions to NA (1 μM), or concentration-contractile response curves to NA.

4 In rat vas deferens, octreotide and somatostatin significantly reduced contractile responses to electrical stimulation with pD_2 values ($-\log IC_{50}$) of 8.19 ± 0.10 ($n=4$) and 8.16 ± 0.26 ($n=4$), respectively. Hence, the lack of effect of these agents in aorta or mesenteric artery was not due to lack of efficacy or inappropriate choice of concentration.

5 In the anaesthetized portal hypertensive rat, intravenous injection of octreotide (1–100 μg kg^{-1}) did not significantly affect systemic blood pressure, nor did it affect mesenteric vascular conductance as measured by laser doppler flow probes. However, octreotide (100 μg kg^{-1}) significantly reduced vascular conductance to $74.2 \pm 7.7\%$ of control ($n=6$) in porto-systemic shunt vessels as measured by laser doppler flow probes.

6 Phenylephrine (1 μg kg^{-1}) significantly raised blood pressure and significantly decreased vascular conductance in both mesenteric ($66.6 \pm 3.7\%$ of control) and porto-systemic shunt vessels ($58.7 \pm 10.0\%$ of control).

7 It was concluded that octreotide has selective effects on porto-systemic shunt vessles *in vivo* in the portal hypertensive rat.

Keywords: Octreotide; somatostatin; portal hypertensive rat; rat mesenteric artery; rat aorta; noradrenaline, phenylephrine

Introduction

The prehepatic portal hypertensive rat is a model of human portal hypertension which is widely used due to the fact that portal-systemic shunting develops consistently (Sikuler *et al*., 1985; Cawley *et al*., 1995a). These shunts develop in response to the increased portal pressure, and a hyperdynamic circulation develops. This hyperdynamic circulation is characterized by increased cardiac output and increased splanchnic blood flow.

Bleeding from oesophageal varices is a frequent, life threatening, complication in patients with portal hypertension. Somatostatin is an effective treatment for patients with bleeding oesophageal varices, and is preferred to vasopressin (Burroughs & Panagou, 1996). However, somatostatin has a short half-life and needs to be given as a continuous intravenous infusion. A long-acting analogue, octreotide, is being increasingly used for the treatment of portal hypertension (Albillos *et al*., 1993; McCormick *et al*., 1993a, 1995). There is evidence that octreotide acts preferentially on the collateral circulation of cirrhotic patients, reducing blood flow through oesophageal varices (McCormick *et al*., 1990), and may also reduce mesenteric flow (McCormick *et al*., 1993b), although octreotide has also been shown to have significant systemic cardiovascular effects in cirrhotic patients to decrease heart rate and cardiac output and increase blood pressure (McCormick *et al*., 1995).

The mode of action of octreotide and its analogues in portal hypertension is unclear: inhibition of glucagon secretion (Kravetz *et al*., 1988), direct vasoconstriction (McCormick *et al*., 1990), interference with neurotransmission (Maynard *et al*., 1991) have all been suggested. In this study we have examined the effects of octreotide on the splanchnic vasculature both *in vivo* and *in vitro* in portal hypertensive rats. In addition, we have examined the actions of octreotide in aorta and vas deferens. Studies in blood vessels *in vitro* were carried out to investigate any possible interaction between octreotide and noradrenaline (NA), and between octreotide and endothelium-dependent relaxations. Effects of octreotide on neurotransmission were investigated to compare concentrations producing effects pre- and postjunctionally.

Methods

Male Wistar rats weighing 250 to 350 g were obtained from Trinity College Dublin, and tissues were obtained from portal hypertensive animals (except for vas deferens and aortic studies: control rats).

Surgical preparation

The animals were anaesthetized with ether, a mid-line incision was made in the abdomen and portal vein were exposed. The bile duct and hepatic artery were separated from the portal vein. A 21-gauge needle (0.8 mm outer diameter) was placed alongside the portal vein, and a 3/0 braided silk sterile suture was tied around both needle and vein; the needle was then removed, resulting in a calibrated stenosis. The abdomen was then closed with the same suture material and a continuous suture technique.

Radioactive microspheres

Seven days after surgery, animals were re-anaesthetized with ether and the abdomen was re-opened. Radioactive micro-

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spheres (^{57}Co, 15 μm in diameter, approximately 100,000) were suspended in 10% dextran (with 0.1% of Tween 80 to prevent clumping) and injected in a volume of 0.5 ml kg^{-1} directly into the spleen. After ten minutes the animals were killed. The lungs, liver, spleen and the kidneys were removed, chopped up, and the radioactivity counted in a gamma scintillation counter.

The degree of portal systemic shunting was calculated as follows: % shunting = lung c.p.m. $\times$ 100/(lung c.p.m. + liver c.p.m.).

Radioactivity was measured in the kidneys to check that leaching of radioactivity and lung shunting were negligible. This was found to be so in all cases.

Mesenteric artery

Following stunning and exanguination, intestines and mesentery were removed from portal hypertensive rats 7 days post ligation and placed in Krebs-Henseleit solution of the following composition (mM): NaCl 119, $NaHCO_3$ 25, D-glucose 11.1, KCl 4.7, $CaCl_2$ 2.5, KH_2PO_4 1.2, $MgSO_4$ 1.0, EDTA 0.03 and ascorbic acid 0.28. Additionally, cocaine (3 μM), propranolol (3 μM) and indomethacin (10 μM) were present. By use of a dissecting microscope, a segment of rat small mesenteric artery, approximately 1.5 mm in length, corresponding to a first- or second-order branch of the superior mesenteric artery, was dissected free from its vein. The artery was mounted on a small vessel myograph with 40 μm tungsten wires. Data were recorded a dual channel electronic display recorder and a pen recorder. The vessels were allowed to equilibrate at 37°C and gassed with 5% CO_2 in O_2. The vessel was set to a tension generated at 0.9 times the diameter of the vessel at 100 mmHg transmural pressure (Mulvany & Warshaw, 1977).

After equilibration under resting tension for 30 min, rat small mesenteric arteries were contracted with KCl (40 mM) and then exposed to acetylcholine (ACh; 10 μM) to test for endothelium-dependent-relaxations. Tissues which failed to relax to ACh were discarded due to the absence of functional endothelium. The bathing fluid was changed every 15 min for the next hour. The tissue was exposed to octreotide (0.1 μM) or vehicle for 1 h. The tissues were then contracted with noradrenaline (NA; 10 μM). When contraction had reached a consistent maximum, ACh (or equivalent volume of vehicle) was administered cumulatively in 1 log unit increments, beginning with 1 nM.

To investigate further the effects of octreotide on contractions to NA, a maintained response was obtained to NA (10 μM) and octreotide (0.001 – 0.3 μM) or vehicle was added during the contraction to NA.

Rat aorta

Aortic rings from control rats were set up in conventional organ baths and bathed in Krebs-Henseleit solution (as described above), under resting tension of 1 g for recording of isometric tension. Two kinds of experiment were carried out to investigate the effects of octreotide and somatostatin on contractions to NA. In the first type, a concentraton-response curve to NA was carried out in 0.5 log unit increments before and after 1 h exposure to somatostatin (1 μM) or vehicle. In the second type, a maintained response was obtained to NA (1 μM), and octreotide (0.001 – 0.3 μM), somatostatin (0.001 – 1 μM) or vehicle was added during the contraction to NA.

Rat vas deferens

Prostatic portions of control rat vas deferens were placed between platinum electrodes in organ baths and bathed in Krebs-Henseleit solution, as described above (but without cocaine, propranolol or indomethacin). Responses to single pulse field stimulation (supramaximal voltage, 0.5 ms pulses) were obtained at intervals of 5 min (see Smith & Docherty, 1992). When consistent control responses had been obtained, octreotide (0.001 – 0.3 μM) or somatostatin (0.001 – 1 μM) or vehicle were administered cumulatively in 0.5 log unit increments at intervals of 5 min and a stimulation-evoked contraction was obtained 5 min after each dose. Vehicle did not significantly affect contractions. Agonist IC_{50} values (concentration producing 50% of maximum inhibition) and maximum inhibition were obtained from individual experiments.

Laser doppler blood flow

Seven days after portal vein ligation, animals were re-anaesthetized with ether. The jugular vein was exposed and cannulated. Anaesthesia was then maintained by intravenous pentobarbitone (Nembutal) and animals were artificially ventilated with room air at a rate of 60 min^{-1}. The carotid artery was then exposed, cannulated and connected to a blood pressure transducer for pressure monitoring and recording. The abdomen was then re-opened, shunt vessels were identified, a shunt vessel was carefully placed on a plastic vessel holder attached to the tip of a laser doppler flow probe and porto-systemic shunt blood flow was recorded and monitored on a microvascular assessment unit (Oxford Optronix 1.10). Porto-systemic shunt blood flow was measured in shunt vessels running from the spleen to the renal vein: these shunt vessels appeared consistently in portal hypertensive rats and are of a similar size to small mesenteric arteries when distended with blood. However, these shunt vessels are very thin walled and proved difficult to examine with the small vessel myograph. In some experiments, mesenteric arterial blood flow was recorded, again by placing the vessel on a plastic vessel holder attached to the tip of a laser doppler flow probe. The abdomen was then loosely closed to conserve body heat and maintain hydration status. Following a fifteen minute calibration period, drug administration was commenced. Octreotide, phenylephrine or an equivalent volume of saline (1 ml kg^{-1}) was infused over one minute through the jugular vein and washed in with saline (1 ml kg^{-1}). In all experiments blood pressure and flow were measured at 2 min after injection. In some preliminary experiments, several concentrations of both octreotide and phenylephrine were investigated. In most experiments, the effects of a single drug concentration were recorded, although in some experiments, a response to saline was obtained before administration of test drug. At the end of the experiment, the animal was killed by an overdose of pentobarbitone while still recording blood flow: if blood flow did not fall to zero the experiment was discarded. Since phenylephrine altered systemic blood pressure, responses to test agents were expressed as percentage changes in vascular conductance, obtained by dividing the percentage change in flow signal by the percentage change in mean arterial pressure. Although the laser doppler technique does not give absolute values of blood flow, it can reliably measure changes in blood flow with results that correlate well with changes in flow as measured by use of microspheres (Ferrell *et al*., 1990; Godden *et al*., 1991).

Drugs

Acetylcholine chloride (Sigma, Poole, U.K.); cocaine hydrochloride (Sigma); octreotide acetate (gift: Sandoz, Switzerland); noradrenaline bitarate (Sigma); phenylephrine hydrochloride (Sigma); propranolol by hydrochloride (Sigma), somatostatin (gift: UCB Pharma, Belgium).

All drugs were dissolved in distilled water and diluted distilled water (isolated vessel experiments) or in normal saline (NaCl 0.9% w/v; experiments *in vivo*).

Statistics

The results are expressed as mean $\pm$ s.e.mean. Effects of test agents on NA or ACh maximum response or potency (expressed as pD_2, $-\log EC_{50}$), blood pressure and blood flow were compared with the effect of vehicle by Student's *t* test or by analysis of variance and Dunnett's test.

Results

Degree of porto-systemic shunting

The effectiveness of surgery was assessed by measuring the degree of portal-systemic shunting with the radioactive microsphere technique. Seven days after portal vein ligation, shunting was 66.5±14.3% ($n=3$). This result correlated well with values for degree of shunting obtained 7 days post ligation by Cawley *et al*. (1995b).

Small mesenteric arteries

In small mesenteric arteries from portal hypertensive rats, octreotide (0.001–0.1 μM) failed to produce direct contractions ($n=3$). NA (10 μM) produced a contraction of 1.24±0.14 g ($n=4$), which was not significantly altered by 1 h exposure to octreotide (0.1 μM) (1.36±0.18 g) as compared to the effects of vehicle (control: 1.03±0.07 g; vehicle 1.15±0.10 g, $n=5$).

In tissues contracted with NA (10 μM), ACh produced concentration-dependent relaxations with a maximum relaxation of 83.0±5.4% ($n=4$) before, and 76.0±10.0% following 1 h exposure to octreotide (0.1 μM). In control experiments, ACh produced a maximum relaxation of 88.1±2.8% ($n=5$) before, and 87.0±2.3% after 1 h exposure to vehicle (no significant differences between first and second responses or between octreotide and vehicle).

In tissues contracted with NA (10 μM), ACh produced concentration-dependent relaxations with a pD_2 of 7.23±0.19 ($n=4$) before, and 7.00±0.17 following 1 h exposure to octreotide (0.1 μM). In control experiments, ACh had a pD_2 of 7.49±0.05 ($n=5$) before, and 7.58±0.09 after 1 h exposure to vehicle (no significant differences).

When octreotide (0.001–0.3 μM) was administered during the maintained contraction to NA (10 μM), there was no significant increase in the contractile response as compared with the effects of vehicle (e.g. octreotide decreased the contraction to 83.5±6.0% of control, $n=3$; vehicle decreased the response to 90.0±5.8% of control, $n=3$).

Aorta

In isolated aortic rings from control rats, NA produced concentration-dependent contractions with a maximum contraction of 0.82±0.17 g ($n=5$), and a pD_2 of 8.50±0.18. This was not significantly affected by somatostatin (1 μM) e.g. NA maximum contraction 0.79±0.21 g). Vehicle did not significantly affect contractions to NA (e.g. NA maximum response, $n=4$: control 0.75±0.10 g, vehicle 0.65±0.15 g).

When somatostatin (0.001–1 μM) or octreotide (0.001–0.3 μM) was administered during the maintained contraction to NA, there was no significant increase in the contractile response as compared with the effects of vehicle (e.g. somatostatin increased the contraction to 108.2±1.6% of control, $n=8$; vehicle increased the response to 102.7±1.3% of control).

Vas deferens

In prostatic portions of rat vas deferens, single pulse electrical stimulation produced a contraction of 0.96±0.16 g ($n=9$). Octreotide and somatostatin produced concentration-dependent inhibition of the response with maximum inhibitions of 34.8±6.8% and 26.3±3.3% (both significantly different from effects of vehicle; $P<0.01$), and pD_2 values ($-\log IC_{50}$) of 8.19±0.10 and 8.16±0.26, respectively ($n=4$, each) (see Figure 1).

Effects on systemic blood pressure

In anaesthetized portal hypertensive rats, resting systolic blood pressure (SBP) was 113.0±3.3 mmHg and resting diastolic blood pressure (DBP) was 82.7±2.1 mmHg ($n=31$ baselines from 27 animals). Octreotide (100 μg kg^{-1}), phenylephrine (1 μg kg^{-1}) and vehicle altered SBP to 100.8±2.2% ($n=10$), 124.7±9.7% ($n=9$) and 101.0±0.6% ($n=12$) of control (measured 2 min after injection), respectively (effects of phenylephrine significantly different from effects of vehicle; analysis of variance and Dunnett's test: $P<0.05$). Octreotide (100 μg kg^{-1}), phenylephrine (1 μg kg^{-1}) and vehicle altered DBP to 97.0±4.1%, 121.8±5.9% and 101.8±1.2% of control, respectively (effects of phenylephrine significantly different from effects of vehicle; analysis of variance and Dunnett's test: $P<0.01$).

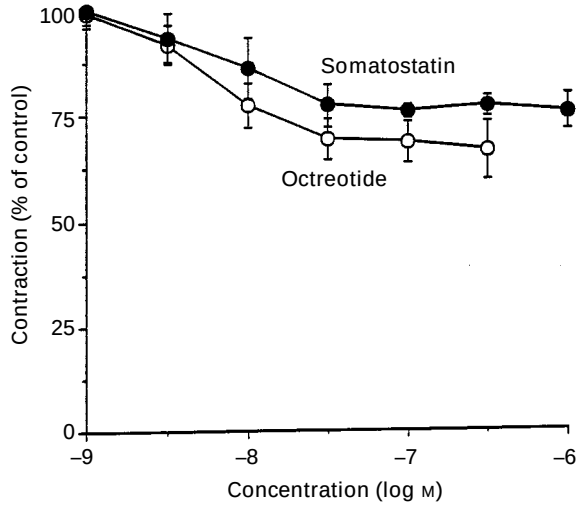

Figure 1 Effects of octreotide and somatostatin on isometric contractions produced by single pulse electrical stimulation in prostatic portions of rat vas deferens. Vertical lines indicate s.e. mean from at least 4 experiments.

Effects on mesenteric and shunt vessel blood flow

The effects of octreotide, phenylephrine or vehicle on mesenteric and porto-systemic shunt vessel flow were investigated by use of the laser doppler blood flow probe technique. Phenylephrine (1 μg kg^{-1}) significantly reduced mesenteric vascular conductance to 66.6±3.7% of control ($n=4$; $P<0.01$ from effects of vehicle). Octreotide (100 μg kg^{-1}) did not significantly affect mesenteric vascular conductance (96.8±6.6%, $n=4$) as compared with the effects of vehicle (101.4±2.3%, $n=4$) (Figure 2). Phenylephrine (1 μg kg^{-1}) significantly reduced porto-systemic conductance to 58.7±10.0% of control ($n=5$; $P<0.01$ from effects of vehicle). In preliminary experiments, octreotide (10 μg kg^{-1}) failed to affect porto-systemic shunt vessel conductance (98.3±4.8% of control, $n=5$). However, octreotide (100 μg kg^{-1}), despite failing to affect mesenteric flow, significantly reduced porto-systemic shunt vessel conductance in the portal hypertensive rat to 74.2±7.7% of control ($n=6$) (vehicle: 103.6±4.6%, $n=8$, $P<0.05$).

Discussion

In this study we confirmed that our animals were portal hypertensive by examining, with the radioactive microsphere techique, the degree of shunting. Porto-systemic shunting is effectively nil up to 3 days post portal vein ligation, but is near maximum 7 days post ligation (Cawley *et al*., 1995b). At seven days post ligation we showed that there was 66.5±14.3% porto-systemic shunting, similar to values obtained by Cawley *et al*. (1995b).

In rat aorta and small mesenteric artery *in vitro*, the somatostatin analogue octreotide did not significantly affect

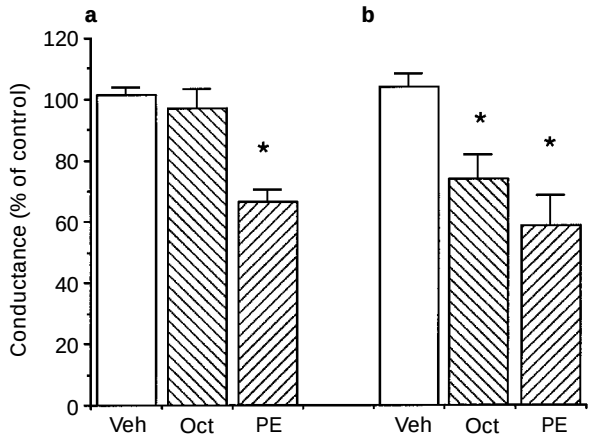

Figure 2 Effects of octreotide (Oct, 100 μg kg^{-1}), phenylephrine (PE, 1 μg kg^{-1}) or vehicle (Veh on (a) mesenteric and (b) shunt vessel blood flow. Values are expressed as % of control. Vertical lines indicate s.e.mean from at least 4 experiments. Asterisks denote significance of difference from effects of vehicle (Student's t test: $^*P<0.05$).

either contractions to noradrenaline (as compared with control) or endothelium-dependent relaxations to acetylcholine, nor did somatostatin affect contractions to NA in rat aorta. Contractions to NA in rat aorta and small mesenteric arteries are mediated via α_1-adrenoceptors (see Aboud *et al*., 1993; Cawley *et al*., 1995a), although the exact nature of these α_1-adrenoceptors has not been fully established (see Van der Graaf *et al*., 1996a, b). Hence, octreotide had no effect on aortic or mesenteric vascular responsivenes either directly or via potentiation or inhibition of the actions of either NA at α_1-adrenoceptors or of endothelium-derived nitric oxide. However, this lack of activity in aorta and mesenteric artery does not rule out such actions in shunt vessels. It has also been found that octreotide has no direct vascular contractile effect in perfused mesenteric arterial beds *in vitro* (Sieber *et al*., 1992).

Since we failed to find any effect of octreotide or somatostatin in our studies of rat isolated mesenteric artery and aorta, we wished to confirm that these compounds were active in our studies by examining their effects in rat vas deferens. Octreotide and somatostatin potently inhibited isometric contractions to a single electrical stimulus in prostatic portions of rat vas deferens. These results agree with previous findings that somatostatin inhibits neurotransmission in rabbit ear artery (Maynard *et al*., 1991) and mouse vas deferens (Feniuk & Humphrey, 1994).

The major findings from this study are those from the laser doppler blood flow experiments *in vivo*. Octreotide decreased shunt vessel blood flow, measured directly with flow probes, but had no significant effect on mesenteric blood flow or SBP or DBP. In contrast, phenylephrine increased blood pressure and reduced both mesenteric and shunt vessel flow to a similar extent, suggesting that its actions are largely produced by constricting mesenteric vessels. The actions of octreotide do not appear to be due to systemic effects and so may well have a selective action on shunt vessels. The most likely mode of action of octreotide in reducing shunt vessel blood flow is by directly constricting the shunt vessel. The effects appear too rapid to be explained by inhibition of glucagon secretion (Kravetz *et al*., 1988), and the sympatho-inhibitory effects on neurotransmissin (see Maynard *et al*., 1991) would not cause vasoconstriction. Interestingly, somatostatin has been shown to constrict human mesenteric veins but not arteries (Tornebradt *et al*., 1987).

In other studies of anaesthetized animals, octreotide decreased portal pressure and flow in portal hypertensive rabbits (Lin & Shan, 1994) and in cirrhotic rats (Hori *et al*., 1994), without affecting systemic arterial pressure. Octreotide treatment (1 day) decreased portal tributary flow without affecting portal pressure, systemic haemodynamics or degree of porto-systemic shunting shunting in portal hypertensive rats (Lin *et al*., 1996). In other studies, somatostatin caused splanchnic constriction to decrease portal venous inflow, decreased portal pressure and increased portal venous resistance (presumably by constricting the shunt vessels) with no systemic effects in portal hypertensive rats (Kravetz *et al*., 1988). These studies did not measure porto-systemic blood flow directly with flow probes, unlike the present study. In normal control rats, octreotide (10 μg kg^{-1}) failed to affect systemic blood pressure or mesenteric blood flow (Pofahl *et al*., 1994).

Some authors have obtained hyporesponsiveness to vasoconstrictors in isolated blood vessels from portal hypertensive rats (e.g. Sieber & Groszmann, 1992), and long-term octreotide has been shown to increase mean arterial pressure (Albillos *et al*., 1993) and to reverse this hyporesponsiveness (Sieber *et al*., 1996). However, other authors have demonstrated hyperresponsiveness of blood vessels from portal hypertensive rats (Cawley *et al*., 1995a, b).

In conclusion, we found that octreotide has a selective action to constrict porto-systemic shunt vessels in portal hypertensive rats *in vivo*, measured directly by use of laser doppler flow probes.

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References

ABOUD, R., SHAFII, M. & DOCHERTY, J.R. (1993). Investigation of the subtypes of α_1-adrenoceptor mediating contraction of rat aorta, vas deferens and spleen. *Br. J. Pharmacol*., **109,** 80–87.

ALBILLOS, A., COLOMBATO, L.A. & GROSZMANN, R.J. (1993). Octreotide ameliorates vasodilatation and Na^+ retention in portal hypertensive rats. *Br. J. Gastroenterol*., **104,** 575–579.

BURROUGHS, A.K. & PANAGOU, E. (1996). Pharmacological therapy for portal hypertension: rationale and results. *Seminars Gastrointest. Dis*., **6,** 148–164.

CAWLEY, T., BRESLIN, E.M., GERAGHTY, J. & DOCHERTY, J.R. (1995a). Investigations of the function of the vascular endothelium in portal hypertensive rats. *Br. J. Pharmacol*., **114,** 791–796.

CAWLEY, T., BRESLIN, E., GERAGHTY, J., OSBORNE, H. & DOCHERTY, J.R. (1995b). Investigations of the function of the vascular endothelium in portal hypertensive rats. *Pharmacology*, **51,** 381–390.

FENIUK, W. & HUMPHREY, P.P.A. (1994). Somatostatin-induced inhibition of neurotransmission in the mouse isolated vas deferens is resistant to pertussis toxin. *Eur. J. Pharmacol*., **261,** 333–337.

FERRELL, W.R., KHOSHBATEN, A. & ANGERSON, W.J. (1990). Responses of bone and joint blood vessels in cats and rabbits to electrical stimulation of nerves supplying the knee. *J. Physiol*., **431,** 677–687.

GODDEN, D.J., BAILE, E.M. & PARE, P.D. (1991). A comparison of laser Doppler flowmetry within the radio labelled microsphere reference flow technique to measure tracheal blood flow in dogs. *Acta Physiol. Scand*., **142,** 49–57.

HORI, N., OKANOUE, T., SAWA, Y., ITOH, Y., MORI, T., TAKAMI, S. & KASHIMA, K. (1994). Hemodynamic effects of combined treatment with somatostatin analogue (SMS 201-995) and low-dose isosorbide dinitrate on portal hypertension in conscious cirrhotic rats. *J. Gastroenterol.*, **29,** 460–468.

KRAVETZ, D., BOSCH, J., ARDERIU, M.T., PIZCUETA, M.P., CASAMITJANA, R., RIVERA, F. & RODES, J. (1988). Effects of somatostatin on splanchnic hemodynamics and plasma glucagon in portal hypertensive rats. *Am. J. Physiol.*, **254,** G322–G328.

LIN, P.W. & SHAN, Y.S. (1994). Effect of octreotide on hemodynamics and glucagon levels in portal hypertensive rabbits. *J. Formosan Med. Assoc.*, **93,** 668–672.

LIN, H.C., YANG, M.C., HOU, M.C., LI, S.M., HUANG, Y.T., YU, P.C., TSAI, Y.T. & LEE, S.D. (1996). Effects of long-term administration of octreotide in portal vein-stenosed rats. *Hepatology*, **23,** 537–543.

MCCORMICK, P.A., DICK, R., SIRINGO, S., WAGSTAFF, D., CHESTA, J., MCINTYRE, N. & BURROUGHS, A.K. (1990). Octreotide reduces azygos blood flow in cirrhotic patients with portal hypertension. *Eur. J. Gastroenterol. Hepatol.*, **2,** 489–492.

MCCORMICK, P.A., GREENSLADE, L., CHIN, J., DICK, R. & BURROUGHS, A.K. (1993a). The effect of the combination of octreotide and metoclopramide on azygos blood flow in cirrhotic patients with portal hypertension. *Eur. J. Gastroenterol. Hepatol.*, **5,** 839–843.

MCCORMICK, P.A., GREENSLADE, L., CHIN, J., DICK, R. & BURROUGHS, A.K. (1995). Cardiovascular effects of octreotide in patients with hepatic cirrhosis. *Hepatology*, **21,** 1255–1260.

MCCORMICK, P.A., SEIFALIAN, A.M., STANSBY, G., MCGANN, G., COLLINS, P., CHIN, J., MCINTYRE, N., DICK, R. & BURROUGHS, A.K. (1993b). Superior mesenteric artery blood flow in man measured with intra-arterial Doppler catheters: effect of octreotide. *J. Hepatol.*, **17,** 20–27.

MAYNARD, K.I., SAVILLE, V.L. & BURNSTOCK, G. (1991). Somatostatin modulates vascular sympathetic neurotransmission in the rabbit ear artery. *Eur. J. Pharmacol.*, **196,** 125–131.

MULVANY, M.J. & WARSHAW, D.M. (1977). Contractile properties of small arterial resistance vessels in spontaneously hypertensive and normotensive rats. *Circ. Res.*, **41,** 19–25.

POFAHL, W.E., ARDEN, W.A., BEIHN, L.D., MARTERRRE, W.F., SMITH, D.W., DERBIN, M., OREMUS, R., GROSS, D.R. & STRODEL, W.E. (1994). Small intestine microcirculatory effects of octreotide. *J. Surg. Res.*, **56,** 3345–3350.

SIEBER, C.C. & GROSZMANN, R.J. (1992). Nitric oxide mediates hyporeactivity to vasopressors in mesenteric vessels of portal hypertensive rats. *Gastroenterology*, **103,** 235–239.

SIEBER, C.C., LEE, F.Y. & GROSZMANN, R.J. (1996). Long-term octreotide treatment prevents vascular hyporeactivity in portal-hypertensive rats. *Hepatology*, **233,** 1218–1223.

SIEBER, C.C., MOSCA, P.G. & GROSZMANN, R.J. (1992). Effect of somatostatin on mesenteric vascular resistance in normal and portal hypertensive rats. *Am. J. Physiol.*, **262,** G274–G277.

SIKULER, E., KRAVETZ, D. & GROSZMANN, R.J. (1985). Evolution of portal hypertension and mechanisms involved in its maintenance in a rat model. *Am. J. Physiol.*, **248,** G618–G625.

SMITH, K. & DOCHERTY, J.R. (1992). Are the prejunctional α_2-adrenoceptors of the rat vas deferens and submandibular gland of the α_{2A}- or the α_{2D}-subtype. *Eur. J. Pharmacol.*, **219,** 203–210.

TORNEBRANDT, K., NOBIN, A. & OWMAN, C. (1987). Contractile and dilatory action of neuropeptides on isolated human mesenteric blood vessels. *Peptides*, **8,** 251–256.

VAN DER GRAAF, P.H., SHANKLEY, N.P. & BLACK, J.W. (1996a). Analysis of the activity of α_1-adrenoceptor antagonists in rat aorta. *Br. J. Pharmacol.*, **118,** 299–310.

VAN DER GRAAF, P.H., SHANKLEY, N.P. & BLACK, J.W. (1996b). Analysis of the effects of α_1-adrenoceptor antagonists on noradrenaline-mediated contractions of rat small mesenteric artery. *Br. J. Pharmacol.*, **118,** 1308–1316.

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