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Comparative effects of frovatriptan and sumatriptan on coronary and internal carotid vascular haemodynamics in conscious dogs

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1 The effects of frovatriptan and sumatriptan on internal carotid and coronary vascular haemodynamics were investigated and compared in conscious dogs.

2 Frovatriptan and sumatriptan ($0.1-100\ \mu g\ kg^{-1}$) induced a transient increase in external coronary artery diameter (eCOD) of up to 2.9 ± 1.2 and $1.8\pm0.6\%$, respectively (both $P<0.05$). This was followed by a prolonged and dose-dependent decrease in eCOD of up to -5.2 ± 1.2 and $-5.3\pm0.9\%$ (both $P<0.05$), with ED_{50} values of 86 ± 21 and $489\pm113\ \mu mol\ kg^{-1}$, respectively. In contrast, only a decrease in the external diameter of the internal carotid artery was observed (-6.0 ± 0.6 and $-6.2\pm1.4\%$, both $P<0.05$, and ED_{50} values of 86 ± 41 and $493\pm162\ \mu mol\ kg^{-1}$, respectively). Frovatriptan was thus 5.7 fold more potent than sumatriptan at the level of both large coronary and internal carotid arteries.

3 After endothelium removal by balloon angioplasty in coronary arteries, the initial dilatation induced by the triptans was abolished and delayed constriction enhanced.

4 The selective antagonist for the 5-HT_{1B} receptors SB224289 dose-dependently blocked the effects of sumatriptan on large coronary and internal carotid arteries whereas the selective antagonist for the 5-HT_{1D} receptors BRL15572 did not affect any of these effects.

5 In conclusion, frovatriptan and sumatriptan initially dilate and subsequently constrict large coronary arteries in the conscious dog, whereas they directly constrict the internal carotid artery. The vascular endothelium modulates the effects of these triptans on large coronary arteries. Finally, 5-HT_{1B} but not 5-HT_{1D} receptors are primarily involved in canine coronary and internal carotid vasomotor responses to sumatriptan.

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Abbreviations: BRL15572, 1-(3-chlorophenyl)-4-[3,3-diphenyl (2-(S,R) hydroxypropanyl) piperazine] hydrochloride; E^-, endothelium removal; eCOD, external coronary artery diameter; eICAD, external diameter of the internal carotid artery; LV, left ventricle; SB224289, 2,3,6,7-tetrahydro-1′-methyl-5-[2′methyl-4′5-(methyl-1,2,4-oxadiazol-3-yl) biphenyl-4-carbonyl] furo [2,3-f] indole-3-spiro-4′-piperidine hydrochloride

Introduction

The development of sumatriptan has provided a well-tolerated and effective acute anti-migraine therapy (The Subcutaneous Sumatriptan International Study Group, 1991; Visser *et al*., 1996). According to the vascular hypothesis of migraine, the therapeutic efficacy of sumatriptan is primarily related to its agonist activity at the level of 5-$HT_{1B/1D}$ receptors which mediate constriction of carotid arteriovenous anastomoses (Saxena, 1995; Saxena *et al*., 1998; De Vries *et al*., 1999a) and intra-cranial cerebral blood vessels (Humphrey & Feniuk, 1991; Ferrari & Saxena, 1993). However, despite the fact that the drug is highly effective at alleviating attacks of migraine, sumatriptan is contraindicated in patients with coronary artery disease since 5-$HT_{1B/1D}$ receptors are also abundant in these vessels as demonstrated in experiments conducted both *in vitro* (Connor *et al*., 1989; Chester *et al*., 1993; Bax & Saxena, 1993; Kaumann *et al*., 1994) and *in vivo* (MacIntyre *et al*., 1993).

To avoid these problems, a number of 'second generation' triptans have been developed. *In vitro* studies have shown that rizatriptan produces less constriction than sumatriptan (Longmore *et al*., 1996) but these observations have not been confirmed (MaassenVanDenBrink *et al*., 1998). Frovatriptan, a tetrahydrocarbazole derivative, has also been shown to produce less constriction than sumatriptan (i.e., it is a partial agonist) in human isolated coronary artery preparations (Parsons *et al*., 1998a) and frovatriptan is approximately 10 times more potent than sumatriptan in terms of increasing carotid vascular resistance as well as having a long duration of effect in anaesthetized dogs (Parsons *et al*., 1997; 1998b). Frovatriptan and sumatriptan have little effect on coronary

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blood flow or vascular resistance in anaesthetized dogs (Feniuk *et al*., 1989; Parsons *et al*., 1997; 1998b) and have little effect on cardiac function (Parsons *et al*., 1998b). However the effects of frovatriptan, sumatriptan and other 5-$HT_{1B/1D}$ receptor agonists have not been extensively investigated in conscious and chronically instrumented animals. Therefore, the first goal of this study was to investigate the effects of frovatriptan and sumatriptan on large (conductance) and small (resistance) coronary arteries in conscious dogs. In addition, in order to compare the coronary effects of these triptans to those simultaneously exerted on the inaccessible cranial vessels, we used an indirect approach, i.e. the measurement of the external diameter of the internal carotid artery which is the smallest artery at the basis of the skull that can be chronically instrumented with ultrasonic crystals and flow probes. Finally, using the highly selective antagonists for the 5-HT_{1B} (SB224289), and 5-HT_{1D} (BRL15572) receptors (Selkirk *et al*., 1998; De Vries *et al*., 1998; 1999b), we investigated in a subgroup of conscious dogs the nature of receptors subtypes involved in the coronary and internal carotid vascular effects of sumatriptan.

The coronary vascular endothelium modulates to a large extent the effects of serotonin (Chu & Cobb, 1987) and ergonovine (Egashira *et al*., 1992; Karila-Cohen *et al*., 1999) at the level of large epicardial coronary arteries. Since it is in these vessels that coronary arterial spasm occurs and atherosclerotic plaques may develop, our second goal was to compare the effects of sumatriptan and frovatriptan on coronary arteries before and after endothelium removal. For this purpose, we used an experimental model in which the direct dilator and/or constrictor effect of a drug can be investigated *in vivo* at the level of a large coronary artery in the presence of a functional vascular endothelium and after its subsequent removal by balloon angioplasty (Drieu La Rochelle *et al*., 1992; Berdeaux *et al*., 1994; Ghaleh *et al*., 1995; Karila-Cohen *et al*., 1999).

All these experiments were conducted in conscious, chronically instrumented dogs, a model in which the animal is its own control and which avoids the deleterious effects of general anaesthesia and acute surgery on coronary and internal carotid dynamics.

Methods

Animal preparation

The animal instrumentation and ensuing experiments were performed in agreement with official regulations under the edict of the French Ministry of Agriculture (approval no. 94148) and conformed to the Guiding Principles in the Care and Use of Animals of the American Physiological Society and the Guide for the Care and Use of Laboratory Animals (DHEW (DHHS) publication no. (NIH) 8523, revised 1985).

Six adult mongrel dogs, weighing 18–28 kg, were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.), intubated and ventilated with a respirator. Muscle paralysis was obtained with pancuronium bromide (0.2 mg kg^{-1}, i.v.). The level of anaesthesia was monitored continuously by evaluation of heart rate and ocular reflexes throughout the whole procedure. Propacetamol (iv) was administered both during and after surgery to ensure proper analgesia. Under sterile surgical conditions, a left thoracotomy through the 5th intercostal space was performed and the heart suspended in a pericardial cradle. Catheters were implanted in the descending thoracic aorta and in the pulmonary artery. A pair of ultrasonic dimension transducers, 5 MHz piezoelectric crystals (model VD 5S, Triton Technology, San Diego, CA, U.S.A.) was attached to a Dacron backing and fixed using 5-0 suture (Ethicon Inc., Sommersville, NJ, U.S.A.) to opposing surfaces of the left circumflex coronary artery 2–4 cm from its origin. Care was taken when positioning the transducers to limit dissection of, and damage to, any visible nerves. Proper alignment of the crystals was confirmed during surgery by monitoring the ultrasonic signal with an oscilloscope. A Doppler flow probe (10 MHz, Crystal Biotech, Hopkinton, MA, U.S.A.) was implanted distal to the dimension transducers. A solid state pressure transducer (model P7A, Konigsberg Instruments, Pasadena, CA, U.S.A.) was introduced into the left ventricle through the apical dimple and secured with purse-string sutures. The pericardium was left partially closed and all wires and catheters were tunnelled subcutaneously and externalized intrascapularly. The pneumothorax was then evacuated through a chest tube inserted in the 6th intercostal space and the thoracotomy was closed in layers. Cefazolin (1 g, i.v.) and gentamicin (80 mg, i.v.) were administered 30 min before incision and at the end of the surgery. All animals received analgesics (propacetamol, 1 g, i.m.) twice a day for 3 days after the surgery.

At least 4 days after the initial surgery, the dogs were re-anaesthetized (sodium pentobarbitone, 30 mg kg^{-1}, i.v. and pancuronium bromide, 0.2 mg kg^{-1}, i.v.), and under aseptic conditions, an incision was made to expose the left internal carotid artery, before its bifurcation with the left vertebral artery. Monitoring of anaesthesia was conducted as previously described and ensuring adequate analgesia. A pair of ultrasonic dimension transducers, 5-MHz piezoelectric crystals (model VD 5S, Triton Technology, San Diego, CA, U.S.A.) was sutured to opposing surfaces of the vessel and a 10-MHz Doppler flow probe (Crystal Biotech, Hopkinton, MA, U.S.A.) was implanted distal to the dimension transducers. All wires were tunnelled subcutaneously as previously described and the animals allowed to recover.

Measurement of haemodynamic and coronary parameters in conscious dogs

Aortic pressure was measured with a Statham P23XL pressure gauge transducer (Statham Instruments, Oxnard, CA, U.S.A.). Left ventricular (LV) pressure was measured from the Konigsberg gauge and LV dP/dt was obtained *via* electrical differentiation of the left ventricular signal. The external diameters of the left circumflex coronary artery and the left internal carotid artery were measured instantaneously and continuously with an ultrasonic transit-time dimension system (System 6 model 200, Triton Technology Inc, San Diego, CA, U.S.A.) with a resolution of ± 0.02 mm. Left circumflex coronary and left internal carotid blood flow velocities were measured with a Doppler flowmeter (System 6 model 200, Triton Technology Inc, San Diego, CA, U.S.A.). Vascular resistances of the left circumflex coronary and left internal carotid arteries were calculated as the ratio of mean arterial pressure to mean coronary and internal carotid blood flow velocities, respectively (expressed in arbitrary units, a.u.).

Experimental protocols

All experiments were conducted at least 2 weeks after instrumentation, when the dogs were healthy, apyrexial and had been trained to lie quietly on their right side on the experimental table. After recording basal haemodynamic parameters in the conscious state, the dogs were given, in a randomized order (Latin square design), increasing doses of frovatriptan and sumatriptan (0.1 to 100 μg kg^{-1}) *via* the pulmonary artery. Each dog received all doses of both drugs, each new administration being performed on a different day and only when all parameters had returned to their corresponding baseline values. It was shown in previous studies (Berdeaux *et al*., 1994; Puybasset *et al*., 1996) that saline administration was devoid of any effect in this experimental setting.

Endothelium removal in large coronary arteries

Three days after the last drug administration, the dogs were lightly re-anaesthetized with propofol (200 mg, i.v.) and 0.5% halothane. Under aseptic conditions, an incision was made to expose the right carotid artery. An 8 French left coronary guiding catheter (Schneider Climo, Lyon, France) was inserted through the right carotid artery and positioned in the left coronary ostium under fluoroscopic guidance. A balloon angioplasty catheter (Thruflex, Medtronic, Fourmies, France) was inserted through the guiding catheter into the left circumflex coronary artery into the area of the piezoelectric crystals. To avoid distension of the coronary artery, care was taken to calibrate the balloon catheter both according to the external coronary diameter measured by the ultrasonic transit-time gauge and by estimation of the internal diameter after serial injections of contrast medium. The balloon was inflated with air, and the catheter was gently moved back and forth three times over the entire segment from the proximal circumflex coronary artery to the area of the crystals. The balloon was then deflated, the catheter withdrawn, and the dog was allowed to fully recover. This technique caused de-endothelialization on each side of the crystals, leaving the distal circumflex, the left anterior descending and the septal coronary arteries intact, as previously demonstrated by histological and pharmacological studies (Berdeaux *et al*., 1994). Two to three days after this procedure, i.e., before any significant endothelial regeneration occurred in this preparation (Hayashi *et al*., 1988; Berdeaux *et al*., 1994), the endothelium-dependent vasodilator, acetylcholine (0.3 μg kg^{-1}), and the endothelium-independent vasodilator, nitroglycerin (1 μg kg^{-1}), were administered in order to test the effectiveness of epicardial coronary endothelium removal. When the required criteria were satisfied (i.e., about 90% reduction in acetylcholine-induced coronary dilatation and less than 15% reduction in nitroglycerin-induced coronary dilatation) (Ghaleb *et al*., 1995), frovatriptan (3 μg kg^{-1}) or sumatriptan (30 μg kg^{-1}) were then administered. Because of the long-lasting effects of frovatriptan and sumatriptan, only one dose of each (i.e., ED_{50}) was administered in random order and only when the effects of the previous one had disappeared, i.e., when all parameters had returned to their corresponding baseline values.

Effects of sumatriptan after SB224289 and BRL15572

In order to investigate the relative contributions of 5 HT_{1B} and 5 HT_{1D} receptors subtypes to the effects of sumatriptan on the external coronary and internal carotid artery diameters, the drug was administered in an additional group of three conscious dogs with an intact coronary endothelium, before (vehicle as control) and after increasing doses of SB224289 and BRL15572, respectively. For this purpose, and after assessment that three successive administrations of the highest dose of sumatriptan (100 μg kg^{-1}) every 3 days induced similar effects, the animals received on separate days, and only when all parameters had returned to their corresponding baseline values, an i.v. infusion (1 ml min^{-1} over a period of 3 min) of either vehicle, or BRL15572, or SB224289 (both at 0.1, 0.3 and 1 mg kg^{-1}). Fifteen minutes after administration of the vehicle or the antagonist agent, sequential and cumulative i.v. doses of sumatriptan (3, 10, 30 and 100 μg kg^{-1}) were given to all animals every 20 min. In these experiments, and because of its exceptionally long-lasting antagonist effect *in vivo*, SB224289 was always administered after the last dose of BRL15572, when all parameters had returned to their corresponding baseline values.

Drugs

The drugs used were sodium pentobarbitone (Sanofi Santé Animale, Libourne, France), acetylcholine hydrochloride (Sigma Chemical Co, St Louis, MO, U.S.A.), pancuronium bromide (Organon Tecknika, Fresnes, France), propacetamol (UPSA, Rueil-Malmaison, France), cefazoline (Allard, Paris, France), gentamicin (Dakota, Paris, France), halothane (Belamont, Paris, France), propofol (Zeneca, Cergy, France), nitroglycerin (Besins-Iscovesco, Paris, France), frovatriptan (VML 251/SB209509 [(+)-6-carboxamido-3-methylamino-1,2,3,4-tetrahydrocarbazole succinate]), sumatriptan succinate, SB224289 and BRL15572 (all gifts from Dr A.A. Parsons, SmithKline Beecham Pharmaceuticals, Harlow, Essex, U.K.). Drug doses refer to their salts (except for calculation of frovatriptan and sumatriptan ED_{50} values at constricting large coronary and internal carotid arteries which were expressed as μmol kg^{-1}). Drugs were dissolved in isotonic and sterile saline (0.9% NaCl wt vol^{-1} except for SB224289 and BRL15572 which were dissolved in sterile distilled water and 20% propylene glycol, v v^{-1}).

Data and statistical analysis

Haemodynamic data were recorded on a multichannel electrostatic recorder (Gould ES 2000; Ballainvilliers, France) and digitized using data-analysis software (HEM 3.1; Notocord Systems, Croissy sur Seine, France). Digitized data were stored on the hard disk of a compatible PC and used in parallel for calculation and display in real time of derived parameters. All parameters were measured just before (baseline values) and at the time of the peak effect of the drug after each bolus administration. Absolute and per cent changes from corresponding baseline values were calculated.

In order to compare the vasoconstrictor effect of frovatriptan and sumatriptan on large coronary and internal carotid arteries, the doses (expressed in μmol kg^{-1}) of the

drug necessary to decrease the external diameter of the corresponding vessels by 50% of the estimated maximal response (i.e., ED_{50}) were determined for each animal.

Data shown are mean ± s.e.mean. Statistical analysis was performed using the Sygmastat program (Jandel statistical software, CA, U.S.A.) on the individual absolute values using a two-way analysis of variance for repeated measures. When overall differences were detected, individual comparisons were made using Student's paired *t*-test with Bonferroni's correction. Comparisons between the effects of frovatriptan and sumatriptan before *vs* after endothelium removal were made on the absolute variation using a two-way analysis of variance followed by Student's paired *t*-test. In all instances, the threshold for significance was taken as $P<0.05$.

Results

Tables 1 and 2 show the baseline values of all investigated parameters as recorded and calculated in conscious dogs. These values are within the normal ranges usually reported in this setting.

Haemodynamic effects of frovatriptan and sumatriptan

As shown in Tables 1 and 2, frovatriptan and sumatriptan induced significant and dose-dependent increases in heart rate, mean arterial pressure and dP/dt max (maximal effects of 14 ± 3 mmHg, 30 ± 13 beats min^{-1}, 297 ± 132 mmHg s^{-1} and 11 ± 3 mmHg, 28 ± 7 beats min^{-1}, 338 ± 115 mmHg s^{-1}, respectively, at 100 $\mu g\ kg^{-1}$). These effects were always observed during the first minute following the onset of drug administration.

Effects of frovatriptan and sumatriptan on coronary and internal carotid vascular beds

Figure 1 illustrates the effects of equi-effective doses of frovatriptan and sumatriptan (3 and 30 $\mu g\ kg^{-1}$, respectively) on coronary and internal carotid vascular beds. On the large coronary arteries, both drugs respectively, caused an initial and transient increase in diameter (25 ± 4 s and 25 ± 3 s) followed by a more prolonged decrease in diameter (more than 1 h at these doses) with peak effects occurring at 6.45 ± 0.05 min (frovatriptan 3 $\mu g\ kg^{-1}$) and 7.10 ± 0.10 min (sumatriptan 30 $\mu g\ kg^{-1}$). In contrast, both drugs only evoked a sustained and significant decrease in left internal carotid artery diameter with peak effects occurring at 1.50 ± 0.15 min (frovatriptan 3 $\mu g\ kg^{-1}$) and 3.50 ± 0.10 min (sumatriptan 30 $\mu g\ kg^{-1}$) and lasting more than 1 h at these doses.

As shown in Tables 1 and 2 and illustrated in Figure 2, the effects of frovatriptan and sumatriptan on large coronary and internal carotid vascular beds were dose-dependent. Since

Table 1 The effects of (i.v.) frovatriptan on systemic, coronary and internal carotid haemodynamics in conscious dogs

		Frovatriptan ($\mu g\ kg^{-1}$)						
	n	*0.1*	*0.3*	*1*	*3*	*10*	*30*	*100*
HR (beats min^{-1})	6							
Baseline		91 ± 9	92 ± 9	94 ± 9	92 ± 10	91 ± 11	94 ± 9	93 ± 7
Δ max		10 ± 2*	7 ± 3*	15 ± 4*	25 ± 9*	26 ± 8*	25 ± 9*	30 ± 13*
MAP (mmHg)	6							
Baseline		95 ± 5	95 ± 6	97 ± 6	97 ± 6	99 ± 4	96 ± 2	91 ± 4
Δ max		2 ± 1	4 ± 2	3 ± 1*	8 ± 2*	10 ± 3*	13 ± 2*	14 ± 3*
dP/dt max (mmHg s^{-1})	6							
Baseline		2206 ± 188	2215 ± 164	2199 ± 171	2236 ± 185	2187 ± 139	2178 ± 147	2058 ± 132
Δ max		69 ± 39	52 ± 24	141 ± 41*	273 ± 91*	172 ± 65	327 ± 177	297 ± 132
eCAD (μm)	6							
Baseline		2652 ± 158	2633 ± 157	2635 ± 160	2615 ± 151	2617 ± 166	2637 ± 136	2658 ± 146
Δ max vasodilation		3 ± 2	23 ± 10*	32 ± 13*	58 ± 15*	73 ± 16*	53 ± 28*	77 ± 30*
Δ max vasoconstriction		−18 ± 3*	−18 ± 7*	−48 ± 14*	−82 ± 15*	−100 ± 22*	−117 ± 29*	−135 ± 30*
CBFv (cm s^{-1})	6							
Baseline		20 ± 4	19 ± 4	20 ± 4	23 ± 4	20 ± 4	21 ± 4	18 ± 4
Δ max		1 ± 1	2 ± 1	6 ± 5	7 ± 4	11 ± 5	13 ± 6	22 ± 9*
CVR (a.u.)								
Baseline		6.1 ± 1.8	6.1 ± 1.8	6.0 ± 1.8	5.1 ± 1.5	6.3 ± 1.8	5.5 ± 1.3	6.5 ± 1.8
Δ max		−0.4 ± 0.2	−0.5 ± 0.1*	−0.7 ± 0.3*	−0.9 ± 0.3*	−1.6 ± 0.6*	−1.3 ± 0.5*	−2.0 ± 0.2*
eICAD (μm)	4							
Baseline		5133 ± 281	5120 ± 280	5103 ± 264	5083 ± 249	5163 ± 244	5090 ± 269	5025 ± 260
Δ max vasoconstriction		−20 ± 5*	−23 ± 7*	−58 ± 18*	−203 ± 51*	−283 ± 47*	−298 ± 61*	−303 ± 29*
ICABFv (cm s^{-1})	6							
Baseline		17 ± 3	16 ± 3	18 ± 3	18 ± 3	17 ± 2	16 ± 2	18 ± 2
Δ max		4 ± 1*	3 ± 1*	4 ± 1*	4 ± 1*	3 ± 1*	5 ± 2*	8 ± 1*
Δ at ICAVR max		−1 ± 0.6	−0.6 ± 0.6	−1.2 ± 1.3	−2.7 ± 1.3	−2.2 ± 1.6	−1 ± 0.6	−0.3 ± 0.9
ICAVR (a.u.)	6							
Baseline		5.5 ± 0.4	5.6 ± 0.5	5.4 ± 0.6	5.5 ± 0.5	6.2 ± 0.6	6.5 ± 0.6	5.3 ± 0.5
Δ max		0.1 ± 0.1	0.4 ± 0.2	0.4 ± 0.3	1.3 ± 0.4*	1.5 ± 0.6*	1.6 ± 0.6*	0.9 ± 0.3*
Δ at ICABFv max		−1.5 ± 0.7	−1.4 ± 0.5*	−2.4 ± 1.2	−0.6 ± 0.5	−0.8 ± 0.4	−0.7 ± 0.6	−1.5 ± 0.4*

All values have been presented as mean ± s.e.mean. *$P<0.05$ vs baseline. HR, heart rate; MAP, mean arterial blood pressure; dP/dt max, maximum of the first derivative of left ventricular pressure; eCAD, external coronary artery diameter; CBFv, coronary blood flow velocity; CVR, coronary vascular resistance; elCAD, external diameter of internal carotid artery; ICABFv, internal carotid artery blood flow velocity; ICAVR, internal carotid artery vascular resistance; a.u., arbitrary units; *n* = number of animals in which the corresponding parameter was measured.

Table 2 The effects of (i.v.) sumatriptan on systemic, coronary and internal carotid haemodynamics in conscious dogs

		Sumatriptan (μg kg^{-1})						
	n	*0.1*	*0.3*	*1*	*3*	*10*	*30*	*100*
HR (beats min^{-1})	6							
Baseline		98±9	98±8	97±7	98±8	96±8	95±11	93±7
Δ max		7±4	8±3*	7±2*	7±2*	13±4*	20±5*	28±7*
MAP (mmHg)	6							
Baseline		90±4	92±4	92±6	96±4	90±5	95±5	99±3
Δ max		3±2	2±1	4±1*	2±1*	5±2*	6±2*	11±3*
dP/dt max (mmHg s^{-1})	6							
Baseline		2391±158	2376±190	2265±122	2348±193	2233±139	2514±313	2252±125
Δ max		65±33	115±41*	104±41*	90±25*	91±37*	203±85*	338±115*
eCAD (μm)	6							
Baseline		2618±160	2615±157	2598±161	2612±152	2697±151	2680±150	2602±181
Δ max vasodilation		7±2	8±4	18±5*	15±5*	43±10*	48±11*	45±15*
Δ max vasoconstriction		−8±3	−17±2*	−23±5*	−33±13*	−60±13*	−77±12*	−137±21*
CBFv (cm s^{-1})	6							
Baseline		19±4	20±5	20±4	22±5	21±4	21±3	19±4
Δ max		4±1	3±2	1±1	3±1*	4±1*	6±2*	12±4*
CVR (a.u.)	6							
Baseline		6.7±2.1	6.7±2.2	6.6±2.1	6.3±1.8	5.6±1.8	5.3±1.1	6.1±1.15
Δ max		−0.5±0.3	−0.4±0.2	−0.5±0.2	−0.6±0.2	−0.7±0.5	−1.3±0.5*	−1.6±0.8*
eICAD (μm)	4							
Baseline		5013±215	4965±226	5005±204	4958±191	5015±203	5113±246	5185±276
Δ max vasoconstriction		−13±3	−10±5	−25±3*	−48±6*	−105±41*	−190±44*	−318±62*
ICABFv (cm s^{-1})	6							
Baseline		20±4	19±4	19±3	21±4	21±4	20±4	19±3
Δ max		2±1	3±1	3±1	4±1*	4±2*	8±2*	5±1*
Δ at ICAVR max		−0.3±0.5	−1.8±0.8	−1.5±1.3	−2.8±1.1*	−1.8±0.9	−3.2±0.5*	−3.5±0.6*
ICAVR (a.u.)	6							
Baseline		5.3±1.0	5.6±1.2	5.4±1.1	5.2±1.1	4.9±0.9	5.9±1.2	6.1±1.3
Δ max		0.5±0.1	0.7±0.3	0.5±0.4	0.9±0.4	1.2±0.5*	2.1±0.6*	2.0±1.0*
Δ at ICABFv max		−0.3±0.2	−0.5±0.2	−0.7±1.6	−0.5±0.3	−0.9±0.2*	−1.5±0.4*	−1.1±0.3*

All values have been presented as mean±s.e.mean. *$P<0.05$ vs baseline. HR, heart rate; MAP, mean arterial blood pressure; dP/dt max, maximum of the first derivative of left ventricular pressure; eCAD, external coronary artery diameter; CBFv, coronary blood flow velocity; CVR, coronary vascular resistance; elCAD, external diameter of internal carotid artery; ICABFv, internal carotid artery blood flow velocity; ICAVR, internal carotid artery vascular resistance; a.u., arbitrary units; n=number of animals in which the corresponding parameter was measured.

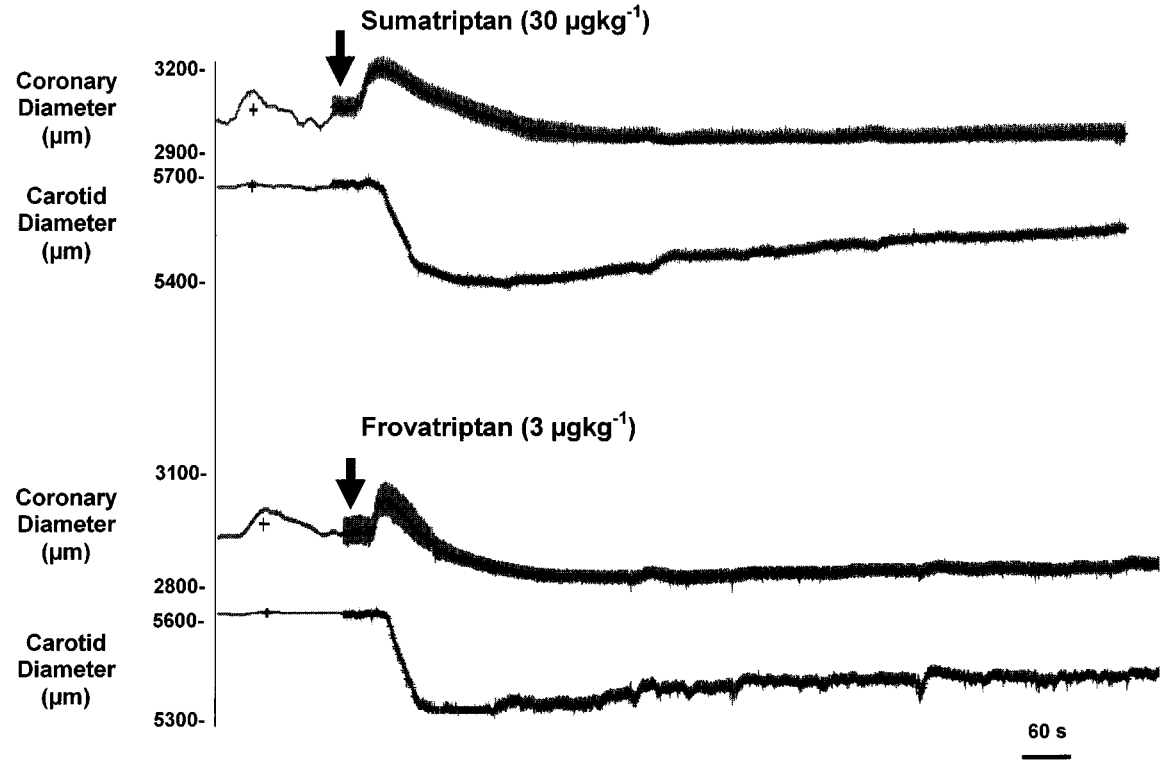

Figure 1 Traces showing the effects (i.v.) of sumatriptan and frovatriptan (30 and 3 μg kg^{-1}, respectively) on phasic epicardial coronary and left internal carotid diameter in a conscious dog. Injection of the drug is indicated by the arrow.

maximal levels of constriction of these vascular beds could not be determined *in vivo*, we assumed that they were the same for the two compounds for the purposes of estimating the molar ED_{50} values from the dose-vasoconstrictor response curves (Figures 2 and 3). For frovatriptan and sumatriptan, these were calculated to be 86 ± 21 and 489 ± 113 μmol kg^{-1}, respectively, at the coronary level and 86 ± 41 and 493 ± 162 μmol kg^{-1}, respectively, at the internal carotid level. Thus, the calculated ED_{50} sumatriptan/ED_{50} frovatriptan ratio was the same (i.e., 5.7) at the level of both large coronary and internal carotid arteries.

Effects of frovatriptan and sumatriptan on small coronary and internal carotid arteries

As shown in Tables 1 and 2, frovatriptan and sumatriptan induced a dose-dependent increase in coronary blood flow and a corresponding dose-dependent decrease in mean coronary resistance. However, these effects were modest in magnitude and variable from one dog to another, the increase in coronary blood flow being significant only with frovatriptan 100 μg kg^{-1} and sumatriptan 3 to 100 μg kg^{-1}. Corresponding coronary vascular resistance significantly decreased from 0.3 to 100 μg kg^{-1} for frovatriptan and at 30 and 100 μg kg^{-1} for sumatriptan, respectively (Figure 4).

In contrast, internal carotid blood flow did not change in a dose-dependent manner following either frovatriptan or sumatriptan administration (Tables 1 and 2). Furthermore, the initial increase in internal carotid blood flow induced by frovatriptan (significant at all doses) and sumatriptan (significant from 3 to 100 μg kg^{-1}) occurred rapidly after drug administration (between 20 and 40 s) but was of very brief duration (<1 min). Considering the simultaneous changes in mean arterial pressure, the calculated internal carotid vascular resistance initially decreased when internal carotid blood flow peaked. It then increased when internal carotid blood flow returned to its baseline value (approximately 1 min after drug administration, regardless of the drug) (Figure 4). In contrast to the initial brief decrease in internal carotid vascular resistance, the subsequent increase in internal carotid vascular resistance was sustained and dose-dependent (i.e., 20 min for frovatriptan 3 μg kg^{-1} and sumatriptan 30 μg kg^{-1}, and >1 h at 100 μg kg^{-1} for both drugs). The maximal changes in internal carotid vascular resistance occurred at the same dose (30 μg kg^{-1}) for frovatriptan ($+23 \pm 7$% from 6.5 ± 0.6 a.u.) and sumatriptan ($+36 \pm 9$% from 5.9 ± 1.2 a.u.).

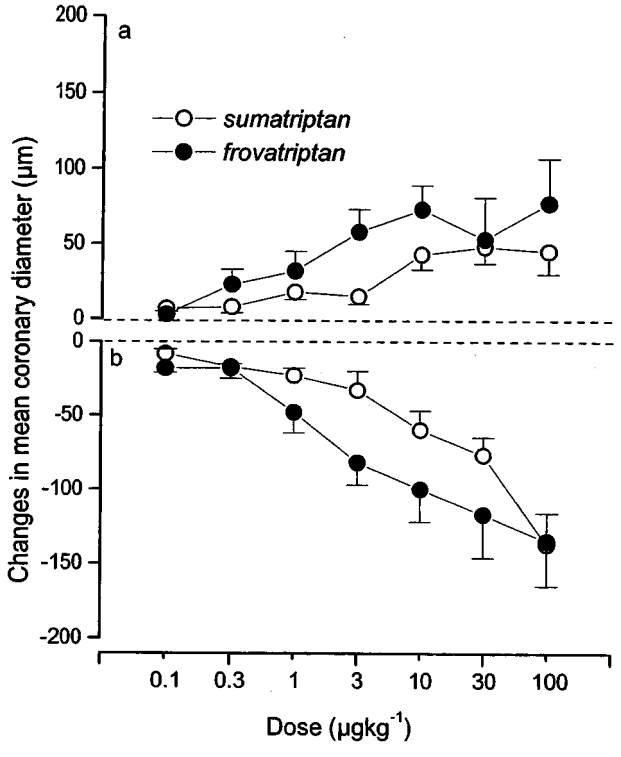

Figure 2 Peak changes (μm) from baseline in the mean external coronary diameter during (a) the vasodilatation phase and (b) the delayed vasoconstriction phase evoked by increasing doses (0.1 to 100 μg kg^{-1}, i.v.) of sumatriptan and frovatriptan in conscious dogs. Each point represents the mean ($n=6$) value and the vertical bars show s.e.mean.

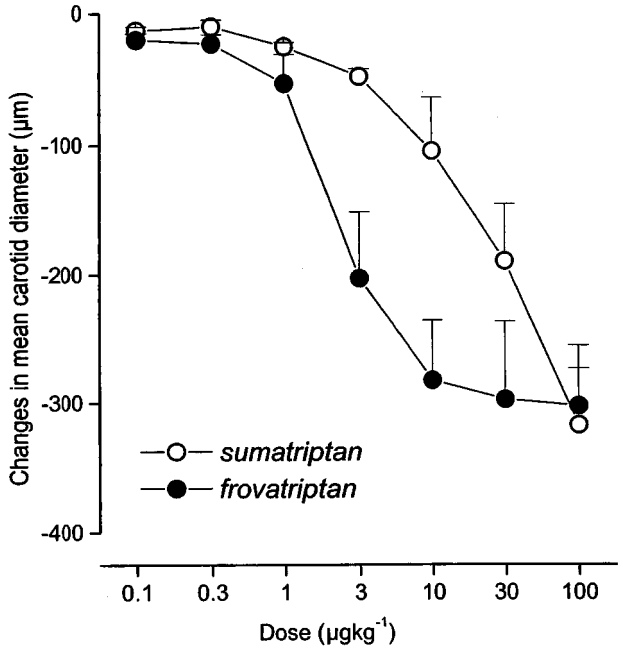

Figure 3 Changes from baseline in mean external diameter (μm) of the left internal carotid measured at the peak vasoconstrictor phase evoked by increasing doses (0.1 to 100 μg kg^{-1}, i.v.) of sumatriptan and frovatriptan in conscious dogs. Each point represents the mean ($n=6$) value and the vertical bars show s.e.mean.

Effects of frovatriptan and sumatriptan on large coronary arteries before and after endothelium removal

As shown in Table 3 and illustrated in Figure 5, both acetylcholine and nitroglycerin increased the diameter of the epicardial circumflex coronary artery when the endothelium was intact. Three days after endothelium removal, the baseline value of the epicardial coronary artery was increased by approximately 300 μm and acetylcholine-induced dilatation was almost abolished whereas nitroglycerin-induced dilatation was not significantly altered as compared with the corresponding dilatation observed before endothelium removal. The effects of both acetylcholine and nitroglycerin on heart rate, mean arterial pressure, coronary blood flow and

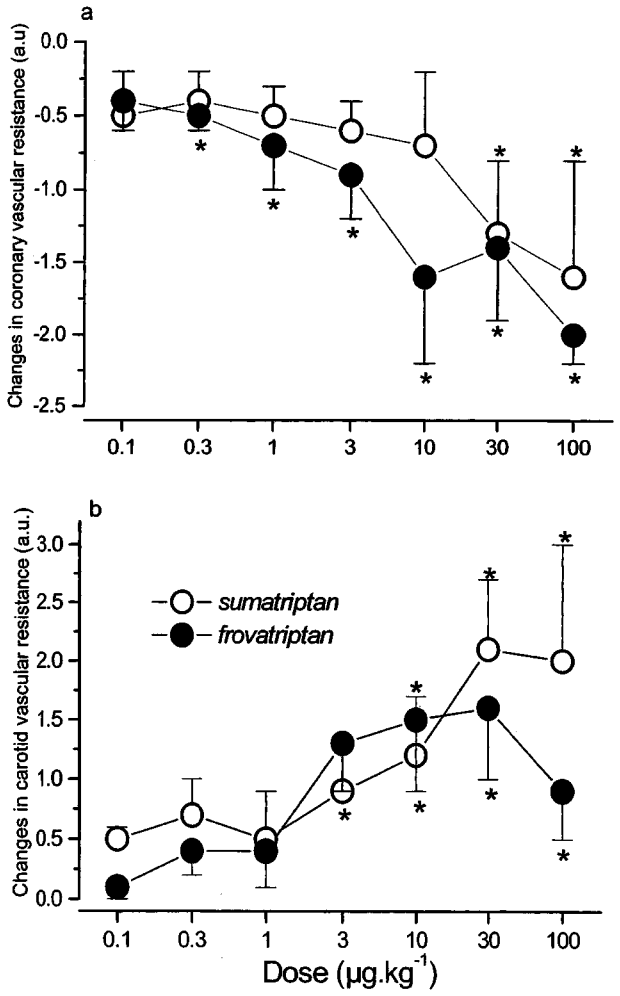

Figure 4 Peak changes (in arbitrary units, a.u.) in (a) coronary and (b) internal carotid vascular resistance evoked by increasing doses (0.1 to 100 μg kg^{-1}, i.v.) of sumatriptan and frovatriptan in conscious dogs. Each point represents the mean ($n=6$) value and the vertical bars show s.e.mean. Changes were compared with corresponding baseline values (see Tables 1 and 2) using two-way analysis of variance followed by Student's paired t-test. *$P<0.05$.

coronary vascular resistance were not significantly different before and 3 days after endothelium removal (Table 3).

As shown in Table 3 and illustrated in Figure 5, the initial coronary dilatation induced by frovatriptan and sumatriptan was abolished after endothelium removal while the change from baseline in the constrictor response was significantly potentiated (frovatriptan: -160 ± 30 μm (i.e., $-5.2\pm0.7\%$) *vs* -130 ± 26 μm (i.e., $-4.6\pm0.7\%$), $P<0.05$; sumatriptan: -156 ± 38 μm (i.e., $-5.0\pm0.9\%$) *vs* -122 ± 33 μm (i.e., $-4.2\pm0.8\%$), $P<0.05$). The effects of both frovatriptan and sumatriptan on heart rate, mean arterial pressure, coronary blood flow and coronary vascular resistance were not significantly different before and 3 days after endothelium removal (Table 3).

Effects of sumatriptan after SB224289 and BRL15572

The highest dose of sumatriptan (100 μg kg^{-1}) administered three times successively at 3 day intervals produced reproducible decreases of the external diameter of the coronary (-6.3, -6.1 and -6.0% respectively) and internal carotid artery (-1.7, -1.9 and -1.4%).

As shown in Table 4, neither the vehicle, nor BRL15572 and SB224289 altered *per se* the systemic haemodynamics and external coronary and internal carotid artery diameters. BRL15572 did not affect the effects of sumatriptan on any of these parameters, regardless of the doses used. In contrast, the sumatriptan-induced tachycardia and increase in arterial blood pressure were blunted after 0.1 and abolished at 0.3 mg kg^{-1} of SB224289. For instance, sumatriptan 100 μg kg^{-1} increased heart rate by 26 ± 4 beats min^{-1} (from 73 ± 3 beats min^{-1}) and mean arterial blood pressure by 28 ± 6 mmHg^{-1} (from 104 ± 6 mmHg^{-1}) after vehicle administration, whereas these increases were only 2 ± 2 beats min^{-1} (from 75 ± 5 beats min^{-1}) and 2 ± 1 mmHg^{-1} (from 96 ± 6 mmHg^{-1}), respectively ($P<0.05$ for both parameters) after SB224289, 0.3 mg kg^{-1}.

BRL15572 (1 mg kg^{-1}) had no effect on, but SB224289 (1 mg kg^{-1}) abolished the early and transient coronary vasodilator effect of sumatriptan (data not shown). As illustrated in Figure 6, BRL15572 had also no significant effects on the vasoconstrictor responses of sumatriptan on coronary and internal carotid arteries, regardless of the dose tested. In contrast, SB224289 dose-dependently decreased the delayed and long-lasting coronary and internal carotid vasoconstrictor effects of sumatriptan. At the highest dose of SB224289, the internal carotid vasoconstriction was abolished whereas only a slight coronary vasoconstriction still persisted (-70 ± 15 μm from 2970 ± 196 μm).

Discussion

In this experimental study conducted in chronically instrumented, conscious dogs, frovatriptan and sumatriptan exhibited modest but dose-dependent tachycardic and hypertensive effects, the latter being probably the result of an increase in peripheral vascular resistance, as previously shown in humans with sumatriptan (MacIntyre *et al*., 1993), rizatriptan (Sciberras *et al*., 1997), alniditan (Goldstein *et al*., 1996) and zolmitriptan (Seaber *et al*., 1996). In a pilot study conducted in two conscious dogs (data not shown), we have observed that whereas sumatriptan still increases mean arterial blood pressure after ganglionic blockade, the drug-induced tachycardia is clearly of neuronal origin since it is prevented by ganglionic blockade. We have presently no explanation about the mechanism(s) underlying such an unusual tachycardia associated with a rise in blood pressure after administration of the two triptans in conscious dogs, except that the sumatriptan-induced increases in heart rate and blood pressure were both blocked by previous administration of SB224289, but not of BRL15572, demonstrating that these haemodynamic effects are mainly mediated through activation of 5-HT$_{1B}$ receptor subtype. Interestingly, the modest increases in blood pressure induced by frovatriptan and sumatriptan in conscious dogs were not previously observed in pentobarbitone anaesthetized dogs (Feniuk *et al*., 1989; Parsons *et al*., 1997; 1998b) but were reported in chloralose anaesthetized dogs (Drieu La Rochelle & O'Connor, 1995). De Vries *et al*. (1996; 1999b) even

Table 3 The effects of (i.v.) acetylcholine, nitroglycerin, frovatriptan and sumatriptan, before (E+) and after coronary endothelium removal (E−)

	HR (beats min^{-1})		*MAP* (mmHg)		*CBFv* (cm s^{-1})		*CVR* (a.u.)		*eCAD* (μm)		
	Base	Δ	*Base*	Δ	*Base*	Δ	*Base*	Δ	*Base*	Δ (max)	Δ (min)
Acetylcholine (0.3 μg kg^{-1})											
E+	94±13	35±8	93±4	−11±2	17±2	10±1	5.9±1.0	−2.4±0.7	2774±203	166±16	–
E−	91±11	37±4	98±2	−16±4	15±5	11±4	5.3±1.3	−3.0±0.7	3074±216*	42±8*	–
Nitroglycerin (1 μg kg^{-1})											
E+	92±12	20±6	94±3	−5±3	17±1	4±1	6.0±1.0	−1.1±0.3	2774±209	234±27	–
E−	90±10	22±4	98±3	−4±1	17±3	6±3	6.4±1.1	−1.2±0.3	3088±228*	168±20	–
Sumatriptan (30 μg kg^{-1})											
E+	93±14	16±7	92±4	6±1	14±2	3±1	7.5±1.1	−1.7±0.5	2810±202	30±11	−122±30
E−	92±13	17±7	96±3	8±2	17±2	5±2	6.9±0.9	−1.8±0.3	3062±231*	0±0*	−156±38*
Frovatriptan (3 μg kg^{-1})											
E+	90±11	14±6	98±6	10±3	14±2	4±2	7.3±1.5	−1.1±0.3	2764±208	34±10	−130±26
E−	89±12	18±6	100±4	8±3	17±3	4±1	6.7±0.8	−1.8±0.9	3064±229*	0±0*	−160±30*

*Significantly different from corresponding value before endothelium removal: $P<0.05$. All values have been presented as means±s.e.mean. $P<0.05$ vs before E−. HR, heart rate; MAP, mean arterial blood pressure; CBFv, coronary blood flow velocity; CVR, coronary vascular resistance; eCAD, external diameter of the coronary artery; a.u., arbitrary units. The effects of the different drugs were measured 3 days after endothelium removal in ($n=6$) conscious dogs.

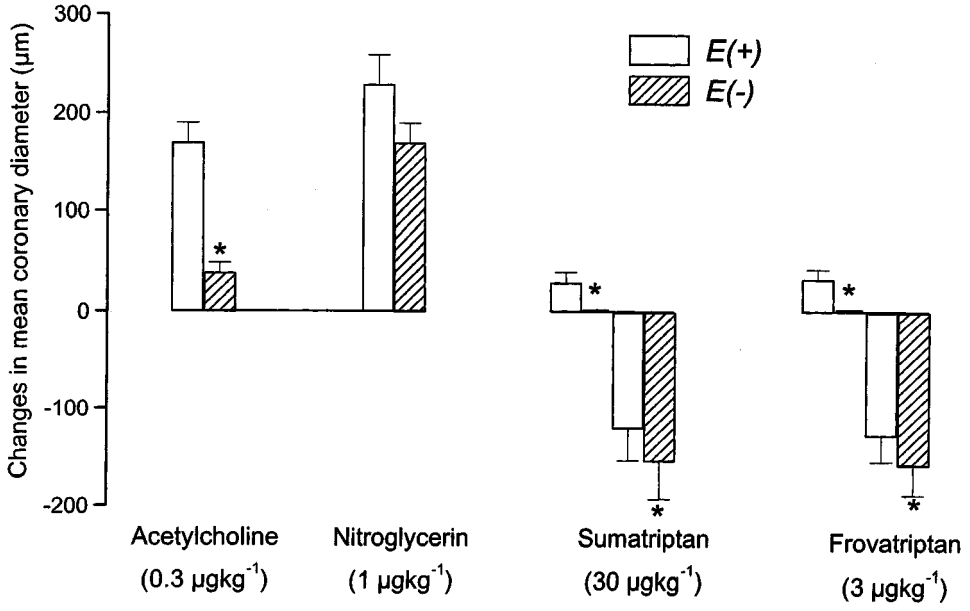

Figure 5 Histograms showing changes (μm) from baseline in mean external coronary artery diameter following (i.v.) acetylcholine, nitroglycerin, sumatriptan and frovatriptan, before (E+) and after (E−) endothelium removal in conscious dogs. Each bar represents the mean ($n=6$) and the lines above the bars show the s.e.mean. Changes are compared with those before endothelium removal using two-way analysis of variance followed by Student's paired t-test. *$P<0.05$. It should be noted that initial dilatation in the coronary artery induced by frovatriptan and sumatriptan was abolished after endothelium removal, whereas the change in the delayed vasoconstrictor phase was significantly ($P<0.05$) potentiated.

observed small bradycardic and hypotensive effects after administration of sumatriptan in pentobarbitone anaesthetized pigs, suggesting that the drug simultaneously stimulates systemic vasodilator and vasoconstrictor mechanisms, of which the latter is amenable to blockade by SB224289. These discrepancies probably originate from the different animal models used and highlight the usefulness of conducting haemodynamic studies in conscious animals. Finally, the increase in dP/dt max observed with sumatriptan, and to a lesser extent with frovatriptan, could be the result of the increase in arterial blood pressure by these drugs through the so-called 'Anrep effect' often observed as a normal LV response to a pressure loading in conscious dogs with low resting heart rates (Vatner *et al*., 1974).

Table 4 The effects of (i.v.) vehicle, SB224289 and BRL15572 on systemic, coronary and internal carotid haemodynamics in conscious dogs

	HR (beats min^{-1})	*MAP* (mmHg)	*eCAD* (μm)	*eICAD* (μm)
Vehicle				
Before	70±6	97±3	2723±196	5213±264
After	73±3	104±6	2662±157	5124±206
SB224289 (0.1 mg kg^{-1})				
Before	71±3	99±4	2635±161	5192±244
After	75±5	101±6	2692±168	5217±261
SB224289 (0.3 mg kg^{-1})				
Before	73±8	99±4	2709±158	5243±224
After	75±5	96±6	2753±180	5154±296
SB224289 (1 mg kg^{-1})				
Before	69±6	92±9	2894±184	5163±224
After	73±9	96±7	2970±196	5090±306
BRL15572 (0.1 mg kg^{-1})				
Before	76±10	93±7	2746±147	5216±215
After	75±9	94±9	2716±136	5186±267
BRL15572 (0.3 mg kg^{-1})				
Before	80±9	96±8	2706±143	5249±257
After	79±7	101±6	2696±196	5310±301
BRL15572 (1 mg kg^{-1})				
Before	78±7	100±2	2723±157	5278±286
After	74±8	94±8	2700±143	5326±316

All values have been presented as mean±s.e.mean. HR, heart rate (beats min^{-1}); MAP, mean arterial blood pressure (mmHg); eCAD, external coronary artery diameter (μm); eICAD, external diameter of the left internal carotid artery (μm). The effects of vehicle or the antagonists were measured 15 min after administration in ($n=3$) conscious dogs.

Large coronary arteries

The biphasic effect of frovatriptan and sumatriptan on large coronary arteries is similar to that previously described with serotonin (Chu & Cobb, 1987) and ergonovine (Egashira *et al*., 1992; Karila-Cohen *et al*., 1999). In agreement with *in vitro* data previously reported by Schoeffter & Hoyer (1989), we observed that the initial and dose-dependent increases in external coronary artery diameter induced by the drugs are totally endothelium-independent, as reflected by their complete blockade following endothelium removal. This vasodilator effect might be the result of at least two mechanisms: (a) the release of nitric oxide or related endothelium derived factors following activation of 5-HT$_{1B/1D}$-receptors located on endothelial cells (Valentin *et al*., 1996; 1998), and (b) an indirect mechanism linked to the concomitant increase in coronary blood flow, which also releases endothelium derived relaxing factors, including nitric oxide, through a flow-dependent mechanism. As SB224289 (1 mg kg^{-1}) but not BRL15572 (1 mg kg^{-1}) abolished the early vasodilator effect of sumatriptan on these vessels, it could be assumed that 5-HT$_{1B}$, but not 5-HT$_{1D}$ receptors, are involved in this endothelium-dependent response. However, as we did not analyse the effects of SB224289 on the coronary vasodilator responses to acetylcholine or to any other endothelium-dependent vasodilator agent, further experiments are necessary to support this assumption. Similarly, there is no clear evidence to date indicating that 5-HT-induced endothelium-dependent vasodilatation is mediated through 5-HT$_{1B}$ receptors activation. Following this initial vasodilatation of large coronary arteries, both frovatriptan and sumatriptan induced a dose and time-dependent coronary constriction which was also well described on isolated large coronary arteries with several other 5-HT$_{1B/1D}$-receptor agonists (MaasenVanDenBrink *et al*., 1998; Valentin *et al*., 1998; Parsons *et al*., 1998b). The present study also shows that such a constriction of epicardial coronary arteries after administration of frovatriptan and sumatriptan *in vivo* may be modulated by the vascular endothelium. We show that endothelium removal enhances the delayed coronary constriction induced by these agents when measured from the resulting increased baseline diameter of the vessel. We also confirm that the 5-HT$_{1B}$ receptor subtype mediates the effects of sumatriptan on large coronary vessels since the delayed vasoconstriction, as well as the initial coronary vasodilatory response elicited by the drug are both antagonized by SB224289, but not by BRL15572. It should be stressed here that despite the absence of control experiments, suppression of the sumatriptan-induced early dilatation and attenuation of the drug's delayed vasoconstrictor effects on large coronary arteries (and internal carotid artery, see below) by SB224289 can most likely not be accounted for by tachyphylaxis to repeated sumatriptan challenge as (a) no suppression/attenuation of these coronary effects of sumatriptan was observed after increasing doses of BRL15572 (Figure 6), and (b) three successive administrations of the highest dose of sumatriptan (100 μg kg^{-1}) performed at 3 day intervals in the same dogs provided almost similar maximal responses. The involvement of 5-HT$_{1B}$ but not 5-HT$_{1D}$ receptors in the coronary effects of sumatriptan are in agreement with previous pharmacological studies (Kaumann *et al*., 1993; 1994; Longmore *et al*., 1998) and on expression of local mRNA (Hamel *et al*., 1993; Sgard *et al*., 1996; Bouchelet *et al*., 2000).

Internal carotid artery

Contrasting with their biphasic action on large coronary arteries, both frovatriptan and sumatriptan induced only a

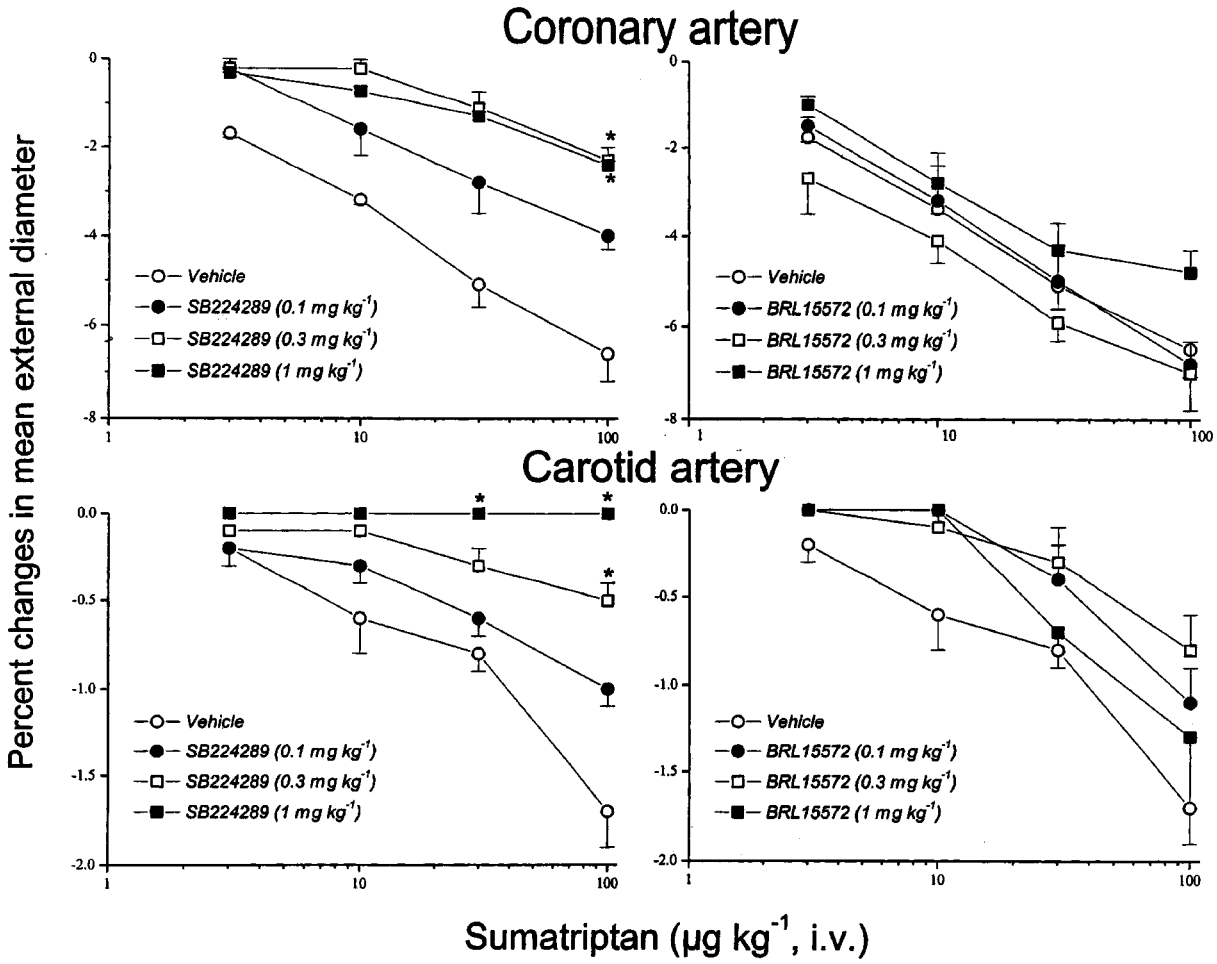

Figure 6 Changes (%) from baseline in mean external diameter of the coronary and the left internal carotid arteries during the vasoconstrictor phase of sumatriptan evoked by increasing doses (i.v., 3 to 100 μg kg^{-1}) in the presence of vehicle or 0.1, 0.3 and 1 mg kg^{-1} of either the 5-HT$_{1B}$ (SB224289) or 5-HT$_{1D}$ (BRL15572) receptor antagonists in conscious dogs. Each point represents the mean ($n=3$) value and the vertical bars show s.e.mean. Changes in the presence of the antagonists were compared with those of vehicle using two-way analysis of variance followed by Student's paired t-test. *$P<0.05$.

monophasic, early, dose-dependent and long lasting constriction of the large carotid arteries. It is well established that there are clearcut differences in the vascular reactivity to 5-HT and related agonists between the common (Mylecharane *et al*., 1990), the internal (Vidrio & Hong, 1976) and the external carotid (Mena & Vidrio, 1979) vascular beds in the dog and this study demonstrates that triptans induce a sustained vasoconstriction at the level of the internal carotid artery in conscious dogs. Identical vasoconstrictor effects have previously been described with sumatriptan in a similar range of doses on peripheral veins in anaesthetized dogs (Drieu La Rochelle & O'Connor, 1995) and this effect was reported to be mediated by 5-HT$_{1B/1D}$-receptors. In agreement with carotid haemodynamic studies performed in anaesthetized dogs (De Vries *et al*., 1998; Centurion *et al*., 1999) and pigs (De Vries *et al*., 1999a,b), the present study confirms that the vasoconstrictor effect of sumatriptan on internal carotid arteries is mediated by 5-HT$_{1B}$ receptors in conscious dogs as previously shown in anaesthetized dogs (Centurion *et al*., 1999). To date, increasing data have also shown that the 5-HT$_{1B}$ receptor subtype selectively mediates the contractions of the human temporal (Verheggen *et al*., 1996; 1998) and middle meningeal arteries (Longmore *et al*., 1998) as well of the temporal ramifications of the middle cerebral artery (Bouchelet *et al*., 2000). Finally, the fact that sumatriptan still elicited some residual vasoconstriction at the level of large coronary (but not of internal carotid) arteries even after the highest tested dose of SB224289, would suggest that receptors other than 5-HT$_{1B}$ subtype could be involved in the effect of the drug in the coronary vascular bed, but this requires further investigations.

Interestingly, the calculated ED$_{50}$ sumatriptan/ED$_{50}$ frovatriptan ratio was the same (i.e., 5.7) at the level of both large coronary and internal carotid arteries in our study, indicating (a) that frovatriptan is 5.7 times more potent than sumatriptan at constricting coronary and internal carotid arteries, and (b) that neither of these drugs displayed a selectivity for any of the two investigated vascular beds when administered intravenously *via* the pulmonary artery. The present estimates of relative activities *in vivo* are in good agreement with those reported by Parsons *et al*. (1998a) demonstrating that frovatriptan was 8.5 fold more potent than sumatriptan in producing contraction of the human isolated basilar artery and 2.9–6.5 fold more potent than

sumatriptan in producing contraction of human isolated coronary arteries from donor and recipient hearts, respectively. This compares to a ratio of 11 for the plasma molar C_{max} values of sumatriptan and frovatriptan in humans following the oral therapeutic doses of 100 and 2.5 mg respectively (P. Buchan, personal communication).

Coronary vascular bed

At the level of small coronary arteries, both drugs induced a dose-dependent increase in coronary blood flow and a simultaneous decrease in coronary vascular resistance. These effects were not previously reported in isolated perfused guinea-pig hearts (Le Grand *et al*., 1998) and in anaesthetized dogs with similar doses of sumatriptan (Cambridge *et al*., 1995; Feniuk *et al*., 1989; Parsons *et al*., 1997) and frovatriptan (Parsons *et al*., 1998b). However, the high levels of basal heart rate and coronary blood flow in these animals necessarily reduced the coronary dilatation reserve of resistance arteries and could explain the discrepancy with our study conducted in conscious dogs with low resting heart rate and high coronary dilatation reserve. Since frovatriptan and sumatriptan increased heart rate and mean arterial blood pressure in this study, one might suggest that the observed increase in coronary blood flow results from an increase in myocardial oxygen demand. However, these haemodynamic effects of frovatriptan and sumatriptan were very brief (<30 s) and of limited magnitude. Activation of presynaptic 5-HT_{1D}-receptors, which mediates inhibition of sympathetic nerve outflow in the human atrium (Schlicker *et al*., 1997), may also limit the release of noradrenaline at the level of coronary arteries, and thereby reduce coronary constriction. This is a much more plausible mechanism to propose for the observed increase in coronary blood flow with frovatriptan and sumatriptan in our model.

Internal carotid vascular bed

At the level of small internal carotid arteries, the initial increase in internal carotid blood flow and decrease in resistance induced by frovatriptan and sumatriptan were very brief, in contrast with the delayed and long lasting increase in internal carotid resistance. The effects of frovatriptan and sumatriptan on internal carotid vascular resistance were less than those observed in previous studies with anaesthetized dogs (Cambridge *et al*., 1995; Feniuk *et al*., 1989; Parsons *et al*., 1997; Centurion *et al*., 1999) and probably reflected the contribution of arteriovenous shunt flow to the total common carotid artery blood flow. The exact location of the increase in internal carotid vascular resistance is not clear from the present results and will require further studies. It was also interesting to note that the dose-response curve for frovatriptan on internal carotid vascular resistance displayed a 'bell-shaped' profile as the 100 $\mu g\ kg^{-1}$ dose produced a smaller vasoconstrictor effect than the 30 $\mu g\ kg^{-1}$ one. This observation is consistent with that reported *in vitro* (Parsons *et al*., 1998a,b) but it should be stressed that no 'bell-shaped' dose-response curve for frovatriptan was observed on epicardial coronary arteries in conscious dogs. We have no explanation for this discrepancy as yet.

In summary, the present study demonstrates that frovatriptan, administered intravenously as a bolus dose, is 5.7 fold more potent than sumatriptan at inducing the constriction of large coronary and internal carotid arteries in conscious dogs. The effects of sumatriptan are all mediated by activation of 5-HT_{1B} receptor subtype. At the level of the coronary vascular bed, the endothelium mediates the initial dilatory effect of frovatriptan and sumatriptan and appears to modulate the subsequent coronary constriction induced by these triptans.

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