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In vivo analysis of adrenergic and serotoninergic constrictions of the rabbit saphenous vein

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Abstract

We aimed to develop a model to study in vivo the rabbit saphenous vein pharmacology and to investigate constrictions mediated by adrenoceptor and 5-HT receptor subtypes. We used the technique of high precision ultrasonic echo-tracking for direct measurement of saphenous vein diameters in pentobarbital anesthetized rabbits. Saphenous vein constrictions induced in rabbits by the α_1-adrenoceptor agonist L-phenylephrine and the 5-HT_{1B} receptor agonist sumatriptan were comparable with those induced in dogs but those induced by the 5-HT_{1B} and 5-HT_7 receptor agonist 5-carboxamidotryptamine failed to appear in dogs. Dose-related constrictions of rabbit veins were obtained with L-phenylephrine and the α_2-adrenoceptor agonist dexmedetomidine. Frequency-related constrictions of rabbit veins induced by nerve stimulation were partially inhibited by an α_1-adrenoceptor or a postsynaptic α_2-adrenoceptor antagonist (prazosin and SKF 104,078) but not affected by the pre- and post-synaptic α_2-adrenoceptor antagonists BRL 44408 or rauwolscine. Constrictions of rabbit veins to sumatriptan and 5-CT were inhibited by GR 127935 and those induced by quipazine, a 5-HT_2 receptor agonist were prevented by ritanserin. The initial constrictions induced by 5-CT were followed by dilatations which were inhibited by the 5-HT_7 receptor antagonist mesulergine. These data indicate that rabbit saphenous veins, in vivo and at rest, respond to activation of 5-HT_{1B} and 5-HT_2 receptors, α_1- and α_2-adrenoceptors and nerve stimulation; the dilator effect mediated by 5-HT_7 receptor activation was also detected. The data validate a new animal model to study superficial vein reactivity and its pharmacological sensitivity.

Keywords: Saphenous vein; In vivo; (Rabbit); Adrenoceptor; 5-HT receptor

1. Introduction

The pharmacology and the physiology of the saphenous vein, a cutaneous blood vessel of the leg, have been extensively studied because this vein is implicated in chronic venous disease, leading to varicose veins and leg ulcers and because this vein has been used for coronary by-pass surgery.

The in vitro pharmacology of the saphenous vein has been largely documented using human, dog or rabbit veins. In vivo, the studies of pharmacology and physiology of the superficial vein have been studied mainly in humans (for review, see Aellig, 1994). Venous reactivity in cutaneous veins in vivo in humans is usually measured via the plethysmography and, more precisely, by the optical method (Nachev et al., 1971; Collier et al., 1972), by the photoelectric device (Steen et al., 1986; Sjöberg et al., 1989) and by the linear variable differential transformer (Aellig, 1979, 1981; Alradi and Carruthers, 1985). The linear variable differential transformer method has also been used in dogs (Müller-Schweinitzer, 1984). However, only a few pharmacological studies have been performed in dogs and none in rabbits. In order to perform preclinical evaluation of new compounds with potential venoselective activities, a better understanding of the in vivo pharmacology of the animal saphenous vein appears necessary.

We have previously shown (Vayssettes-Courchay et al., 1997) that the diameter of the saphenous vein can be measured in vivo in the anesthetized dog using a non-invasive high resolution echo-tracking device which had been developed to measure arterial diameter and pulsatile changes in arterial diameter (Tardy et al., 1991; Hayoz et al., 1992; Laurent et al., 1993; Lacolley et al., 1995). We

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discussed the limit of the method, which does not allow measurements without anesthesia in animals, but also its major interest in that it allows a non-invasive approach and a high precision of the internal venous diameter measurements. We have also shown that the venous compliance can be studied by increasing the venous pressure with an inflatable cuff and measuring simultaneously the increases in venous diameter and venous pressure (Vayssettes-Courchay et al., 1997).

In humans, the saphenous vein or the dorsal hand vein is constricted by noradrenaline and by 5-hydroxytryptamine (5-HT). The effect of activation of adrenoceptors has been well documented in vitro. Activation of α_1- and α_2-adrenoceptors induces contractions of cutaneous veins of dogs (De Mey and Vanhoutte, 1981; Hieble and Woodward, 1984; Ruffolo and Zeid, 1985; Flavahan et al., 1985), rabbits (Daly et al., 1990; Gordon et al., 1992; Jinsi and Deth, 1995; Aburto et al., 1995) and human (Descombes et al., 1995). It has been demonstrated that both α_1- and α_2-adrenoceptors participate in the response to noradrenaline either applied exogenously or released from the sympathetic nerves by stimulation (Daly et al., 1990; MacDonald et al., 1992; Gordon et al., 1992). The α_1-adrenoceptors are mainly responsible for a rapid and transient contraction while the α_2-adrenoceptors participate to the maintenance of a sustained contraction. It has been shown in the rabbit saphenous vein that its contraction is mainly due to α_1-adrenoceptor activation when $[Ca^{2+}]$ is low (Daly et al., 1990; Gordon et al., 1992) and to α_2-adrenoceptor activation when neuronal uptake is blocked (MacDonald et al., 1992).

The constrictor effects of α_1- and α_2-adrenoceptor activation have also been observed in vivo in humans (Nachev et al., 1971; Aellig, 1985; Schulte et al., 1985; Steen et al., 1986; Sjöberg et al., 1989; Sekkarie et al., 1990; Blöchl-Daum et al., 1991). Activation of α_1-adrenoceptors seems predominant in some of these studies (Sjöberg et al., 1989; Coffman, 1992, Haefeli et al., 1993).

Potent constrictor responses to 5-HT have been obtained on superficial veins in vitro (Cushing et al., 1994; Perren et al., 1991; Kemp and Cocks, 1995; Valentin et al., 1996) and in vivo in dogs (Müller-Scheinitzer, 1986; Drieu la Rochelle and O'Connor, 1995) and humans (DelBianco et al., 1975; Collier et al., 1972; Aellig, 1981). Both $5\text{-HT}_{1B/D}$ and 5-HT_2 receptor subtypes are involved in the constrictions induced by 5-HT (Arner and Högestätt, 1986; Borton et al., 1990; Sgard et al., 1996).

We aimed to adapt the ultrasonic echo-tracking technique to the measurement of rabbit saphenous vein diameter and performed two series of experiments in order to evaluate its in vivo reactivity to 5-HT receptor and α-adrenoceptor activation. In the first part of the study, we compared the venoconstrictor action of some compounds in dogs and rabbits. In the second series of experiments, we investigated the receptor subtypes which mediate the constriction of the rabbit saphenous vein.

2. Materials and methods

2.1. Experimental procedure

The experiments were performed with 60 New-Zealand rabbits weighing 2.1–3.4 kg, anesthetized with sodium pentobarbital (SANOFI) 30 $mg \cdot mg^{-1}$ i.v. into the auricular vein, followed by i.v. infusion of 15 $mg \cdot 0.2\ ml^{-1}$ of sodium pentobarbital (5 $mg\ kg^{-1}$) (Braun secure perfusor) in order to maintain a continuous level of anaesthesia. A low dose of flaxedil (gallamine triiodo-ethylate) was added to the infusion (2.5 $mg \cdot kg^{-1}\ h^{-1}$) to stabilize the respiratory rhythm movements. The animal lay on a homeothermic blanket (Harvard), with a rectal probe and the body temperature was maintained at 39–40°C. The trachea was cannulated and the rabbits were artificially ventilated with a Harvard respirator at a frequency of 36–42 cycles min^{-1}, and a volume of 4 ml kg^{-1}. Some experiments were performed with mongrel dogs weighing 8–19 kg, anesthetized with sodium pentobarbital 30 mg kg^{-1} in the cephalic vein, followed by i.v. infusion of 1 $ml \cdot h^{-1}$ of sodium pentobarbital 6% (Braun secure perfusor). Dogs were not immobilised, respiration was monitored by Bird mark VII respirator at 10–14 cycles min^{-1} and 2.5–3 l min^{-1} and body temperature was maintained at 38°C.

Arterial blood pressure was recorded via a catheter inserted into the carotid or the femoral artery, connected to a Statham P23 *L Gould transducer. Direct and mean arterial blood pressure were measured by a Gould pressure transducer and a Gould DC amplifier. In some experiments, the carotid artery blood flow was recorded via an electromagnetic probe, connected to a flow meter (MDL1401, Skalar).

The compounds were administered i.v. through the auricular or jugular vein.

2.2. Saphenous vein diameter recordings

A non-invasive ultra-sound probe was positioned on the dorsal branch of the small saphenous vein for measuring its internal diameter (Tardy et al., 1991; Laurent et al., 1993; Vayssettes-Courchay et al., 1997) by an ultrasonic echo-tracking device (Asulab Research Laboratory). The probe consisted of a 10-MHz focused piezoelectric transducer. Using a Doppler mode, the probe was positioned by the characteristic sound of the vein, perpendicularly to the vein and so that its focal zone was close to the center of the vein. The transducer operating in the pulse-echo mode, the back-scattered echoes from both the anterior and posterior walls of the vein could be visualised close to the echoes from the skin (Fig. 1). The signals of the venous walls were tagged by an electronic tracker, allowing the continuous measurement of the venous diameter.

In some experiments, an incision was made through the leg in order to expose the sural and tibial branches of the sciatic nerve, innervating the vein studied. The nerves

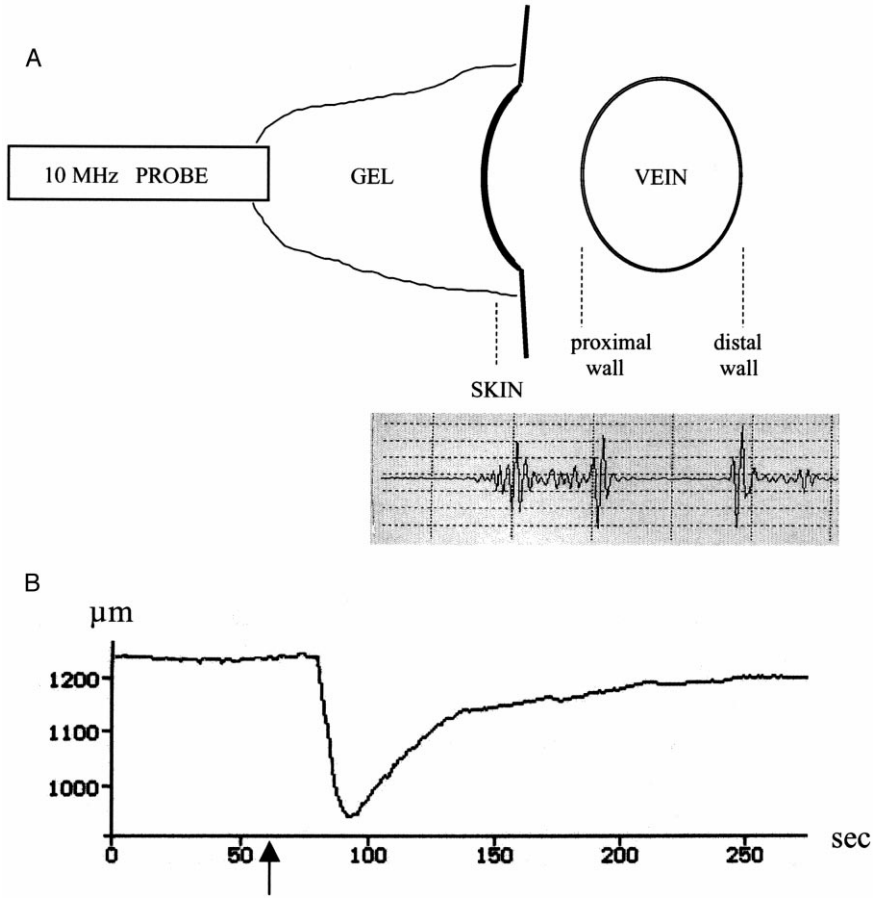

Fig. 1. (A) Description of the ultrasonic echo-tracking device, its position over the vein and example of typical echoes from the skin and the venous walls recorded in an anesthetized rabbit. (B) Typical example of recording of the saphenous vein diameter and a constriction induced by L-phenylephrine administered i.v. (10 µg kg^{-1}) at 60 s.

were dissected free, cut upstream, placed on a bipolar electrode and protected with fluorinert (Sigma). Stimulations were made with a Harvard stimulator at 5–8 V, 2 ms and increasing frequency: 2–4–6–8–10 Hz during 60 s and with 60-s intervals.

2.3. Protocols

The effect of the agonists administered i.v. was determined after stabilization, by continuous recording of the arterial blood pressure and of the saphenous vein diameter. The basal values of the parameters were measured over a 1-min recording period before administration. Mean arterial blood pressure was measured in mmHg and venous diameter in µm. Changes were calculated in mmHg and %, respectively, versus the basal values. Only one agonist was administered in each experiment.

In protocol 1, the effect of a single dose of an agonist was studied. After determination of the basal values, the compound was administered i.v. and measurements were performed 30 s, 1, 2, 3, 5, 10 min and then every 5 min after the injection, until the parameters had returned to their basal values.

In protocol 2, the effects of the antagonists were studied by i.v. administration, 10 min previous to the injection of the agonist. The parameters were continuously recorded before administration of the antagonist and during 10 min after its administration. Then the effect of the agonist was studied as mentioned above.

In protocol 3, the effects of increasing doses of an agonist were studied. After determination of the basal values, the compound was administered, at 3-min intervals, and changes were measured at maximal effect for each dose and before the injection of the subsequent dose.

Protocol 4 was used to study the venous constriction induced by nerve stimulation and the blocking effect of some antagonists. Increasing frequencies of nerve stimulation (2–4–6–8–10 Hz) were applied during 60 s with 60-s intervals and the 6-Hz stimulation was repeated to assess the reproducibility of the constrictions obtained. One of the antagonists studied was then administered and, after 10 min, the same increasing frequencies of stimulation were applied, followed by the supplemental 6-Hz stimulation.

2.4. Analysis

Arterial blood pressure and saphenous vein diameter were recorded and analysed by the Omega Nius02 angiometer coupled to a computer PC 486-33 MHz. The arterial blood pressure, heart rate and carotid artery blood flow were also visualized on a Gould RS 3600 recorder (Vayssettes-Courchay et al., 1997).

Means ± S.E.M. were calculated. The effect of the treatment was assessed with two-way analysis of variance (ANOVA) without replication and paired or unpaired Student's *t* test. The difference between means was considered to be statistically significant if $p \leq 0.05$.

2.5. Drugs

The drugs used were: S 18149, (5*S*)-spiro[(1,3-diazacyclopent-1-ene)-5:2′-(7′-methyl-1′,2′,3′,4′-tetra-hydronaphthalene)] fumarate, BRL 44408, SKF 104,078 maleate, dexmedetomidine tartrate (Dr. Cordi, Servier Research Institute); noradrenaline (arterenol bitartrate, Sigma); GR 127935, sumatriptan (Dr. Lavielle, Servier Research Institute); prazosin, L-NAME (*N*-nitro-L-arginine-methyl-ester HCl), L-Phenylephrine (Sigma); quipazine maleate, ritanserin, mesulergine, 5-CT (5-carboxamidotryptamine, RBI) and nitroglycerin (Bes ins Iscovesco). S 18149 was dissolved in 5% glucose solution. L-Phenylephrine HCl, dexmedetomidine, sumatriptan, mesulergine, 5-CT and L-NAME were dissolved in saline. Noradrenaline and SKF 104,078 were dissolved in warm saline solution. BRL44408 was dissolved in 11% HCl N/10, 89% glucose solution and 0.2% NaOH N/10 (pH 7.35). Quipazine was dissolved in saline with NaOH to adjust pH at 7. Ritanserin was dissolved with 3% dimethylsulfoxid (DMSO). Prazosin was dissolved in saline with 1% DMSO. GR127935 was dissolved glucose solution with 1% DMSO.

3. Results

3.1. Recording of saphenous vein diameter

The saphenous vein diameter was recorded in rabbits at a level comparable to that in dogs (Fig. 2A): on the dorsal

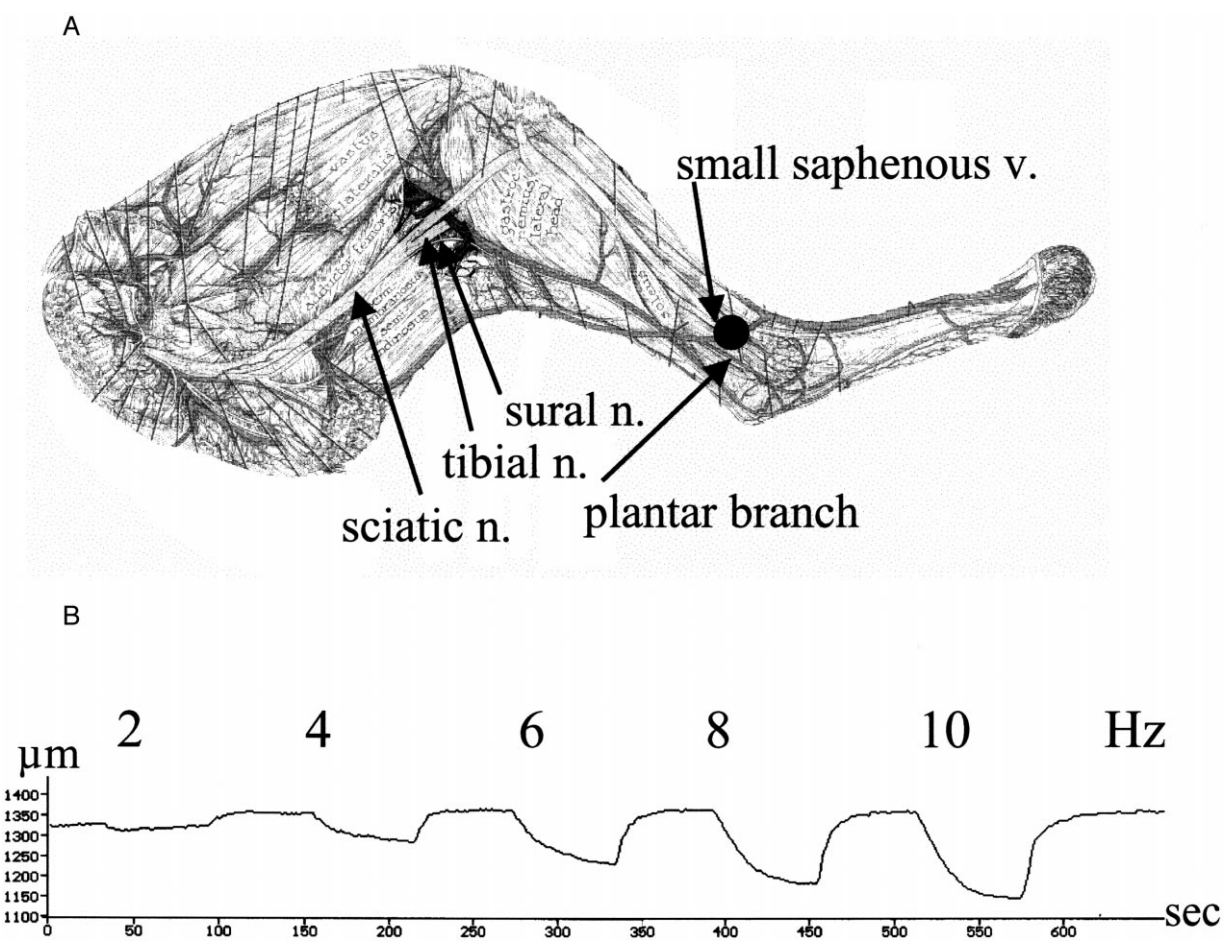

Fig. 2. (A) Localisation of the position of the ultrasonic probe over the saphenous vein (black dot) and indication of the sural and tibial nerves which were stimulated. (B) Example of recording of the saphenous vein diameter and constrictions induced by stimulation of the sural and tibial nerves with increasing frequencies.

branch of the small saphenous vein (or external saphenous vein), under the bifurcation with the plantar branch. The rabbit saphenous vein diameter could be detected and recorded during periods as long as 1 h and varied between 985 and 1380 μm. Canine saphenous vein diameters varied between 1550 and 3480 μm, for dogs weighing 8–19 kg. We measured in comparison the diameter of the dog saphenous vein by echography: in five dogs weighing 15–18 kg, the saphenous vein diameter varied between 2.2 and 3.2 mm.

The constrictor effect of L-phenylephrine at 10 μg kg^{-1} i.v. was tested on the rabbit vein kept at its resting basal tone, without previous dilatation ($n = 4$). The constriction averaged $-10 \pm 0.7\%$ (from -7.8 to -10.9, S.D. = 1.5), with a basal diameter of 1169 ± 61 μm. The associated increase in mean blood pressure was $+35 \pm 5$ mmHg, from 91 ± 6 mmHg (Fig. 1B).

3.2. Reactivity of dog and rabbit saphenous veins

3.2.1. Effects of L-phenylephrine and S 18149

The effect of L-phenylephrine at 5 μg kg^{-1} was similar in dogs and in rabbits (Fig. 3A). Resting values were 2085 ± 228 μm in dogs ($n = 4$) and 1205 ± 48 μm in rabbits ($n = 6$). The saphenous vein diameter was decreased by $-8 \pm 1\%$ in dogs (from -4.4 to -10.3, S.D. = 2.7). The response in the rabbits was $-8 \pm 2\%$ with a high variability (from -3 to -16, S.D. = 4.3). The maximal effect was measured at 1 min after the injection in both species. The resting values of mean blood pressure averaged 110 ± 8 mmHg in dogs and 81 ± 6 mmHg in rabbits and L-phenylephrine induced an increase in mean blood pressure of $+25 \pm 4$ mmHg in dogs and $+18 \pm 3$ mmHg in rabbits. The maximal effect on mean blood pressure was reached after 60 s in dogs and after 30 s in rabbits.

The partial α_1–α_2-adrenoceptor agonist S 18149 at 5 μg kg^{-1} produced a more pronounced effect in dogs than in rabbits. In dogs, the saphenous vein was constricted by $-20 \pm 3\%$ (from 2887 ± 156 μm, $n = 6$) and mean blood pressure was increased by $+18 \pm 1$ mmHg (from 116 ± 7 mmHg). In rabbits, the saphenous vein, with a resting diameter of 1267 ± 36 μm, constricted by $-6 \pm 1\%$ (from -3.3 to -7.9, S.D. = 1.9, $n = 4$) and mean blood pressure was increased by $+9 \pm 2$ mmHg (from 81 ± 6 mmHg).

3.2.2. Effects of sumatriptan and 5-CT

Sumatriptan at 300 μg kg^{-1} i.v. induced comparable constrictor effects in saphenous veins of both species: $-26 \pm 6\%$ from 3417 ± 222 μm ($n = 6$) in dogs and $-27 \pm 3\%$ from 1032 ± 24 μm ($n = 5$) in rabbits. In both species the maximal effect on saphenous vein diameter was reached 2 min after the injection and remained at about -15% at 30 min after injection (Fig. 3B). Mean

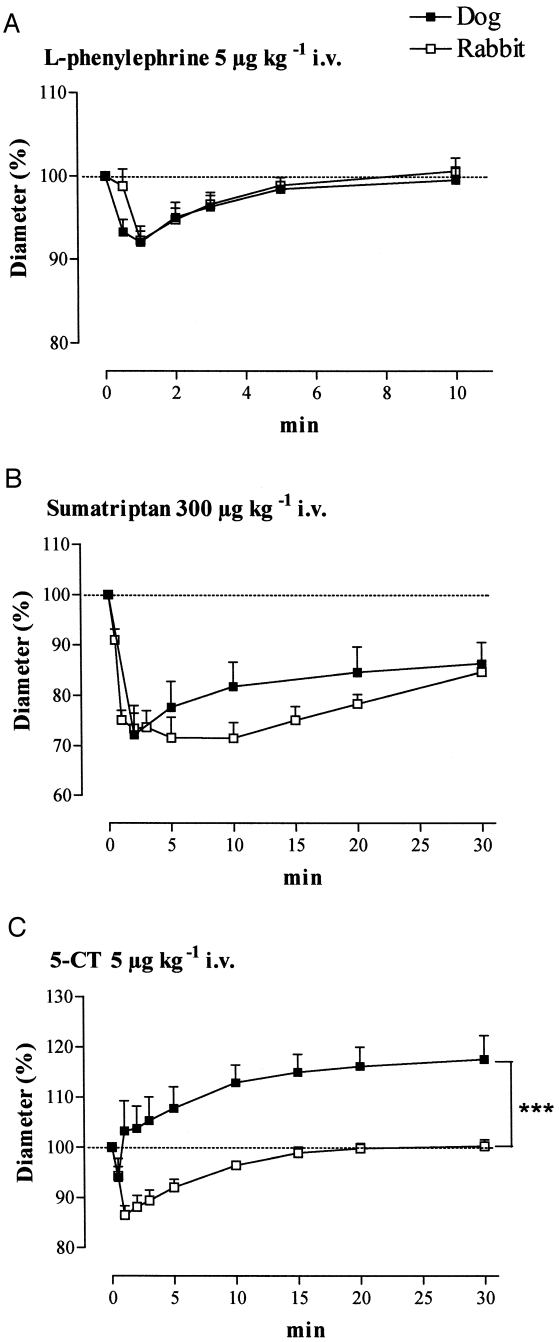

Fig. 3. The curves show the effect of L-phenylephrine at 5 μg kg^{-1} (A), sumatriptan at 300 μg kg^{-1} (B) and 5-CT at 5 μg kg^{-1} (C) on the saphenous vein diameter in dogs and rabbits. *** Difference between rabbit and dog vein is significant ($p = 0.001$, two-way ANOVA).

blood pressure was increased in dogs, by $+18 \pm 2$ mmHg at 2 min after injection from 123 ± 7 mmHg; however, mean blood pressure was decreased in rabbits, by -16 ± 1 mmHg at 30 s after injection from 90 ± 3 mmHg.

The administration of 5-CT at 5 μg kg^{-1} induced opposite changes in saphenous vein diameter in dogs and rabbits (Fig. 3C). In dogs the saphenous vein diameter slowly increased, reaching $+17 \pm 5\%$ of dilatation from 1995 ± 181 μm ($n = 4$) at 30 min after the injection. In

contrast 5-CT induced a rapid and short lasting constriction of the rabbit saphenous vein, with a maximal effect of $-13 \pm 2\%$ from 1322 ± 78 μm ($n = 4$) at 1 min after the injection. 5-CT induced a potent hypotensive effect in both species, of -54 ± 7 mmHg from 117 ± 5 mmHg in the dogs and -37 ± 7 mmHg from 76 ± 7 mmHg in the rabbits.

3.3. Activation of 5-HT and adrenoceptor subtypes in the rabbit saphenous vein

3.3.1. α-Adrenoceptor subtypes

The effects of increasing doses of the α_1-adrenoceptor agonist L-phenylephrine and the α_2-adrenoceptor agonist dexmedetomidine were tested in rabbits.

L-Phenylephrine at 3–10–30 μg kg^{-1} induced dose-dependent constrictions of the saphenous vein (Fig. 4), with a maximum effect of $-18 \pm 2\%$, associated with dose-dependent increases in mean blood pressure (maximum: $+58 \pm 4$ mmHg, Fig. 4, $n = 4$). Dexmedetomidine at 1–3–10 μg kg^{-1} also induced dose-dependent constrictions of the saphenous vein with a maximum of $-28 \pm 5\%$ (Fig. 4, $n = 4$). The effect of dexmedetomidine on mean blood pressure was biphasic, with a short lasting increase in mean blood pressure (maximal effect: $+30 \pm 1$ mmHg), followed by a sustained decrease in mean blood pressure (maximal effect: -30 ± 4 mmHg, Fig. 4).

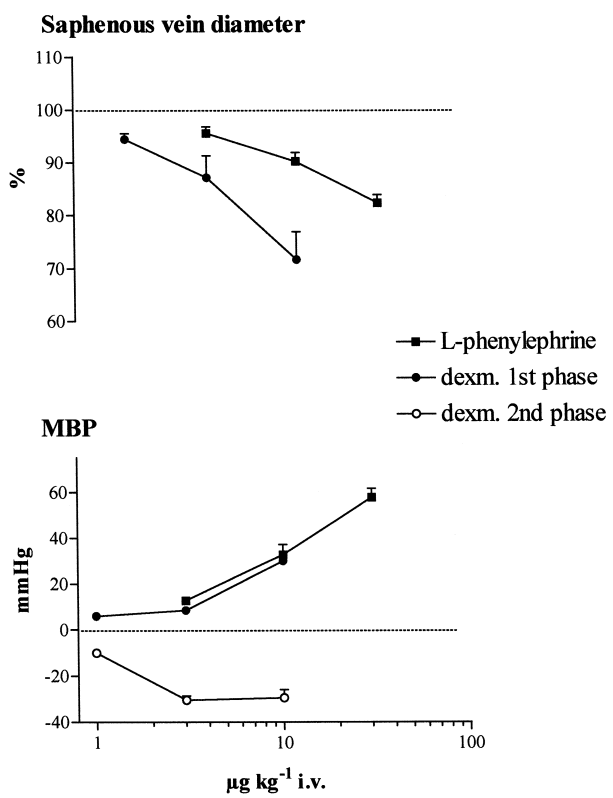

Fig. 4. Effects of L-phenylephrine and dexmedetomidine (dexm.) administered cumulatively in anesthetized rabbits on the saphenous vein diameter (top) and mean arterial blood pressure (mean blood pressure, bottom). The open circle indicate the long lasting hypotensive effect of dexmedetomidine. Baseline values averaged for L-phenylephrine: saphenous vein diameter 1417 ± 60 μm ($n = 3$) and mean blood pressure 78 ± 6 mmHg; for dexmedetomidine, saphenous vein diameter 1159 ± 115 μm ($n = 4$) and mean blood pressure 75 ± 6 mmHg.

3.3.2. Constriction induced by peripheral nerve stimulation

The saphenous vein diameter was slightly but significantly increased by the section of the sural and tibial nerves, from 1425 ± 68 μm to 1524 ± 52 μm ($n = 11$), thus by 5%, shortly after the section (within 2 min). After stabilisation, about 30 min after section, the venous diameter recorded before control nerve stimulation was, however, 1522 ± 42 μm ($n = 20$), thus 25% higher than the basal diameter recorded in 20 rabbits used in the paragraphs above.

The increasing frequencies of stimulation applied on sural and tibial nerves produced increasing constrictions of the saphenous vein (Fig. 2B). These effects of control stimulation did not differ between groups; the maximal effect was $17 \pm 3\%$ before prazosin, $16 \pm 3\%$ before rauwolscine, $16 \pm 4\%$ before BRL 44408, $14 \pm 1\%$ before SKF 104,078 and $16 \pm 2\%$ before mixed prazosin and SKF 104,078 administration. Therefore, the mean of control stimulation in all experiments ($n = 20$) was calculated and reported in Fig. 5. These control stimulation with 2–4–6–8–10 Hz induced constrictions of 1.4 ± 0.4, 6 ± 0.7, 12 ± 1, 15 ± 1 and $16 \pm 1\%$, respectively. A subsequent 6-Hz stimulation decreased venous diameter by $-11 \pm 1\%$.

The α_1-adrenoceptor antagonist prazosin at 100 μg kg^{-1} ($n = 4$) inhibited the stimulation-induced constrictions and the maximal effect was limited to $5 \pm 3\%$ at 10 Hz (Fig. 5A). The post junctional α_2-adrenoceptor antagonist SKF 104,078 at 1 mg kg^{-1} ($n = 4$) also decreased the effect of nerve stimulation with a maximal effect limited to $7 \pm 2\%$ at 10 Hz (Fig. 5A). In contrast the α_2-adrenoceptor antagonists rauwolscine ($n = 4$) or BRL 44408 ($n = 4$), both at 300 μg kg^{-1} i.v., failed to alter significantly the effect of nerve stimulation on the venous diameter (Fig. 5B). After both prazosin at 100 μg kg^{-1} and SFK 104,078 at 1 mg kg^{-1} ($n = 4$), the venous constriction by nerve stimulation was inhibited to $3 \pm 2\%$ at 10 Hz (Fig. 5A).

3.3.3. 5-HT receptor subtypes

The role of 5-$HT_{1B/D}$ receptors in the constriction of the saphenous vein induced by sumatriptan was checked in the rabbit by measuring the effect of sumatriptan at 300 μg kg^{-1} 10 min after administration of the 5-$HT_{1B/D}$ receptor antagonist GR 127935 at 30 μg kg^{-1} ($n = 4$). The saphenous vein diameter was 1302 ± 116 μm before and 1294 ± 100 μm after the administration of GR 127935. Mean blood pressure was 80 ± 2 mmHg and was not modified by GR 127935. After GR 127935 the sumatriptan-induced constriction was totally abolished (Fig. 6A)

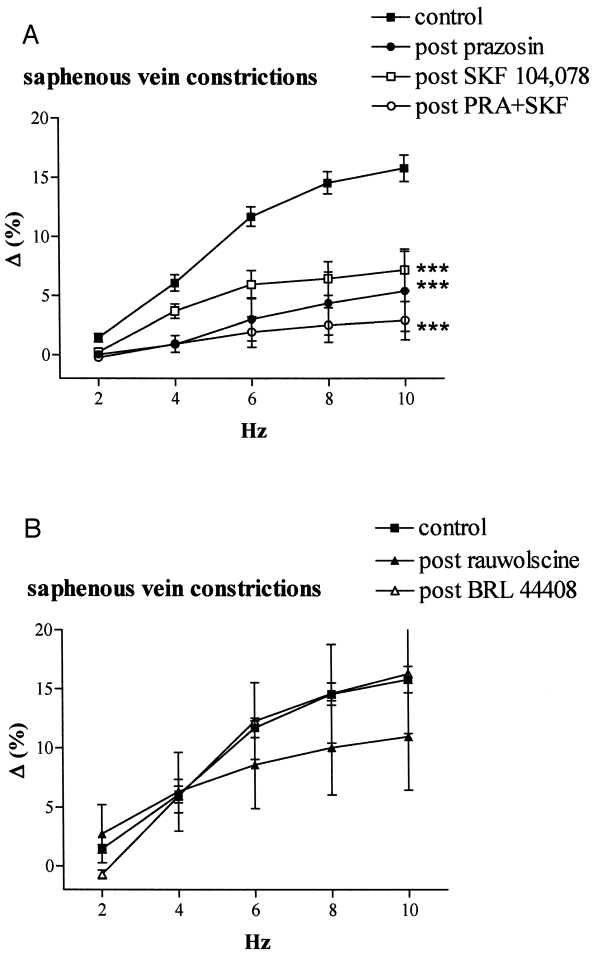

Fig. 5. Constrictions of the rabbit saphenous vein induced by increasing tibial and sural nerves stimulation frequencies. (A) Under control conditions, after prazosin (100 μg kg^{-1}), after SKF 104,078 (1 mg kg^{-1}), and after prazosin + SKF 104,078 (PRA + SKF). (B) Under control conditions, after rauwolscine (300 μg kg^{-1}) and after BRL 44408 (300 μg kg^{-1}). *** Responses significantly different from control ($p = 0.001$, two-way ANOVA).

and the decrease in mean blood pressure was reduced to -2 ± 1 mmHg.

Since 5-CT (5 μg kg^{-1}) evoked different responses in dogs and rabbits (see above) a dose–response study to this agonist was performed in a preliminary study and the dose of 10 μg kg^{-1} was selected for further pharmacological analysis in the rabbit. At 10 μg kg^{-1}, 5-CT induced a biphasic effect on the rabbit saphenous vein diameter (Fig. 6B), from 1465 ± 118 μm ($n = 5$). First a constriction was observed, with a maximum of $-9 \pm 3\%$ at 1 min after the injection with a high variability (from -3.8 to -17.9, S.D. = 5.7) followed by a slow dilatation of the vein, reaching $+7 \pm 1\%$ at 30 min after the injection (from $+2.5$ to $+10.4$, S.D. = 3.2). Mean blood pressure was decreased by -38 ± 7 mmHg (from 96 ± 4 mmHg). 5-CT at the dose of 10 μg kg^{-1} was then administered in two other groups of rabbits, 10 min after administration of the 5-HT$_{1B/D}$ receptor antagonist GR 127935 at 30 μg kg^{-1} ($n = 4$) or the 5-HT$_7$ receptor antagonist mesulergine at 30 μg kg^{-1} ($n = 5$). The saphenous vein diameter and mean blood pressure averaged 1425 ± 98 μm and 86 ± 5 mmHg before administration of GR 127935 and 1445 ± 99 μm and 86 ± 4 mmHg after GR 127935 ($n = 4$). Subsequent administration of 5-CT failed to constrict the vein which was dilated to $+10 \pm 5\%$ at 2 min and remained dilated 30 min after (Fig. 6B). Mean blood pressure was only decreased by -15 ± 4 mmHg by 5-CT after GR 127935. The saphenous vein diameter and mean blood pressure were 1427 ± 155 μm and 76 ± 5 mmHg before mesulergine administration and 1499 ± 135 μm and 74 ± 4 mmHg after mesulergine. Subsequent administration of 5-CT constricted the saphenous vein by $-7 \pm 2\%$ but failed to dilate the vein (Fig. 6B). The hypotensive effect of 5-CT was not modified by mesulergine: -32 ± 3 mmHg.

The constrictor effect of 5-HT$_2$ receptor activation was studied by the administration of the 5-HT$_2$ receptor agonist quipazine at 300 μg kg^{-1}. The administration of quipazine induced a marked and sustained constriction of the saphenous vein (Fig. 7), the maximal effect was $-36 \pm 6\%$ between 3 and 10 min after the injection, from a basal diameter of 1277 ± 68 μm ($n = 5$). The resting mean

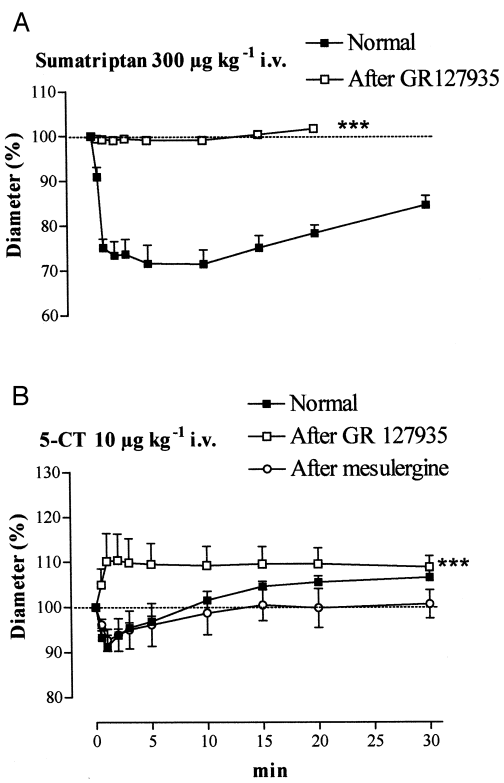

Fig. 6. Effects of intravenous administration of sumatriptan at 300 μg kg^{-1} and 5-CT at 10 μg kg^{-1} on the saphenous vein diameter in anesthetized rabbits. (A) Sumatriptan in control rabbits and sumatriptan after administration of GR 127935 (30 μg kg^{-1}). (B) 5-CT in control rabbits, 5-CT after administration of GR 127935 and 5-CT after administration of mesulergine (30 μg kg^{-1}). *** Effect of treatment with the antagonist is significant ($p = 0.001$, two-way ANOVA).

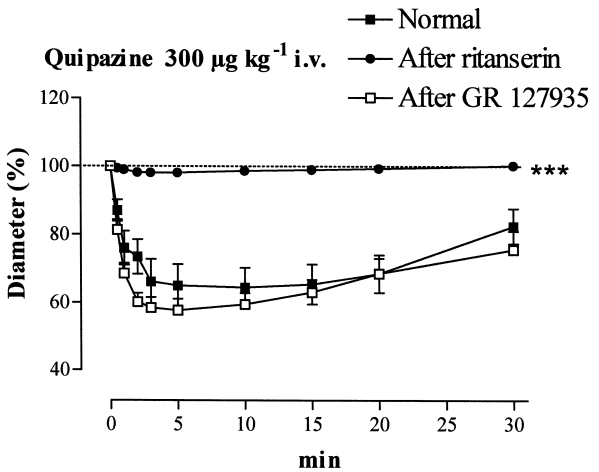

Fig. 7. Constrictions of the saphenous vein in anesthetized rabbits induced by quipazine at 300 μg kg^{-1} in control rabbits, after administration of GR 127935 (30 μg kg^{-1}) and after ritanserin (30 μg kg^{-1}). *** Effect of treatment with the antagonist is significant ($p = 0.001$, two-way ANOVA).

blood pressure was 85 ± 2 mmHg; quipazine produced a hypotensive effect of -19 ± 3 mmHg which remained stable during the 30 min of recording. The 5-HT$_2$ nature of the receptor involved in this effect was tested by the administration of quipazine at the same dose in two further groups of rabbits, treated by the 5-HT$_{1B/D}$ receptor antagonist GR 127935 at 30 μg kg^{-1} ($n = 4$) or the 5-HT$_2$ receptor antagonist ritanserin at 300 μg kg^{-1} ($n = 4$), 10 min before quipazine injection. The basal values of saphenous vein diameter and mean blood pressure were 1381 ± 121 μm and 81 ± 3 mmHg before and 1454 ± 92 μm and 87 ± 4 mmHg after the administration of GR 127935. The effect of subsequent injection of quipazine on the saphenous vein diameter was not modified, $-42 \pm 3\%$ (Fig. 7) and mean blood pressure was decreased by -24 ± 6 mmHg. The effect on mean blood pressure was of shorter duration (-6 ± 2 mmHg instead of -20 ± 6 mmHg 30 min after the injection). The values of saphenous vein diameter and mean blood pressure were 1193 ± 22 μm and 88 ± 9 mmHg before and 1201 ± 23 and 75 ± 9 mmHg after the administration of ritanserin. The constrictor effect of quipazine was inhibited by the previous administration of ritanserin (maximal effect: $-2 \pm 1\%$, Fig. 7), but not the hypotensive effect of quipazine (-18 ± 7 mmHg).

4. Discussion

The first goal of our study was to develop a new animal model to study the superficial vein reactivity in vivo; this was achieved by adapting the technique of high precision ultrasonic echo-tracking to measure the saphenous vein diameter in the rabbit. The second and major aim of our study was to investigate the constrictor responses of the rabbit saphenous vein after i.v. administration of 5-HT receptor and adrenoceptor agonists.

The saphenous vein reactivity is well documented in vitro but barely studied in vivo, except in humans. The first experiments in dogs were performed with perfused veins and pressure recordings, which afforded interesting data on the effect of nerve stimulation, cooling and adrenoceptor activation (Webb-Peploe and Shepherd, 1968a,b; Abdel-Sayed et al., 1970; Gardiner and Peters, 1982). In order to progress the studies performed in humans, non-invasive and more precise techniques were developed. This was realised with the optical method (Nachev et al., 1971; Collier et al., 1972), the photoelectric device (Steen et al., 1986; Sjöberg et al., 1989) and the linear variable differential transformer (Aellig, 1979, 1981; Alradi and Carruthers, 1985). The latter has also been used in dogs (Müller-Schweinitzer, 1984). The ultrasonic echo-tracking device that we used in the present experiments has been developed to record arterial compliance in humans with a systolo-diastolic calculation. This was possible because of the high precision of the recording. In previous experiments, we showed that the use of this method was possible in dogs and allowed the precise and non-invasive measurement of the internal diameter of the saphenous vein and the measurement of venous dilatation/pressure curve (Vayssettes-Courchay et al., 1997). Because of its high precision, we hypothesised that the echo-tracking technique could be adapted for measurement of saphenous vein diameters in the rabbit. This approach would allow to obtain in vivo data in this animal model for which numerous pharmacological data exist on the saphenous vein reactivity in vitro; for obvious reasons, the rabbit appears as an alternative to the use of dogs. This technique of echo-tracking device offers the advantage to be noninvasive and as stated above allows to detect the diameter of the vein with high precision.

The current technique mostly used for human studies is the linear variable differential transformer (LVEDT) which is noninvasive but measures, as with the optical or photoelectric methods, the movement of the skin over the vein. Weak effects cannot be detected and constrictor agents are injected after dilatation of the vein. The use of the echo-tracking device allows the determination of the saphenous vein diameter at its resting level, and neither emptying nor congesting conditions are necessary to test the constrictor or dilator compounds. This point needs to be considered when comparisons with results obtained in humans are made.

Under the present experimental conditions we could record a stable diameter of the rabbit saphenous vein and measure a constriction induced by i.v. administration of L-phenylephrine. Thus, the first part of our results provided us the evidence for a possible technical and physiological use of this technique in rabbits. Further experiments were then designed to perform a pharmacological study in this model allowing us to analyse the constrictor effect of

adrenergic and serotoninergic compounds. For some studies, comparison was made with the effect of compounds in dogs but the major effort of the study was devoted to the rabbit vein.

It has been shown that α_1- and α_2-adrenoceptors are present in the canine (De Mey and Vanhoutte, 1981), rabbit (Daly et al., 1990) and human (Steen et al., 1986; Descombes et al., 1995) saphenous veins. A constrictor effect on human superficial veins in vivo has been shown with noradrenaline and adrenaline (Nachev et al., 1971, 1972; Aellig, 1985; Alradi and Carruthers, 1985) as well as with the α_1-adrenoceptor agonist L-phenylephrine (Schulte et al., 1985; Eichler et al., 1989). Constrictions of the saphenous vein induced by α_2-adrenoceptor agonists have been described in vitro in the dog (Lee et al., 1990; Pereira et al., 1991; Guimaraes et al., 1987; Guimaraes and Nunes, 1990), the rabbit (Jinsi and Deth, 1995; Aburto et al., 1995; Daly et al., 1990) and human (Connaughton and Docherty, 1990) and in vivo in human (Schulte et al., 1985; Sjöberg et al., 1989; Sekkarie et al., 1990). However, in some studies, using mainly clonidine, α_2-adrenoceptor activation seems less efficient than α_1-adrenoceptor activation (Sjöberg et al., 1989; Kongpatanakul et al., 1990a,b; Blöchl-Daum et al., 1991; Coffman, 1992). It has been suggested that the α_2-adrenoceptor agonists lose their specificity in vivo (Blöchl-Daum et al., 1991); a possible conflicting EDRF liberation has been ruled out by Haefeli et al. (1993) who suggested that the effect of clonidine was due to an α_1-adrenoceptor agonist action of the compound. In the present study, we observed in vivo in the rabbit potent and dose-related venoconstrictor effects to both the α_1-adrenoceptor agonist L-phenylephrine and the α_2-adrenoceptor agonist dexmedetomidine. Dexmedetomidine has been described as a selective α_2-adrenoceptor agonist, more selective than clonidine or UK 14,304 (Aantaa et al., 1993), data which we confirmed in the pithed rat using yohimbine or prazosin (data not shown). Thus, our results indicate that in vivo in the rabbit, α_2-adrenoceptor activation is able to constrict the saphenous vein. This observation seems different from the data described in the human veins (see above); one possible explanation could be that the receptor subtype involved may be more efficient in the rabbit than in humans. However, various other hypothesis may be proposed to explain the differences. Thus, α_1- and α_2-adrenoceptor mediated contractions could depend on the experimental conditions used; indeed, it has been shown in vitro that even if α_2-adrenoceptor agonists fail to contract the saphenous vein, the α_2-adrenoceptors are present (Daniel et al., 1991). The potency of α_2-adrenoceptor activation appears to be dependent on α_1-adrenoceptor activation (Guimaraes et al., 1987; Daly et al., 1988), on Ca^+ concentration (Daly et al., 1990; Aburto et al., 1993), on temperature (Flavahan et al., 1985), and/or on neuronal uptake (MacDonald et al., 1992). It may also depend on the adrenoceptor subtype affinity of the compounds used and the role of the α_2-adrenoceptor subtypes has been recently investigated (Gavin et al., 1997; MacLennan et al., 1997). Moreover, in the dog in vivo, α_1- and α_2-adrenoceptors have been shown to participate in the venous responses to exogenously added noradrenaline or to noradrenaline released via nerve stimulation (Gardiner and Peters, 1982). A variable density of α_2-adrenoceptors on the canine saphenous vein has been described (Pereira et al., 1991; Guimaraes and Nunes, 1990), which is higher in the proximal part of the vein. All these observations need to be taken into account in order to explain the variable results with α_2-adrenoceptor activation.

In another series of experiments, we aimed to study the saphenous vein constrictions induced by the release of noradrenaline via nerve stimulation. Increasing constrictions were observed with increasing frequencies of stimulation. These constrictions were partly blocked by previous administration of the α_1-adrenoceptor antagonist prazosin but not by the α_2-adrenoceptor antagonists rauwolscine or BRL44408. We hypothetized that the post-synaptic and the pre-synaptic α_2-adrenoceptor antagonist action of these compounds might compensate each other. Indeed, the selective post-synaptic α_2-adrenoceptor antagonist SKF 104,078 partly blocked the venous constrictions which were almost completely abolished by previous administration of a combination of prazosin and SKF 104,078. Thus, these experiments confirm that activation of α_1-adrenoceptors and α_2-adrenoceptors produces constriction of the rabbit saphenous vein.

In the present study, the response to L-phenylephrine was comparable in dogs and rabbits under comparable experimental conditions. We were interested in measuring the effect of S 18149, (5*S*)-spiro[(1,3-diazacyclopent-1-ene)-5:2′-(7′-methyl-1′,2′,3′,4′-tetra-hydro-naphthalene)] fumarate, in the rabbit. This compound, which was selected as a partial α_1–α_2-adrenoceptor agonist, induces in vitro contractions of the canine saphenous vein at concentrations which do not affect the canine femoral artery (Cordi et al., 1995; Verbeuren et al., 1996). We have previously shown that S 18149 in vivo decreased the saphenous vein diameter and the saphenous vein compliance in the dog (Vayssettes-Courchay et al., 1997). The response to S 18149 in the rabbit was lower than that in dogs in the present study. Two hypotheses could be considered. A lesser proportion of reserve receptors in rabbit could exist, as the response to the partial adrenoceptor agonist (S 18149) but not to the full adrenoceptor agonist (L-phenylephrine) is weaker in rabbits than in dogs. As rather young rabbits were used for our present study, a difference due to the age of the animals may also be involved. Preliminary experiments in vivo with mature rabbits as well as in vitro data seem to be in agreement with the second hypothesis which will have to be addressed in future experiments.

The constrictor effects of 5-HT receptor activation have been less well documented in vivo than those of adreno-

ceptor activation. It has nevertheless been shown in humans that 5-HT constricts the saphenous vein and the dorsal hand vein (DelBianco et al., 1975; Collier et al., 1972; Aellig, 1981). 5-HT contracts superficial veins in vitro (Cushing et al., 1994; Sgard et al., 1996; Perren et al., 1991; Kemp and Cocks, 1995; Valentin et al., 1996) and in vivo in dogs (Müller-Scheweinitzer, 1986; Drieu la Rochelle and O'Connor, 1995). The receptor subtypes involved in the constrictions induced by 5-HT have been studied in vitro on human veins and the 5-$HT_{1B/D}$ and 5-HT_2 receptor subtypes appear to be involved (Arner and Högestätt, 1986; Borton et al., 1990).

We tested the effect of 5-HT receptor activation by injecting the 5-$HT_{1B/D}$ agonist sumatriptan, the 5-$HT_{1B/D}$ and 5-HT_7 agonist 5-CT, 5-HT_2 and the 5-HT_3 receptor agonist quipazine. These drugs are not selective for one subtype of receptor and thus the receptors involved were confirmed by administration of the 5-HT receptor antagonists GR 127935 (5-$HT_{1B/D}$), ritanserin (5-HT_2) and mesulergine (5-HT_7). The results obtained on the rabbit vein in vivo are in agreement with the in vitro experiments cited above and indicate that profound constriction of the saphenous vein was obtained by activation of 5-$HT_{1B/D}$ receptors and 5-HT_2 receptors. Indeed, sumatriptan induced constrictions which could be prevented by the 5-$HT_{1B/D}$ antagonist GR 127935 and quipazine-induced constrictions which were prevented by administration of the 5-HT_2 receptor antagonist ritanserin but not by GR 127935. The effect of sumatriptan on the rabbit and dog saphenous veins was comparable and in agreement with in vitro studies. Moreover, it has been shown that the 5-HT_{1B} receptor of the rabbit presents similarities with the human 5-HT_{1B} receptor (Wurch et al., 1997). The rabbit is therefore an interesting model for studying the effects of 5-HT_{1B} compounds on the saphenous vein.

The response of the saphenous vein to 5-CT appeared more complex. We observed in the rabbit a constriction of the vein at a dose which induced a dilatation of the vein in the dog. With a higher dose in the rabbit, we obtained a biphasic response: a constriction followed by a dilatation. In vitro, 5-CT acts as a potent constrictor of the dog and rabbit saphenous vein. In contrast, a dilator effect of this compound and 5-HT has been described on the jugular vein (Martin et al., 1987) and was attributed to 5-HT_7 receptor activation in the monkey jugular vein and in the rabbit femoral vein (Martin and Wilson, 1995; Leung et al., 1996). In the carotid vascular bed, the dilator effect of 5-HT was suggested to be due to either a presynaptic effect, likely at 5-HT_{1like} receptors, or to an unknown 5-HT receptor subtype, later suggested to be 5-HT_7 receptor (Villalon et al., 1993, 1997). Our experiments are in agreement with this hypothesis; the effect of the 5-$HT_{1B/D}$ receptor antagonist GR 127935 and the 5-HT_7 receptor antagonist mesulergine on the biphasic action of 5-CT indicate that the constriction is due to 5-$HT_{1B/D}$ receptor activation and the dilatation is likely due to 5-HT_7 receptor activation. 5-CT and mesulergine possess a high affinity for the 5-HT_7 receptors (Hoyer et al., 1994). In vitro, contractions or dilatations are observed with 5-HT and 5-CT, depending on the tissue and also on the experimental conditions. Our results demonstrate that in vivo the dilatator effect of 5-CT is predominant on the saphenous vein in the dog, and appears in the rabbit when doses increase. It would be interesting to study which one of these species reacts as the human saphenous vein.

In conclusion, our data show that the ultrasonic echotracking device can be used in the rabbit to perform precise measurements of the saphenous vein diameter. The use of this model seems to offer an interesting new and precise technique to investigate the superficial vein pharmacology.

Our results indicate that in the rabbit, activation, either by pharmacological agents or by nerve stimulation, of α_1- and α_2-adrenoceptors induces constriction of the saphenous vein in vivo; the role of each α_1- and α_2-adrenoceptor subtype will be studied in further experiments. Such venoconstriction is also obtained by activation of 5-HT_{1B} and 5-HT_2 receptors. The dual constrictor/dilatator effect of compounds such as 5-CT, which had been observed in vitro, is detected in vivo in this species and the present data indicate that the dilator effect was likely due to activation of 5-HT_7 receptors.

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