Naunyn-Schmiedeberg's Arch Pharmacol (1998) 358: 212–219

ORIGINAL ARTICLE

Edwin Willems · Peter De Vries · Jan P.C. Heiligers
Pramod R. Saxena

Porcine carotid vascular effects of eletriptan (UK-116,044): a new 5-$HT_{1B/1D}$ receptor agonist with anti-migraine activity

Received: 9 February 1998 / Accepted: 28 March 1998

Abstract It has been suggested that opening of cephalic arteriovenous anastomoses may be involved in the headache phase of migraine. Indeed, a number of acutely acting anti-migraine drugs, including the ergot alkaloids and sumatriptan, constrict porcine carotid arteriovenous anastomoses. In this study, using pentobarbital anaesthetised pigs, we investigated the effects of eletriptan, a close structural analogue of sumatriptan, on the distribution of common carotid artery blood flow into arteriovenous anastomotic and nutrient (capillary) fractions. Eletriptan (10, 30, 100, 300 and 1000 µg kg^{-1}, i.v.) decreased the total carotid blood flow, exclusively by decreasing cephalic arteriovenous anastomotic blood flow; nutrient blood flow, particularly to the ear, skin and fat, was significantly increased. The doses of eletriptan needed to reduce arteriovenous anastomotic blood flow and conductance by 50% (ED_{50}) were, respectively, 117±21 µg kg^{-1} (251±45 nmol kg^{-1}) and 184±42 µg kg^{-1} (396±91 nmol kg^{-1}); the highest dose caused reductions of 84±3% and 77±4%, respectively. The eletriptan-induced changes in carotid haemodynamics were clearly attenuated by pretreating the pigs with the selective 5-$HT_{1B/1D}$ receptor antagonist GR127935 (0.5 mg kg^{-1}). On the basis of these results, we conclude that (1) the eletriptan-induced constriction of cephalic arteriovenous anastomoses as well as the arteriolar dilatation in head tissues is predominantly mediated by 5-$HT_{1B/1D}$ receptors, and (2) eletriptan should be effective in aborting migraine headache. Clinical studies have already demonstrated its therapeutic action in migraine patients.

Key words 5-HT receptors · Arteriovenous anastomoses · Arteriovenous shunts · Carotid artery · Eletriptan · Migraine headache · Pig · Sumatriptan

E. Willems · P. De Vries · J.P.C. Heiligers · P.R. Saxena (✉)
Department of Pharmacology, Faculty of Medicine
and Health Sciences, Erasmus University Rotterdam,
P.O. Box 1738, 3000 DR Rotterdam, The Netherlands

Introduction

Migraine is a disorder with a complex and multifactorial pathophysiology. Based on the early findings of Heyck (1969), dilatation of cranial arteriovenous anastomoses may be involved in the headache phase of migraine (Saxena 1995). Indeed, a number of anti-migraine agents, such as ergotamine, dihydroergotamine and sumatriptan, selectively constrict porcine carotid arteriovenous anastomoses. This effect is mediated exclusively (sumatriptan) or partly (ergots) by 5-HT_1-like receptors (Den Boer et al. 1991a,b; Hoyer et al. 1994), which are most probably identical to the 5-HT_{1B} receptor. This assumption is based on two lines of evidence. The selective 5-$HT_{1B/1D}$ receptor antagonist GR127935 potently blocks sumatriptan-induced responses (Clitherow et al. 1994; De Vries et al. 1996, 1998a; Skingle et al. 1996) and *m*RNA for the 5-HT_{1B} (not 5-HT_{1D}) receptor has been located in cerebral vessels (Hamel et al. 1993; Bouchelet et al. 1996).

The success of sumatriptan in the treatment of migraine (The Subcutaneous Sumatriptan International Study Group 1991; Visser et al. 1996), combined with some shortcomings of the drug (e.g. coronary artery constriction, high headache recurrence rate, low oral bioavailability), has prompted several pharmaceutical companies to develop new 5-$HT_{1B/1D}$ receptor agonists. The indole derivative eletriptan (UK-116,044; Pfizer Limited, Sandwich, Kent, UK) is one such compound (Fig. 1). Eletriptan displays a similar

Table 1 Binding affinity constants (pK_i values) of eletriptan, sumatriptan and GR127935 for human 5-HT_1 receptor subtypes

	5-HT_{1A}	5-HT_{1B}	5-HT_{1D}	5-HT_{1E}	5-HT_{1F}
Eletriptan[a]	7.35	8.00	8.94	7.25	8.18[c]
Sumatriptan[a]	5.96	7.37	8.04	5.79	7.94[b]
GR127935[b]	7.16	9.56	9.73	5.93	7.34

[a] Data from Gupta et al. 1997
[b] P.J. Pauwels, personal communication
[c] Value for the rat receptor

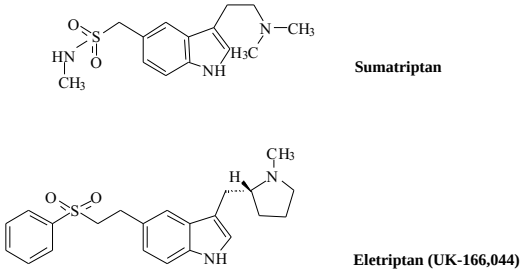

Fig. 1 Chemical structure of eletriptan and sumatriptan

5-HT receptor binding profile as sumatriptan (Table 1) and, like sumatriptan, it can constrict dog isolated saphenous vein (Gupta et al. 1997) and decrease carotid blood flow in anaesthetised dogs. In view of the shortcomings of the current available anti-migraine drugs, e.g. coronary artery constriction, the partial agonistic activity of eletriptan, as reported in the dog (Gupta et al. 1996), might be a major advantage for eletriptan as an anti-migraine drug. Finally, clinical studies show that eletriptan is effective in the treatment of migraine (Jackson 1996; Milton et al. 1997; Olesen et al. 1997).

In the present investigation, we have examined the potential of eletriptan to constrict carotid arteriovenous anastomoses in the anaesthetised pig, which serves as an in vivo experimental animal model for therapeutic activity in migraine (Saxena 1995; Saxena et al. 1997b). In addition, the involvement of 5-$HT_{1B/1D}$ receptors was studied by comparing the effects of eletriptan in animals pretreated with either saline or GR127935.

Materials and methods

General

After an overnight fast, 23 domestic pigs (Yorkshire × Landrace; 11–12 kg) were anaesthetised with azaperone (120 mg, i.m.), midazolan hydrochloride (5 mg, i.m.) and pentobarbitone sodium (600 mg, i.v.). The animals were intubated and connected to a respirator (BEAR 2E; BeMeds AG, Baar, Switzerland) for intermittent positive pressure ventilation with a mixture of room air and oxygen. Respiratory rate, tidal volume and oxygen supply were adjusted to keep arterial blood gas values within physiological limits (pH: 7.35–7.48; pCO_2: 35–48 mmHg; pO_2: 100–120 mmHg). Anaesthesia was maintained with a continuous i.v. infusion of pentobarbitone sodium at 20 mg kg^{-1} h^{-1}. With this anaesthetic regimen, arteriovenous anastomotic blood flow is considerably higher than that in pigs in a conscious state or under thiopentone anaesthesia (Den Boer et al. 1993). Catheters were placed in the inferior vena cava (via the left femoral vein) for drug administration and in the aortic arch (via the left femoral artery) for blood pressure measurement (Combitrans disposable pressure transducer; Braun, Melsungen, Germany) as well as blood withdrawal (for determining arterial blood gases; ABL-510; Radiometer, Copenhagen, Denmark). After identifying the common carotid arteries, external jugular veins and vagus nerves, both vagi and the accompanying cervical sympathetic nerves were cut between two ligatures. Another catheter was placed in the right external jugular vein for the withdrawal of blood samples for determining blood gases (ABL-510; Radiometer, Copenhagen, Denmark). The right common carotid artery was dissected free and a needle was inserted against the direction of blood flow for the administration and uniform mixing of radioactive microspheres. Right common artery blood flow was measured with a flow probe (internal diameter: 2.5 mm) connected to a sine-wave electromagnetic flow meter (Transflow 601-System; Skalar, Delft, The Netherlands). Heart rate was measured with a tachograph (CRW; Erasmus University, Rotterdam, The Netherlands) triggered by ECG signals. Arterial blood pressure, heart rate and carotid blood flow were continuously monitored on a polygraph (CRW; Erasmus University, Rotterdam, The Netherlands). During the experiment, body temperature was kept about 37°C and the animal was continuously infused with saline to compensate for fluid losses.

Distribution of carotid blood flow. The distribution of common carotid blood flow was determined with 15.5±0.1 µm diameter microspheres labelled with ^{141}Ce, ^{113}Sn, ^{95}Nb, ^{103}Ru or ^{46}Sc (NEN Dupont, Boston, Mass., USA). For each measurement, about 200,000 microspheres, labelled with one of the radioisotopes, were mixed and injected into the carotid artery. At the end of the experiment, the animal was killed by an overdose of pentobarbitone sodium and the heart, lungs, kidneys and the different cranial tissues (skin, muscles, bones, ear, eye, brain, tongue, salivary glands and dura mater) were dissected out, weighed and put in vials. The radioactivity in these vials was counted for 10 min in a γ-scintillation counter (Packard, Minaxi autogamma 5000), using suitable windows to discriminate the different isotopes. All data were processed by a set of specially designed programs (Saxena et al. 1980). The fraction of carotid blood flow distributed to the different tissues ($CaBF_{tis}$) was calculated by the following equation:

$$CaBF_{tis}=(I_{tis}/I_{tot})\times CaBF, \quad (1)$$

where I_{tis} and I_{tot} denote the tissue and total radioactivity, respectively, of each radioisotope and CaBF represents the common carotid artery blood flow at the time of microsphere injection. Since little or no radioactivity was detected in the heart and kidneys, all microspheres trapped in lungs reached this tissue from the venous side after escaping via carotid arteriovenous anastomoses. Therefore, the amount of radioactivity in the lungs was used as an *index* of the arteriovenous anastomotic fraction of carotid blood flow (Saxena and Verdouw 1982).

Experimental protocol. After a stabilisation period of about 1 h, the animals were divided into three groups. In the first group (n=7), values of heart rate, mean arterial blood pressure, carotid blood flow and its distribution, as well as femoral arterial and jugular venous blood gases were measured at baseline and after four consecutive injections of physiological saline (0.5 ml, every 20 min). The second (n=9) and third (n=7) groups of animals were pretreated with saline or GR127935 (0.5 mg kg^{-1}), respectively; both were administered intravenously over a period of 5 min at a rate of 1 ml min^{-1}. After a waiting period of 15 min, baseline values of heart rate, mean arterial blood pressure, carotid blood flow and its distribution, as well as arterial and jugular venous blood gases were measured. Subsequently, the saline-pretreated group received sequential i.v. injections of either 10, 30 and 100 µg kg^{-1} (n=1), or 10, 30, 100 and 300 µg kg^{-1} (n=5), or 30, 100, 300 and 1000 µg kg^{-1} (n=3) of eletriptan. The GR127935-pretreated group received sequential i.v. injections of 30, 100, 300 and 1000 µg kg^{-1} of eletriptan. Fifteen minutes after each dose of eletriptan, all haemodynamic variables were assessed again.

Ethical approval. The Ethics Committee of the Erasmus University Rotterdam, dealing with the use of animals for scientific experiments, approved the protocol for this investigation.

Data presentation and statistical analysis. All data have been expressed as means ± SEM. The significance of the difference between the variables within one group was evaluated with Duncan's new multiple range test, once an analysis of variance (randomised block design) had revealed that the samples represented different populations (Steel and Torrie 1980). The changes caused by eletriptan in saline- and GR127935-pretreated groups were compared at corresponding doses by using Student's unpaired *t*-test. In the saline-pretreated

group, the dose of eletriptan eliciting a 50% decrease from baseline values of arteriovenous anastomotic blood flow or conductance (ED_{50}) was calculated using linear regression analysis. Statistical significance was accepted at $P<0.05$ (two-tailed).

Drugs. Apart from the anaesthetics azaperone (Stresnil; Janssen Pharmaceuticals, Beerse, Belgium), midazolan hydrochloride (Dormicum; Hoffmann La Roche b.v., Mijdrecht, The Netherlands) and pentobarbitone sodium (Apharmo, Arnhem, The Netherlands), the compounds used in this study were: eletriptan hydrobromide ((R)-3-(1-methyl-2-pyrrolidinyl-methyl)-5-[2-(phenylsulphonyl)ethyl]-1H-indole; UK-116,044) and GR127935 (N-[methoxy-2-(4-methyl-1-piperazinyl)phenyl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl), both from Pfizer Central Research, Sandwich, Kent, UK. Finally, heparin sodium (Leo Pharmaceutical Products, Weesp, The Netherlands) was used to prevent clotting in the catheters. Eletriptan was dissolved in physiological saline, whereas GR127935 was solubilised according to the instructions of the supplier by heating the dispersion in distilled water to about 70°C for 10 s and then allowing to cool down to room temperature. The doses of the drugs refer to their respective salts.

Results

Systemic haemodynamics

The effects of i.v. injections of saline (5 ml, four times) and eletriptan (10, 30, 100, 300 and 1000 μg kg^{-1}) on systemic haemodynamics in anaesthetised pigs are shown in Table 2. No significant change in either heart rate or arterial blood pressure was observed with saline. On the other hand, in animals pre-treated with saline, eletriptan caused a slight bradycardia (maximum change: –11±3%) and a more pronounced hypotension (maximum change: –32±1%). Pretreatment with GR127935 (0.5 mg kg^{-1}, i.v.) did not modify eletriptan-induced changes in heart rate (maximum change: –10±2%). However, the hypotension in the GR127935-pretreated animals, induced by eletriptan at the highest dose (–19±3%), was significantly less compared to that in the saline-pretreated animals (–32±1%).

Arterio-jugular venous oxygen saturation difference

No significant changes were observed in the arterio-jugular venous oxygen saturation difference in the control group receiving saline (Table 2). In the animals pretreated with saline, there was a dose-dependent upward trend with eletriptan, but statistical significance was achieved only at the 300 μg kg^{-1} dose. No changes were observed with eletriptan in animals pretreated with GR127935.

Carotid haemodynamics

Carotid vascular haemodynamic data are depicted in Figs. 2 (absolute values) and 3 (% changes from baseline). There were no significant changes in either carotid blood flow or vascular conductance following four consecutive injections of saline. In pigs pretreated with saline, eletriptan caused a clear and dose-dependent decrease in the total carotid blood flow (maximum change: –40±11% after 1000 μg kg^{-1}) and conductance (maximum change: –25±6% after 300 μg kg^{-1}). The eletriptan-induced changes in the arteriovenous anastomotic blood flow (maximum change: –84±3% after

Table 2 Absolute values of heart rate, mean arterial blood pressure and the difference in femoral arterial and jugular venous oxygen saturation at baseline and after cumulative doses of eletriptan (10, 30, 100, 300 and 1000 μg kg^{-1}, i.v.) in pigs pretreated with either saline (n=6, 9, 9, 8 and 3, respectively) or GR127935 (0.5 mg kg^{-1}; n=7). The control animals (n=7) received only i.v. injections of saline (5 ml, four times). All values are presented as means ±SEM. ANOVA was followed by Duncan's new multiple range test

Experimental group	Saline or eletriptan (μg kg^{-1})					
	Baseline	10	30	100	300	1000
Heart rate (beats min^{-1})						
Control	98 ± 2	–	97 ± 2	96 ± 2	96 ± 2	95 ± 2
Saline-pre-treated	101 ± 3	98 ± 4	97 ± 3[a]	95 ± 2[a]	92 ± 3[a]	90 ± 3[a]
GR127935-pretreated	99 ± 5	–	98 ± 5[b]	95 ± 4	93 ± 4[a]	89 ± 4[a]
Mean arterial blood pressure (mmHg)						
Control	100 ± 3	–	95 ± 3	96 ± 3	96 ± 2	97 ± 3
Saline-pre-treated	96 ± 3	91 ± 4	89 ± 2[a]	85 ± 2[a]	80 ± 3[a]	69 ± 1[a]
GR127935-pretreated	94 ± 2	–	91 ± 1	86 ± 1[a]	82 ± 2[a]	76 ± 2[a,b]
Arteriovenous difference in oxygen saturation (%)						
Control	7 ± 2	–	7 ± 2	7 ± 2	7 ± 1	8 ± 2
Saline-pre-treated	14 ± 5	11 ± 3	16 ± 5	20 ± 5	22 ± 5[a]	33 ± 5
GR127935-pretreated	18 ± 8	–	18 ± 7	21 ± 7	21 ± 7	22 ± 6

[a] $P<0.05$ vs. baseline
[b] $P<0.05$ vs. corresponding dose in saline-pretreated group

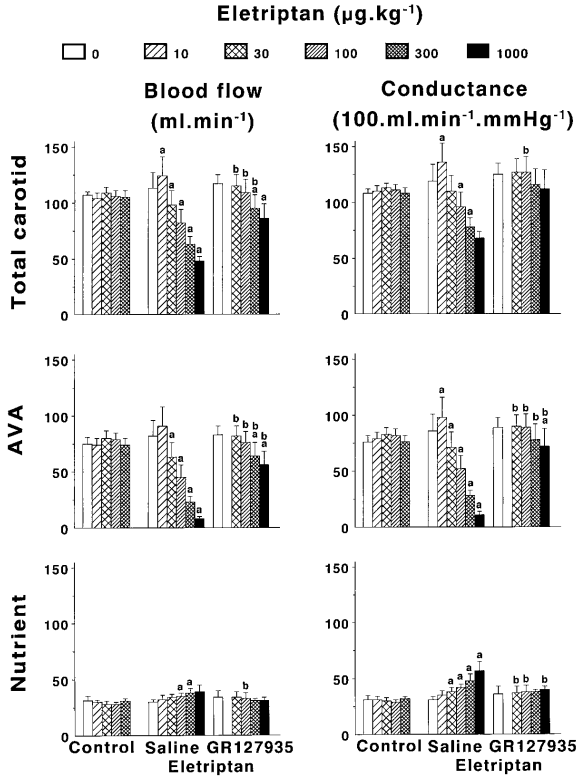

Fig. 2 Effect of eletriptan (10, 30, 100, 300 and 1000 μg kg^{-1}) on the total carotid blood flow and its arteriovenous anastomotic (AVA; *non-nutrient*) and capillary (*nutrient*) fractions in anaesthetised pigs, pretreated with either 5 ml saline (*middle column in panels*; n=6, 9, 9, 8 and 3, respectively) or 0.5 mg kg^{-1} GR127935 (*right column in panels*; n=7). Control animals received four times 5 ml saline (*left column in panels;* n=7). The *white bars* represent baseline values. All values are presented as means ± SEM. Please note that 10 μg kg^{-1} dose was not used in GR127935-pretreated animals. [a] P<0.05 vs. baseline; [b] P<0.05 vs. corresponding dose in the saline-pretreated animals

1000 μg kg^{-1}) and conductance (maximum change: –77±4% after 1000 μg kg^{-1}) were more marked than those observed in the total carotid blood flow. The doses of eletriptan producing a 50% decrease (ED_{50}) in the arteriovenous anastomotic blood flow and conductance were found to be 117±21 μg kg^{-1} (251±45 nmol kg^{-1}) and 184±42 μg kg^{-1} (396±91 nmol kg^{-1}), respectively. Eletriptan increased the nutrient blood flow and conductance by up to 33±18% and 95±26%, respectively. Compared to the responses in saline-pretreated pigs, the eletriptan-induced decreases in the total and arteriovenous anastomotic blood flow and conductance were clearly less, if not entirely absent, in animals previously receiving GR127935 (0.5 mg kg^{-1}, i.v.). Eletriptan did not produce any significant change in the nutrient blood flow or conductance after GR127935 (Figs. 2, 3).

As shown in Fig. 4, the increase in the nutrient conductance by eletriptan in saline-pretreated pigs was observed in several head tissues (muscles, tongue, bones, salivary glands, dura mater, skin, ear and fat). This increase was most pronounced in the skin, ear and fat, but was absent in the eye and evident only with the highest dose of eletriptan in the tongue. Pretreatment of the animals with GR127935 completely eliminated the eletriptan-induced increases in tissue vascular conductances.

Discussion

Systemic haemodynamic changes

Eletriptan caused a small bradycardia (unaffected by GR127935) and a more pronounced hypotension; the latter was partly sensitive to GR127935. These effects seem to be drug-induced, as four consecutive bolus injections of saline

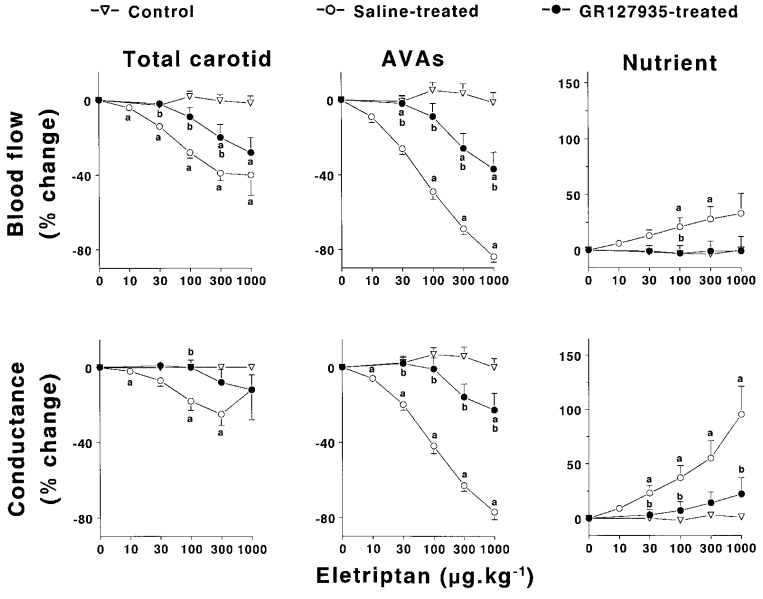

Fig. 3 Percent changes from baseline values caused by eletriptan (10, 30, 100, 300 and 1000 μg kg^{-1}) in the total carotid blood flow and its arteriovenous anastomotic (*AVA*; *non-nutrient*) and capillary (*nutrient*) fractions in anaesthetised pigs, pretreated with either 5 ml saline (*open circles*; n=6, 9, 9, 8 and 3, respectively) or 0.5 mg kg^{-1} GR127935 (*closed circles*; n=7). Control animals received four times 5 ml saline (*left column in panels;* n=7). All values are presented as means ± SEM. Please note that 10 μg kg^{-1} dose was not used in GR127935-treated animals. [a] P<0.05 vs. baseline; [b] P<0.05 vs. corresponding dose in the saline-pretreated animals

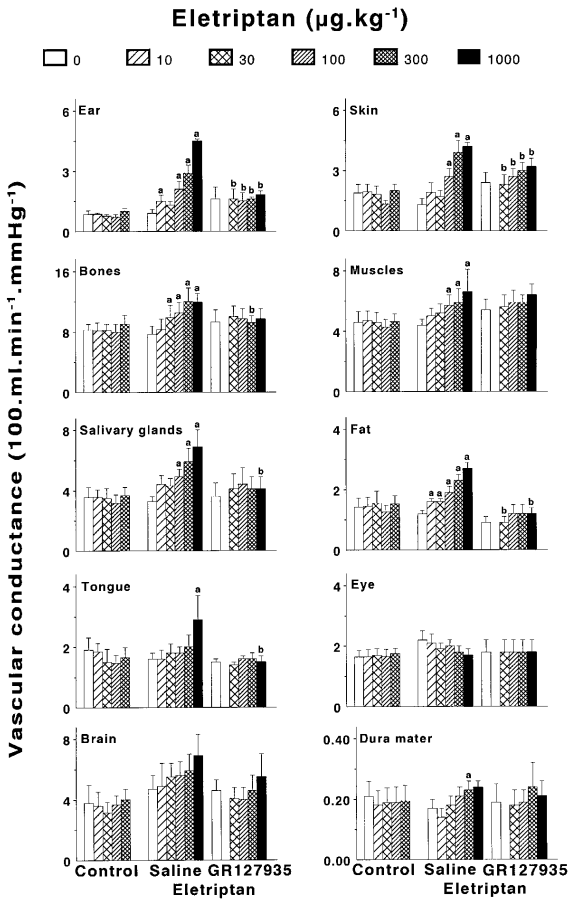

Fig. 4 Percent changes from baseline values by eletriptan (10, 30, 100, 300 and 1000 μg kg^{-1}) on the distribution of carotid conductance in several cranial tissues in anaesthetised pigs, pretreated with either 0.5 ml saline (*middle columns in panels*; *n*=6, 9, 9, 8 and 3, respectively) or 0.5 mg kg^{-1} GR127935 (*right columns in panels*; *n*=7). Control animals received four times 5 ml saline (*left column in panels; n*=7). The *white bars* represent baseline values. All values are presented as means ± SEM. Please note that 10 μg kg^{-1} dose was not used in GR127935-treated animals. [a] $P<0.05$ vs. baseline; [b] $P<0.05$ vs. corresponding dose in the saline-pretreated animals

did not elicit systemic haemodynamic changes (present study; Saxena et al. 1997a). Moreover, similar bradycardic or hypotensive effects have also been reported in the pig with other 5-HT$_{1B/1D}$ receptor agonists, including alniditan (De Vries et al. 1998b), avitriptan (Saxena et al. 1997a) and GMC2021 (Saxena et al. 1996). As described previously, these effects could be due to central 5-HT$_{1A}$ receptor activation (Dreteler et al. 1989; Saxena and Villalón 1990; Pagniez et al. 1998) and/or presynaptic inhibition of sympathetic neurones (Humphrey et al. 1988, 1990). Indeed, eletriptan displays a reasonable affinity at (human) 5-HT$_{1A}$ receptors (see Table 1). The moderate blockade of eletriptan-induced hypotension by GR127935 may suggest some involvement of 5-HT$_{1B/1D}$ receptors, but, on the other hand, GR127935 also has a moderate affinity at 5-HT$_{1A}$ receptor (Table 1). In any case, bradycardia or hypotension following therapeutic doses of eletriptan is of no clinical relevance, since high doses of eletriptan in human volunteers tend to increase (*not* decrease) diastolic blood pressure with no changes in heart rate (Milton et al. 1997).

Carotid haemodynamic changes

Whereas consecutive infusions of saline were devoid of carotid haemodynamic effects (present experiments; Saxena et al. 1997a), eletriptan (10–1000 μg kg^{-1}, i.v.) dose-dependently decreased the total carotid blood flow, exclusively at the expense of the arteriovenous anastomotic fraction; the nutrient fraction increased. These carotid haemodynamic changes are similar to those we previously reported in the same experimental model with several other acutely acting anti-migraine compounds. Thus, the ergot derivatives ergotamine and dihydroergotamine (Den Boer et al. 1991a), sumatriptan (Den Boer et al. 1991b; De Vries et al. 1996), avitriptan (Saxena et al. 1997a) as well as alniditan (De Vries et al. 1998b) potently constrict porcine carotid arteriovenous anastomoses. The dose of eletriptan producing a 50% decrease (ED_{50}) in the arteriovenous anastomotic conductance (396±91 nmol kg^{-1}) appears to be higher than that reported for sumatriptan (156±54 nmol kg^{-1}; De Vries et al. 1996), ergotamine (3.8±1.0 nmol kg^{-1}), dihydroergotamine (7.8±3.0 nmol kg^{-1}; Den Boer et al. 1991a), avitriptan (150±21 nmol kg^{-1}; Saxena et al. 1997a) or alniditan (66±21 nmol kg^{-1}; De Vries et al. 1998b). However, the maximum effect of eletriptan on arteriovenous anastomotic conductance (–77±4%; Fig. 3) is comparable to those observed with the above anti-migraine drugs (–67 to –88%; Den Boer et al. 1991b; De Vries et al. 1996, 1998b; Saxena et al. 1997a;). It therefore appears that, in contrast to its lower efficacy than sumatriptan in contracting the dog isolated saphenous vein (Gupta et al. 1997), eletriptan elicits a comparable maximum decrease in the carotid arteriovenous anastomotic blood flow in the present experiments. This difference may be due a higher receptor reserve in the porcine carotid vascular bed than in the dog saphenous vein. This suggestion is strengthened by the fact that another 5-HT$_{1B/1D}$ receptor agonist BMS-181885, which behaves as a competitive antagonist in the dog isolated saphenous vein and guinea pig pressurised iliac artery (Yocca et al. 1997), effectively reduces porcine carotid arteriovenous anastomotic blood flow (Saxena et al. 1998).

Nature of receptors mediating constriction of carotid arteriovenous anastomoses

As can be expected from the receptor binding profile (Table 1), the eletriptan-induced constriction of carotid arteriovenous anastomoses was potently blocked by the selective 5-HT$_{1B/1D}$ receptor antagonist GR127935 (Clitherow et al. 1994; Pauwels 1996; Skingle et al. 1996). Thus, porcine carotid vasoconstriction by eletriptan is mainly mediated by 5-HT$_{1B/1D}$ receptors. It should be noted, however, that the dose of GR127935 used in the present experiments (0.5 mg kg^{-1}), which abolishes sumatriptan-induced arteriovenous anastomotic constriction (De Vries et al. 1996), did not

completely block the effect of eletriptan. We concede that a higher dose of GR127935, which is precluded due to its intrinsic activity (De Vries et al. 1998a), may have completely blocked the effect of eletriptan. On the other hand, an incomplete blockade by GR127935 implies that a non-5-$HT_{1B/1D}$ receptor may also play some minor role in the eletriptan-induced constriction of porcine carotid arteriovenous anastomoses. Evidence in favour of such non-5-$HT_{1B/1D}$ receptors has recently been provided in the pig (De Vries et al. 1998a).

In view of the presence of *m*RNA for the 5-HT_{1B} receptor, but not for the 5-HT_{1D} receptor, in human cranial blood vessels (Hamel et al. 1993; Bouchelet et al. 1996), it seems likely that the 5-HT_{1B} receptor plays a more important role within the carotid circulation. The use of recently described compounds SB-216641 and BRL-15572, which show a reasonable selectivity for the recombinant h5-HT_{1B} and h5-HT_{1D} receptors, respectively (Price et al. 1997; Schlicker et al. 1997), may help to elucidate the involvement of these receptor subtype(s).

5-HT_{1F} receptors and eletriptan

Phebus and coworkers (Johnson et al. 1997; Phebus et al. 1997) have recently argued that the inhibition of dural plasma extravasation as well as the therapeutic activity of sumatriptan is mediated via the 5-HT_{1F} receptor. Since, like sumatriptan, eletriptan has an appreciable affinity at 5-HT_{1F} receptors (Table 1), one may ask whether these receptors play a role in the constriction of porcine carotid arteriovenous anastomoses by eletriptan and, indeed, in its therapeutic activity in migraine. As discussed above, the arteriovenous anastomotic constriction by eletriptan is predominantly mediated by 5-$HT_{1B/1D}$ receptors. However, in view of the presence of 5-HT_{1F} receptor *m*RNA in cranial vessels (Bouchelet et al. 1996), we cannot categorically rule out that the non-$HT_{1B/1D}$ receptor, playing, at most, a minor role in the arteriovenous anastomotic constriction (see above), is not identical to the 5-HT_{1F} receptor. Notwithstanding, the role of 5-HT_{1F} receptors in the anti-migraine action based on the inhibition of dural plasma protein extravasation does not seem very likely for several reasons: (1) some compounds, for example neurokinin NK_1 and endothelin $ET_{A/B}$ receptor antagonists and CP-122,288, all of which potently inhibit plasma protein extravasation (Gupta et al. 1995; Shepheard et al. 1995; Brändli et al. 1996), failed to show clinical efficacy in migraine (Diener 1995; May et al. 1996; Goldstein et al. 1997; Roon et al. 1997); (2) BMS-181885, which does not inhibit dural plasma protein extravasation but constricts porcine arteriovenous anastomoses, can effectively abort migraine attacks (see Yocca et al. 1997; Saxena et al. 1998); (3) sumatriptan (pK_i: 7.94) has a higher affinity than ergotamine (pK_i: 6.76) for the 5-HT_{1F} receptor (P.J. Pauwels, pers. commun.; Adham et al. 1993) and yet sumatriptan is a less potent anti-migraine agent on the basis of parenteral doses used in migraine (sumatriptan: 6 mg, s.c.; ergotamine: 0.25–0.5 mg, i.m.); (4) the inhibitory action of sumatriptan on plasma protein extravasation, but not of CP-122,288, is blocked by GR127935 (Yu et al. 1997); and (5) the 5-$HT_{1B/1D}$ receptor agonist alniditan, which is effective in migraine (Goldstein et al. 1996), has little affinity for the 5-HT_{1F} receptor (Leysen et al. 1996). Still, the results of clinical trials in migraine with 5-HT_{1F} receptor agonists, such as LY344864 (Phebus et al. 1997), are awaited with great interest.

Nature of receptors mediating carotid arteriolar dilatation

As mentioned above, eletriptan produced arteriolar dilatation within the porcine carotid vascular bed. This dilatation was most prominent in the skin, ear and fat. Similar effects were obtained with sumatriptan (Den Boer et al. 1991b), GMC2021 (Saxena et al. 1996), avitriptan (Saxena et al. 1997a) and to a larger extent by 5-HT (Den Boer et al. 1992). Since vasodilatation elicited by eletriptan was not observed in animals pretreated with GR127935, 5-$HT_{1B/1D}$ receptors seem to mediate this response. Such a vasodilator mechanism has indeed been demonstrated in the pig isolated coronary artery (Schoeffter and Hoyer 1990).

Conclusion

The present study performed in anaesthetised pigs shows that eletriptan, a close analogue of the successful anti-migraine agent sumatriptan, decreased the total carotid blood flow, exclusively by constricting arteriovenous anastomoses, mainly mediated by 5-$HT_{1B/1D}$ receptors. As constriction of porcine carotid arteriovenous anastomoses has been shown to be predictive of anti-migraine potential, eletriptan should be able to abort migraine headache. Indeed, clinical studies indicate that eletriptan is effective in aborting migraine headache (Jackson 1996; Olesen et al. 1997).

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