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Sumatriptan-induced saphenous venoconstriction in the anaesthetized dog through 5-HT_1-like receptor activation

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1 The role of vasoconstrictor 5-HT_1-like receptors in the control of vascular reactivity *in vivo* has been relatively little studied, particularly with regards to venous function. Using an anaesthetized dog model, we have investigated the haemodynamic profile of the selective 5-HT_1-like agonist, sumatriptan, focussing on the reactivity of the saphenous venous bed. The key feature of our experimental model was the implantation of ultrasonic crystals on the adventitial surface of the lateral saphenous vein to provide direct and continuous measurement of drug-induced changes in vein diameter. Saphenous vein pressure was measured simultaneously via a proximal branch.

2 Sumatriptan 1-30 $\mu g\ kg^{-1}$, i.v., produced pronounced dose-related reductions in saphenous vein diameter which reached $\simeq 40\%$ at the highest dose tested. Sumatriptan also produced modest increases in mean blood pressure, total peripheral resistance and left ventricular end diastolic pressure but had little or no effect on cardiac output, heart rate, cardiac contractility or saphenous venous pressure. Sumatriptan-induced reductions in saphenous vein diameter were strongly antagonized by the 5-HT_1-receptor antagonist, methiothepin (0.3 $mg\ kg^{-1}$, i.v.) but were unaffected by the 5-HT_2 antagonist, ketanserin (0.3 $mg\ kg^{-1}$, i.v.).

3 Hence, 5-HT_1-like receptor stimulation *in vivo* can result in a powerful local venoconstrictor effect.

Keywords: 5-HT_1-like receptors; sumatriptan; venoconstriction; anaesthetized dog

Introduction

The vasoconstrictor effects of 5-hydroxytryptamine (5-HT) are mediated by activation of two receptor types, 5-HT_2 and 5-HT_1-like receptors (Saxena & Villalon, 1990). 5-HT_2 receptors, which are sensitive to antagonism by ketanserin, are widely distributed in the vascular system and mediate 5-HT-induced pressor responses in certain models (Fozard, 1982). By contrast, the location of vasoconstrictor 5-HT_1-like receptors is subject to considerable tissue and species variation. The most extensively studied examples of the 5-HT_1-like subtype are the main cerebral arteries of various species including man (Parsons *et al.*, 1989), canine saphenous vein (Humphrey *et al.*, 1988) and canine and human coronary arteries (Cushing & Cohen, 1992; Kaumann *et al.*, 1994). In addition, certain other vessels (e.g. rabbit mesenteric artery) demonstrate prominent 5-HT_1-like mediated contractile responses only in the presence of another vasoconstrictor agent (Choppin & O'Connor, 1995).

Interest in and understanding of the role and physiological significance of vasoconstrictor 5-HT_1-like receptors has progressed with the identification and development of sumatriptan, a novel selective agonist for 5-HT_1-like/5-HT_{1D} receptors (Humphrey *et al.*, 1988), which has proved to be a highly effective anti-migraine agent (The Subcutaneous Sumatriptan International Study Group, 1991). According to the vascular hypothesis of migraine, the therapeutic efficacy of sumatriptan may be due to 5-HT_1-like receptor mediated constriction of intra-cranial cerebral blood vessels (Humphrey & Feniuk, 1991; Ferrari & Saxena, 1993).

The functional importance of vasoconstrictor 5-HT_1-like receptors *in vivo* has been relatively little explored. Published haemodynamic investigations of sumatriptan in intact anaesthetized animals describe a relatively selective constriction of the carotid arterial circulation with little or no change in blood pressure (Feniuk *et al.*, 1989; den Boer *et al.*, 1991). The effects of sumatriptan on venous function are unknown. We have investigated the haemodynamic profile of sumatriptan administered systemically to the anaesthetized dog focussing, in particular, on the saphenous venous circulation. This vascular bed was chosen for study because isolated tissue experiments have demonstrated the presence of 5-HT_1-like receptors in the canine saphenous vein (Humphrey *et al.*, 1988). We have evaluated the reactivity of the lateral saphenous vein *in situ* in the anaesthetized dog using a sonomicrometric technique which allows vein diameter to be recorded continuously. This technique has been used previously to measure the diameter of large coronary arteries (Drieu la Rochelle *et al.*, 1992).

Methods

Surgical procedure

Eighteen Alsatian dogs of either sex with an average weight of 27.2 ± 0.6 kg were anaesthetized initially with sodium thiopentone (20 $mg\ kg^{-1}$, i.v.), a short-acting barbiturate, and anaesthesia maintained throughout the experiment with α-chloralose (80 $mg\ kg^{-1}$, i.v. + 20 to 30 $mg\ kg^{-1}\ h^{-1}$, i.v.). After endotracheal intubation, the animals were artificially ventilated (Braun respiratory pump) with ambient air enriched with oxygen such as to maintain blood gas parameters (P_{O_2}, P_{CO_2}, pH) within normal limits. Body temperature was maintained at 38-39°C with a heating blanket.

A catheter was introduced into the right brachial artery and advanced into the thoracic aorta for measurement of mean arterial blood pressure (MAP) with a Gould Statham transducer connected to a Gould preamplifier. The anaesthetic infusion and administration of drugs were effected via catheters placed in left brachial and right femoral veins, respectively. A left thoracotomy was performed in the fourth intercostal space and an electromagnetic flow probe positioned around the ascending aorta to measure mean aortic blood flow (ABF), an index of cardiac output, with an electromagnetic flowmeter (Carolina Medical Electronics Inc.). Total peripheral vascular resistance (TPR) was calculated by dividing MAP by ABF. Left ventricular pressure was monitored with a MIKRO-TIP catheter pressure transducer (No. 5F, Millar Instruments Inc.)

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introduced into the left ventricle via the muscular branch of the right femoral artery which enabled the measurement of left ventricular end diastolic pressure (LVEDP). The first derivative of left ventricular pressure (dP/dt) was obtained using a differentiator and dP/dt_{max} was used as the index of myocardial contractility. The electrocardiogram (ECG, Lead II) was recorded continuously with subcutaneous needle electrodes, and heart rate (HR) calculated. Two circular disk ultrasonic vessel diameter transducer crystals of 2.0 mm diameter (Triton Technology Inc.) were placed on opposite sides of the dorsal branch of the left lateral saphenous vein. The crystals were first glued to polyester patches, these were then sewn to the adventitia of the saphenous vein with 6-0 suture after first ensuring parallel alignment by monitoring the ultrasonic signal with an oscilloscope, and saphenous vein diameter (SVD) was measured instantaneously and continuously with a sonomicrometer (120.2 Triton Technology Inc.). The sonomicrometer has been modified in accordance with Triton Technology in order to reduce the lower measurement limit from 2.0 to 1.0 mm. A small catheter of PE50 tubing was introduced into the plantar branch of the left lateral saphenous vein and positioned in the saphenous vein downstream to the site of crystal implantation for measurement of mean saphenous vein pressure (SVP) using a Gould Statham transducer. All procedures were performed in accordance with European Council official guidelines for animal experimentation.

Experimental protocol

Animals were randomised into three experimental groups ($n=6$ per group). Each animal received ascending bolus i.v. doses ($1-30\ \mu g\ kg^{-1}$) of sumatriptan ('control' responses). Following this, the animals received a 10 min i.v. infusion of either vehicle (5 ml distilled water + 5 ml saline; Group 1), or ketanserin $0.3\ mg\ kg^{-1}$ (Group 2) or methiothepin $0.3\ mg\ kg^{-1}$ (Group 3), and a second dose-response curve to sumatriptan was performed. After methiothepin, sumatriptan was administered at doses up to $300\ \mu g\ kg^{-1}$. Recovery of basal cardiovascular parameters was awaited between consecutive doses of sumatriptan.

Data and statistical analysis

Haemodynamic data were recorded on a multichannel electrostatic recorder (ES 1000, Gould Inc.) and digitized at a sampling rate of 2 kHz per channel at full 12-bit resolution using HEM software (Notocord Systems). Digitized data were filtered and stored at 500 Hz on the hard disk of a compatible PC and used in parallel for calculation and display in real time of derived parameters. Cardiovascular parameters were measured just before (basal values) and at the time of the peak effect on SVD after each bolus administration of sumatriptan and the percentage changes from corresponding basal values

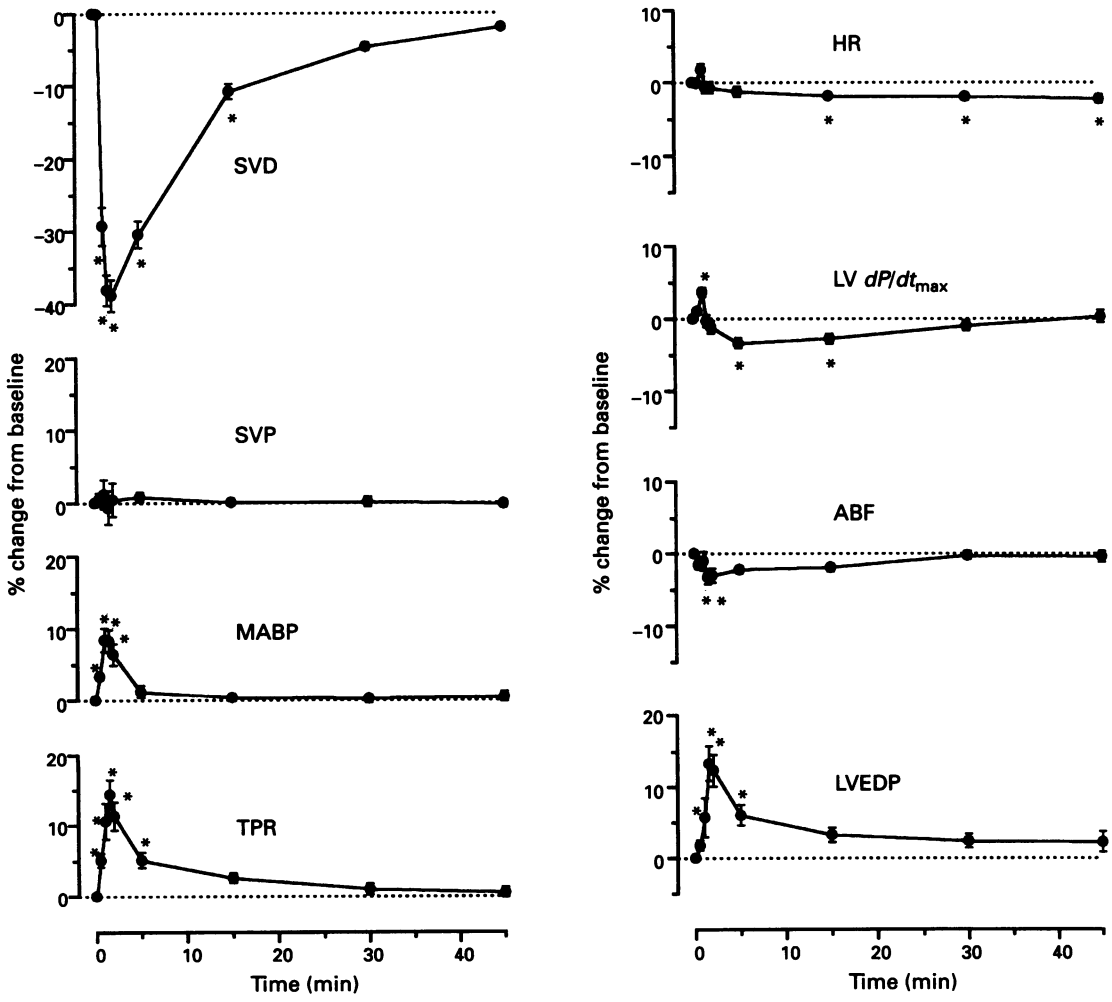

Figure 1 Cardiovascular changes following injection of sumatriptan ($30\ \mu g\ kg^{-1}$, i.v. bolus) in the anaesthetized dog during the control dose-response curves ($n=18$). Points on the graphs represent mean % changes from corresponding basal value with s.e.mean SVD, saphenous vein diameter; SVP, saphenous vein pressure; MABP, mean arterial blood pressure; TPR, total peripheral resistance; HR, heart rate; LV dP/dt_{max}, maximal rate of rise of left ventricular pressure; ABF, aortic blood flow; LVEDP, left ventricular diastolic pressure. $^*P<0.05$ vs basal value.

were calculated. To describe the time course of the effects of sumatriptan, cardiovascular parameters were measured just before and 0.5, 1, 1.5, 2, 5, 15, 30 and 45 min after the administration of sumatriptan 30 $\mu g\ kg^{-1}$ during the control dose-response curves. In order to quantify the venoconstrictor potency of sumatriptan, the dose necessary to decrease SVD by 20% (ED_{20} SVD) was determined for each animal before and after treatment. Results are expressed either as absolute or percentage changes from basal values. Data shown are mean ± s.e.mean. Statistical analysis was performed on the individual absolute values using a two-way analysis of variance. When overall differences were detected, individual comparisons were made with Student's paired t test with Bonferroni's correction or a Dunnett test. Comparisons between the effects of sumatriptan before *vs.* after treatment were made on the absolute variation by two-way analysis of variance followed by Student's paired t test. ED_{20} SVD values were compared before and after treatment in each experimental group using Student's paired t test. For all cases the threshold for significance was fixed at $P<0.05$.

Drugs

Sumatriptan succinate (Synthélabo Recherche) was dissolved in saline (0.9%). Ketanserin tartrate (Janssen Research Foundation) and methiothepin methanesulphonate (Research Biochemicals International) were dissolved in 5 ml distilled water and volume was adjusted to 10 ml with saline. Drug dosages refer to the free base. Other drugs used were α-chloralose (Prolabo) and sodium thiopentone (Rhone Merieux).

Results

Effects of sumatriptan

The most potent and pronounced haemodynamic effect of sumatriptan (1–30 $\mu g\ kg^{-1}$, i.v.) observed in this study was a dose-related reduction in SVD. At the higher doses this was accompanied by mild increases in TPR, MAP and LVEDP. By contrast, ABF, HR, dP/dt_{max} and SVP were little affected. The time course of the effects of sumatriptan on SVD and other cardiovascular parameters are presented in Figure 1 for the highest dose (30 $\mu g\ kg^{-1}$) of the control dose-response curves ($n=18$). At that dose, sumatriptan induced a marked reduction in SVD (−39 ± 2% from 2520 ± 80 μm) without modifying SVP. This effect was accompanied by modest increases in MAP (+8 ± 2% from 109 ± 3 mmHg), TPR (+14 ± 2% from 29 ± 1 mmHg l^{-1} min) and LVEDP (+13 ± 2% from 12 ± 1 mmHg). The effects of sumatripan on MAP, TPR and LVEDP were rapid in onset, peaking after 60-90 s and recovering rapidly (within 5–15 min). The decrease in SVD induced by sumatriptan was maximal 2 min following i.v. administration and was sustained for 30–45 min.

Table 1 summarizes the basal values of cardiovascular parameters and their percentage change after increasing doses of sumatriptan, these effects being measured at the time of the peak decrease in SVD. As shown in Table 1 and Figure 2, decreases in SVD induced by sumatriptan were dose-dependent and were not accompanied by concomitant variation in SVP. Administration of vehicle had no effect on haemodynamic parameters except a small but statistically significant decrease in HR (from 161 ± 6 to 155 ± 5 beats min^{-1}). Table 2 and Figure 2 show that the SVD dose-response curve to sumatriptan was unchanged by administration of vehicle. Accordingly, ED_{20} SVD values for sumatriptan were not significantly different (4.7 ± 1.3 $\mu g\ kg^{-1}$ and 6.0 ± 1.6 $\mu g\ kg^{-1}$ for control and vehicle, respectively).

Effects of 5-HT receptor antagonists on the responses produced by sumatriptan

Ketanserin (0.3 mg kg^{-1}, i.v.) slightly but significantly decreased LVEDP (from 14 ± 3 to 11 ± 1 mmHg), MAP (from 108 ± 6 to 99 ± 5 mmHg), TPR (from 33 ± 2 to 30 ± 2 mmHg l^{-1} min) and HR (from 159 ± 7 to 150 ± 7 beats min^{-1}). As shown in Figure 2, ketanserin did not modify the dose-dependent reduction in SVD induced by sumatriptan and ED_{20} SVD values in control conditions and in the presence of ketanserin were not significantly different (6.0 ± 1.7 $\mu g\ kg^{-1}$ and 8.1 ± 2.1 $\mu g\ kg^{-1}$, respectively. In addition, ketanserin had no effect on the slight increase in MAP induced by sumatriptan (after sumatriptan 30 $\mu g\ kg^{-1}$ MAP increased by +10 ± 3% and +11 ± 3% in absence and presence of ketanserin, respectively). Ketanserin did not modify any of the other effects of sumatriptan (data not shown).

Table 1 Effects of increasing i.v. bolus doses of sumatriptan on haemodynamic parameters before administration of vehicle (Group 1) or methiothepin 0.3 mg kg^{-1} (Group 3)

Sumatriptan ($\mu g\ kg^{-1}$)			*HR* (beats min^{-1})	*dP/dt_{max}* (mmHg s^{-1})	*LVEDP* (mmHg)	*MAP* (mmHg)	*ABF* ($l\ min^{-1}$)	*TPR* (mmHg l^{-1} min)	*SVP* (mmHg)	*SVD* (μm)
Group 1	1	Basal	170 ± 5	2430 ± 403	10.6 ± 2.5	110 ± 7	4.2 ± 0.2	26.0 ± 1.5	9.4 ± 0.7	2425 ± 123
		Δ%	−0.3 ± 0.4	−0.8 ± 0.7	0.4 ± 0.6	0.9 ± 0.6	−1.3 ± 1.1	2.2 ± 1.2	0.5 ± 1.6	−5.1 ± 2.8
	3	Basal	169 ± 5	2397 ± 404	10.7 ± 2.4	108 ± 7	4.2 ± 0.2	25.8 ± 1.5	9.4 ± 0.7	2442 ± 130
		Δ%	−0.6 ± 0.8	−2.2 ± 1.1	3.1 ± 2.2	0.3 ± 0.8	0.6 ± 1.5	−0.3 ± 0.9	2.2 ± 2.4	−17.0 ± 5.1*
	10	Basal	166 ± 5	2328 ± 382	11.2 ± 2.2	108 ± 7	4.2 ± 0.2	26.1 ± 1.4	9.4 ± 0.7	2438 ± 134
		Δ%	−1.2 ± 0.9	−2.7 ± 0.7	8.3 ± 2.7	0.7 ± 0.8	−1.9 ± 1.7	2.9 ± 2.3	2.1 ± 3.3	−33.8 ± 4.0*
	30	Basal	161 ± 6	2242 ± 342	12.0 ± 1.8	108 ± 7	4.1 ± 0.3	26.3 ± 1.7	9.0 ± 0.7	2435 ± 144
		Δ%	−1.3 ± 1.3	−2.8 ± 1.3	9.6 ± 2.9	2.6 ± 1.3	−4.8 ± 2.3	8.1 ± 2.8*	6.7 ± 4.6	−37.7 ± 4.2*
Group 3	1	Basal	150 ± 4	1814 ± 150	12.2 ± 1.0	110 ± 4	4.2 ± 0.4	27.9 ± 3.6	10.1 ± 0.3	2735 ± 173
		Δ%	−1.0 ± 0.5	−0.2 ± 0.4	2.7 ± 1.0	0.5 ± 0.4	0.4 ± 0.5	0.0 ± 0.5	0.5 ± 0.9	−1.2 ± 0.4
	3	Basal	147 ± 5	1823 ± 149	12.1 ± 1.0	110 ± 4	4.2 ± 0.4	27.8 ± 3.7	10.1 ± 0.4	2732 ± 168
		Δ%	−1.3 ± 0.8	−0.7 ± 0.7	4.7 ± 1.8	1.3 ± 0.9	−0.7 ± 0.8	2.1 ± 1.6	−0.6 ± 0.9	−16.1 ± 4.1*
	10	Basal	145 ± 4	1828 ± 145	11.1 ± 1.0	109 ± 4	4.2 ± 0.4	27.5 ± 3.4	10.0 ± 0.4	2729 ± 167
		Δ%	−0.4 ± 0.9	0.4 ± 1.5	9.5 ± 2.6*	5.6 ± 1.7*	−2.4 ± 1.2	8.3 ± 2.6*	−3.5 ± 1.3*	−35.5 ± 5.0*
	30	Basal	146 ± 2	1882 ± 119	10.2 ± 0.9	108 ± 4	4.2 ± 0.3	27.0 ± 3.1	9.9 ± 0.4	2728 ± 166
		Δ%	0.3 ± 1.2	1.3 ± 1.6	14.2 ± 3.2*	10.0 ± 2.5*	−3.7 ± 1.0	14.3 ± 3.0*	−0.7 ± 2.1	−42.8 ± 4.1*

HR (heart rate), dP/dt_{max} (maximal rate of rise of left ventricular pressure), LVEDP (left ventricular end diastolic pressure), MAP (mean aortic pressure), ABF (mean aortic blood flow), TPR (total peripheral vascular resistance), SVP (mean saphenous vein pressure), SVD (mean saphenous vein diameter).

These effects were measured at the time corresponding to the peak decrease in saphenous vein diameter. Values are mean ± s.e.mean ($n=6$ per group).

*$P<0.05$ versus corresponding basal value.

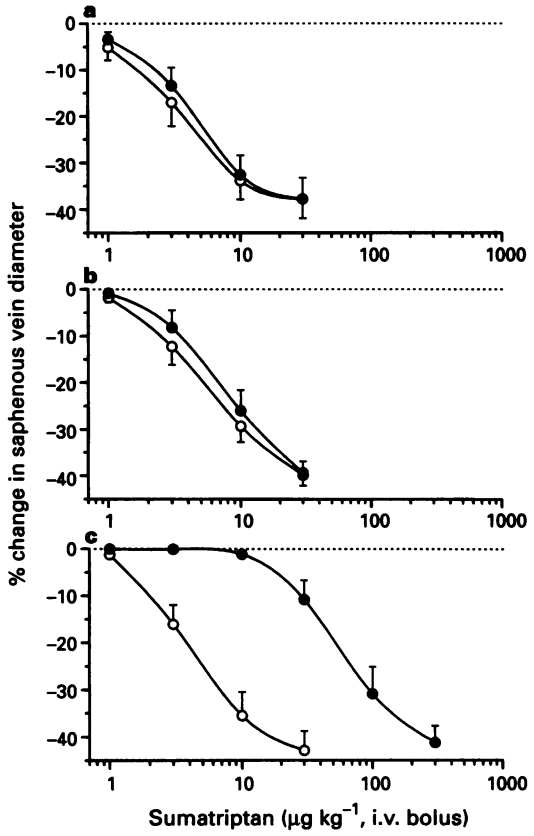

Figure 2 Graphs showing dose-response relationship for sumatriptan-induced reductions in saphenous vein diameter in the anaesthetized dog before (○) and after (●) treatment by vehicle (a), ketanserin 0.3 mg kg^{-1} (b), or methiothepin 0.3 mg kg^{-1} (c). Points on the graphs represent mean % changes from corresponding basal value and s.e.mean is shown by vertical bars ($n=6$ animals in each panel.).

The effects of methiothepin on haemodynamic and SVD responses to sumatriptan are presented in Tables 1 and 2 and Figure 2, respectively. Methiothepin (0.3 mg kg^{-1}, i.v.) significantly decreased LVEDP (from 10±1 to 9±1 mmHg), MAP (from 108±4 to 92±4 mmHg) and TPR (from 27 ± 3 to 21±1 mmHg l^{-1} min), and increased HR (from 146±2 to 157±3 beats min^{-1}) and dp/dt_{max} (from 1882± 119 to 2036±143 mmHg s^{-1}) but did not change other parameters, notably SVD (from 2728±166 to 2752±163 μm, NS). Methiothepin caused a parallel rightward shift of the sumatriptan dose-respose curve for SVD, with no apparent change in maximum effect (Figure 2). The ED_{20} SVD value in presence of methiothepin was significantly increased compared to that in control conditions (71±23 μg kg^{-1} versus 5.0±1.9 μg kg^{-1}, respectively $P<0.05$), representing a 14.8±1.5 fold antagonism at this response level. Methiothepin also antagonized the sumatriptan-induced increases in MAP (+15±3% and +9±2% after sumatriptan 30 μg kg^{-1} in the absence and presence of methiothepin, respectively), LVEDP and TPR. Statistical analysis indicated that these effects of methiothepin were significant ($P<0.05$ Table 2).

Discussion

In this study we demonstrate a powerful local saphenous venoconstrictor effect of sumatriptan following contralateral intravenous administration. The effect was dose-related and attained ≃40% reduction in diameter of the lateral saphenous vein after the dose of 30 μg kg^{-1}. Given that the ultrasonic crystals were positioned on the external surfaces of the vein, the actual reduction in lumen diameter may be underestimated by this technique. Furthermore, the corresponding reduction in lumen cross-sectional area would be even greater. Saphenous venous pressure measured proximally to the site of crystal implantation was not significantly modified by sumatriptan administration. This indicates that the observed reductions in vein diameter were not passively related to a reduction in perfusion pressure and represent active constriction of the

Table 2 Effects of increasing i.v. bolus doses of sumatriptan on haemodynamic parameters after administration of vehicle (Group 1) or methiothepin 0.3 mg kg^{-1} (Group 3)

Sumatriptan (μg kg^{-1})			*HR* (beats min^{-1})	*dP/dt*$_{max}$ (mmHg s^{-1})	*LVEDP* (mmHg)	*MAP* (mmHg)	*ABF* (l min^{-1})	*TPR* (mmHg l^{-1} min)	*SVP* (mmHg)	*SVD* (μm)
Group 1	1	Basal	155±5	2327±341	12,5±1.8	110±7	4.1±0.3	27.5±2.0	9.1±0.6	2407±140
		Δ%	-0.2±0.2	0.0±0.7	1.2±1.3	1.4±1.1	-0.7±0.9	2.2±1.4	-2.1±1.0	-3.3±1.5
	3	Basal	155±5	2370±353	12.1±1.7	110±6	4.1±0.3	27.0±2.1	9.1±0.7	2402±137
		Δ%	0.5±0.3	0.4±0.8†	-0.4±1.9	2.6±1.2	0.0±0.9	2.8±1.7	1.2±1.0	-13.4±3.9*
	10	Basal	158±5	2503±276	12.4±2.2	114±4	4.2±0.2	27.5±2.1	9.2±0.7	2415±142
		Δ%	-0.7±0.9	-2.1±1.0	5.4±2.3	2.0±0.6	-2.4±0.6	4.5±1.1	1.5±3.5	-32.5±4.1*
	30	Basal	156±5	2461±281	12.4±2.3	113±5	4.2±0.2	27.3±1.9	9.2±0.7	2418±141
		Δ%	-0.8±0.7	-2.7±0.4	6.6±2.0	1.6±1.4	-2.6±1.4	4.5±1.7*†	1.9±1.9	-37.7±4.5*
Group 3	1	Basal	157±3	2036±143	9.0±0.7	92±4	4.4±0.2	21.4±1.4	9.8±0.5	2752±163
		Δ%	0.2±0.8	-0.1±1.22	0.0±1.3	1.3±1.0	1.3±0.6	-0.1±0.7	-0.1±0.5	0.0±0.0
	3	Basal	155±3	1995±132	9.1±0.7	93±4	4.4±0.2	21.5±1.5	9.8±0.4	2753±163
		Δ%	-0.6±0.3	-1.4±0.5	1.5±0.6†	1.1±0.2	-0.9±0.8	2.1±0.8	-0.1±0.5	0.0±0.1†
	10	Basal	154±3	1951±128	9.3±0.8	93±4	4.2±0.2	22.3±1.5	9.7±0.4	2749±163
		Δ%	-1.1±0.5	-0.2±0.3	4.2±1.2†	3.3±0.2†	-0.9±0.3	4.2±0.5†	-0.7±0.4	-1.1±0.6†
	30	Basal	151±3	1883±118	9.4±0.7	93±5	4.1±0.2	23.2±1.9	9.6±0.4	2746±162
		Δ%	-2.7±0.9	-0.1±0.8	7.7±1.7†	6.7±2.0*†	-3.4±0.5	10.5±2.6*†	-1.3±1.0	-10.8±4.1*†
	100	Basal	147±3	1856±140	9.8±0.8	94±5	4.0±0.3	24.3±2.2	9.6±0.4	2724±158
		Δ%	-1.9±1.3	0.1±1.8	12.1±2.5*	11.9±2.8*	-3.5±1.1	16.1±3.9*	-2.5±1.5*	-30.8±5.8*
	300	Basal	142±2	1857±150	9.8±0.7	97±6	4.0±0.3	24.9±2.5	9.5±0.4	2665±149
		Δ%	0.2±1.4	0.8±0.9	13.6±2.4*	11.2±2.3*	-1.3±1.1	12.7±2.5*	1.2±1.6	-41.2±3.5*

HR (heart rate), dP/dt_{max} (maximal rate of rise of left ventricular pressure), LVEDP (left ventricular end diastolic pressure), MAP (mean aortic pressure), ABF (mean aortic blood flow), TPR (total peripheral vascular resistance), SVP (mean saphenous vein pressure), SVD (mean saphenous vein diameter).

These effects were measured at the time corresponding to the peak decrease in saphenous vein diameter. Values are mean±s.e.mean ($n=6$ per group).

*$P<0.05$ versus corresponding basal value. †$P<0.05$ versus corresponding control response to sumatriptan in Table 1.

vein. At low doses the reductions in SVD produced by sumatriptan were relatively selective since few other significant haemodynamic changes were noted. However, at higher doses, sumatriptan-induced saphenous venoconstriction was accompanied by modest increases in MAP, LVEDP and TPR and minor changes in HR and ABF.

The excellent reproducibility shown by two consecutive sumatriptan dose-response curves on SVD in the vehicle (saline-treated) group, both in terms of sensitivity ($ED_{20\%}$) and 'maximum' response, enabled us to perform a within-animal evaluation of the receptor mechanism involved in this effect by the use of 5-HT receptor antagonists. The 5-HT_2 antagonist, ketanserin, had no influence on sumatriptan-induced saphenous venoconstriction at a dose which has been demonstrated to produce sustained abolition of 5-HT_2-mediated increases in blood pressure (Fozard, 1982). In contrast, the 5-HT_1-like/5-HT_2 antagonist, methiothepin, was highly effective, displacing the dose-response curve for sumatriptan on SVD rightwards $\simeq$15 fold in a parallel fashion. The antagonist effect of methiothepin in our study is consistent with its reported effects against sumatriptan-induced carotid vasoconstriction in anaesthetized dogs (Feniuk *et al.*, 1989), a 5-HT_1-like mediated response. Hence, the effect of sumatriptan on lateral saphenous vein diameter in the dog probably involves 5-HT_1-like receptor stimulation, a conclusion which was anticipated given the selective 5-HT_1-like/5-HT_{1D} agonist characteristics of sumatriptan (Humphrey *et al.*, 1988; Hoyer & Schoeffter, 1991). Responses of the isolated canine saphenous vein were originally characterized as 5-HT_1-like receptor mediated on the basis of pharmacological (functional) criteria. The extent of the similarity between functional 5-HT_1-like receptors and the 5-HT_{1D} ligand binding site has remained a source of some debate. However, the recent documentation of 5-HT_{1D} receptor mRNA in this tissue suggests that the 5-HT_{1D} receptor could be implicated in the observed functional response (Cushing *et al.*, 1994). Methiothepin, although widely used, is not the ideal antagonist because it shows relatively poor selectivity. Recently, selective antagonists of the 5-HT_{1D} receptor have been described (e.g. GR127935 and GR133867, Clitherow *et al.*, 1994). It would be interesting to test the sensitivity of sumatriptan-induced saphenous venoconstriction *in vivo* to these antagonists. This would help to confirm the nature of the receptor type involved in this functional response.

Sumatriptan 10–30 $\mu g\ kg^{-1}$ produced modest increases in MBP, TPR and LVEDP which were of short duration and which were sensitive to antagonism by methiothepin. The increase in TPR is indicative of a moderate systemic vasoconstriction, although which vascular beds are implicated cannot be determined from our study. Elevation of LVEDP, in association with little change in cardiac output, could imply increased venous return due to venoconstriction. This suggests that, in addition to a local saphenous venoconstrictor effect, sumatriptan may also constrict other capacitance veins. However, this interpretation should be made with caution since the changes in LVEDP, although statistically significant, were of relatively minor physiological importance. In addition, the fact that saphenous vein pressure measured locally remained constant and did not increase, argues against a generalized sumatriptan-induced venoconstriction. The most likely explanation for this phenomenon (sumatriptan-induced reduction in saphenous vein diameter without increase in corresponding venous pressure) is that the venoconstrictor effect is relatively localized to the large saphenous veins which presumably do not make a major contribution to saphenous venous resistance. Alternatively, there may have been a redistribution of superficial venous blood towards the deep venous circulation. The present study provides no information on these aspects. Our observation of increased MBP and TPR after sumatriptan contrasts slightly with published studies in anaesthetized dog (Feniuk *et al.*, 1989), anaesthetized cat (Perren *et al.*, 1989) and anaesthetized pig (den Boer *et al.*, 1991) which generally report little change in blood pressure following i.v. administration of sumatriptan. However, it is interesting to note that our data correspond well to two recent haemodynamic evaluations of sumatriptan in man, using i.v. and subcutaneous routes, which report significant increases in arterial pressure (MacIntyre *et al.*, 1992; 1993).

Reduction in saphenous vein diameter *in vivo* appears to be a sensitive model of vasoconstrictor 5-HT_1-like activity. The threshold dose of sumatriptan necessary for this effect was $\simeq 1\ \mu g\ kg^{-1}$, i.v. and statistically significant saphenous venoconstriction was always seen at $3\ \mu g\ kg^{-1}$, i.v. By comparison, it has been shown (Feniuk *et al.*, 1989) that sumatriptan-induced carotid vasoconstriction in the anaesthetized dog has a threshold of $3-10\ \mu g\ kg^{-1}$, i.v. and only achieves statistical significance at the $30\ \mu g\ kg^{-1}$ dose. Even higher doses were necessary to increase vascular resistance in vertebral, coronary, femoral or mesenteric arterial beds (Feniuk *et al.*, 1989). In the anaesthetized pig, $10\ \mu g\ kg^{-1}$, i.v. sumatriptan produced a significant fall in arteriovenous anastomotic blood flow (den Boer *et al.*, 1991). Recently, a potent renal vasoconstrictor effect of sumatriptan has been reported in anaesthetized dogs (Cambridge *et al.*, 1995) after administration of low doses into the left atrium. The dose-range of sumatriptan over which we have observed reductions in SVD ($1-30\ \mu g\ kg^{-1}$, i.v.) is somewhat lower than the dose at which this compound demonstrates anti-migraine efficacy in man after bolus intravenous administration (90% response rate after $64\ \mu g\ kg^{-1}$, Perrin *et al.*, 1989). Therefore, it is possible that local effects of sumatriptan on the saphenous venous circulation could occur during its clinical use.

Coronary artery bypass graft operations represent an established surgical option for cardiac ischaemic conditions caused by occlusive atherosclerotic lesions of the coronary arteries. One of the most commonly used graft tissues is the saphenous vein (Bourassa, 1991). Human saphenous veins are similar to their canine counterparts in that they contain a 5-HT_1-like receptor (as well as a 5-HT_2 receptor) which responds to 5-HT and sumatriptan with constriction (Bax *et al.*, 1992). Apparently, the function of this receptor pathway is retained even after chronic arterial grafting, according to *ex vivo* observations (Bax *et al.*, 1992). It is uncertain whether our *in vivo* evaluation of saphenous venous reactivity in the anaesthetized dog can be extrapolated to this clinical situation with sufficient accuracy. However, if so, our results suggest that endogenous 5-HT released from platelets at the site of a local thrombosis could exert a powerful vasoconstrictor effect (mediated by 5-HT_1-like receptors) on saphenous vein tissue grafted into the coronary arterial circulation. Contraction of human saphenous vein following exposure to aggregating platelets has been clearly demonstrated *in vitro* (Yang *et al.*, 1991).

In conclusion we have demonstrated that, following administration of low i.v. doses, the selective 5-HT_1-like agonist, sumatriptan, causes pronounced saphenous venoconstriction in the anaesthetized dog. These observations suggest that a more extensive investigation of the effects of sumatriptan on venous function and, in particular, on other large capacitance veins would be worthwhile. Measurement of saphenous vein diameter offers a sensitive and reproducible model for the *in vivo* evaluation of compounds which interact with vasoconstrictor 5-HT_1-like receptors.

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