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Effect of antimigraine drugs on dural blood flows and resistances and the responses to trigeminal stimulation

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Abstract

The effects of 2 antimigraine drugs sumatriptan and dihydroergotamine on dilatation of the middle meningeal artery elicited by stimulation of the trigeminal ganglion at the entry point of the first and second divisions was investigated in cats. Carotid and middle meningeal arterial blood flows and resistances were measured in 9 cats anesthetised with chloralose. Electrical stimulation of either trigeminal ganglion produced a frequency-dependent decrease in resistance of the carotid artery ipsilaterally and the middle meningeal artery bilaterally. The intravenous injection of sumatriptan increased carotid and meningeal vascular resistance, but this response was not prolonged. The intravenous injection of dihydroergotamine produced a larger and more prolonged vasoconstriction in these 2 beds than did sumatriptan. Dihydroergotamine, but not sumatriptan, blocked some components of the vascular response induced by stimulation of the trigeminal ganglion. Dihydroergotamine and sumatriptan have a different spectrum of activity on cranial circulatory beds and neither of them is able to reduce trigeminal-induced vasodilatation by blocking antidromic activation of trigeminal nerve fibres in cats at the doses used in these experiments.

Keywords: Trigeminal; Middle meningeal artery; Ergot alkaloid; Sumatriptan; Migraine

1. Introduction

Migraine headache is characterised by pain and vascular change – 2 prominent phenomena which are interrelated. The pain arises, or is perceived to arise, from dilated blood vessels – principally from those of the dura mater and the proximal parts of the large cerebral arteries which are innervated by trigeminal sensory nerves containing sensory neuropeptides that are released during migraine headache (Goadsby et al., 1990). Migraine headache can be mimicked by chemical or electrical stimulation of these vessels or the dura associated with them (Ray and Wolff, 1940). In experimental animals, electrical stimulation of dural vessels, such as the superior sagittal sinus, dilates cranial blood vessels (Lambert et al., 1988). Whether vasodilatation is the primary cause of headache or a secondary phenomenon remains unclear. It is not known whether these vessels are the primary generators of the pain and the nature of the causal link between the pain and the vascular changes is not yet established.

The mode of action of the antimigraine drugs sumatriptan and dihydroergotamine is also not clear, although their therapeutic effect is usually ascribed to vasoconstriction (Lance, 1993). The vessels vasoconstricted have been variously identified as large arteries (Wolff, 1963), small resistance vessels (Mellander and Mordenfelt, 1970), veins (Muller-Schweinitzer, 1974), capacitance vessels (Muller-Schweinitzer, 1974), the vessels of the dura (Moskowitz, 1993) and arterio-venous anastomoses (Saxena, 1978).

There is little doubt that dilatation of the cranial blood vessels plays an important role in migraine headache and the hypothesis that the primary event in migraine is neurological and that the vasodilatation is secondary has been advanced (Goadsby et al., 1991; Lance et al., 1983). Evidence has also been presented that dihydroergotamine may act to block trigeminal sensory input at relay sites in the spinal cord (Lambert et al., 1992), an effect which may depend on the blockade of release of sensory neuromodulators, such as substance P and calcitonin gene-related peptide. If such a block occurs, it would be the central

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analogue of a peripheral effect described by Moskowitz (1990).

In the present experiments, we examined the effect of stimulation of the trigeminal ganglion on flow in the carotid and meningeal blood vessels before and after administration of 2 antimigraine drugs. Frequency-response curves before and after intravenous administration of sumatriptan or dihydroergotamine were used to characterise the site of action of these 2 drugs.

2. Materials and methods

Nine domestic cats (*Felis catus*) (mean ± S.D. weight 3.4 ± 0.7 kg) were anesthetized with intraperitoneal injections of α-chloralose (60 mg/kg). The femoral artery and vein were cannulated to measure blood pressure and heart rate and to administer intravenous drugs and fluids. Animals were intubated and ventilated with 30% oxygen in air to keep end-expiratory CO_2 in the range 3.5–4.0%. Arterial blood samples were analysed with a Radiometer ABL300 blood gas machine and a Radiometer KNA2 sodium/potassium analyser.

Throughout the experiment, neuromuscular blockade was maintained with intravenous gallamine triethiodide, 20 mg/kg (May and Baker). The depth of anesthesia was assessed periodically during the experiment by testing for sympathetic responses to foot pinch (pupillary dilatation, tachycardia, raised blood pressure and withdrawal reflexes during gallamine-free periods). Supplementary doses of either chloralose or gallamine were given when necessary. Rectal temperature was monitored throughout the experiment with a thermistor, and was maintained at 37–38°C by means of a servo-controlled heating blanket.

Animals were mounted in a David Kopf stereotaxic frame (David Kopf, Tujunga, CA, USA) and craniotomies drilled with a 0.06-cm dental burr at low speed. The inner and outer diploe were removed in layers, to expose the underlying translucent layer of periosteum adherent to the dura. During drilling, the surgical field was bathed in normal saline to minimise possible thermal injury to the underlying cortex.

A standard 3-fibre Laser-Doppler probe (Vasomedix) was modified by removing it from its protective pencil and separating the fibres. One receiving fibre was disabled by cutting it back and the remaining pair were glued together tangentially. Either the main trunk or major branch of middle meningeal artery was chosen for measurement, the criterion being that blood velocity in the artery was at least 20% below the maximum measurable with the LaserFlo system (8 kHz). The techniques have been described previously (Michalicek et al., 1996). A standard Laser-Doppler flow probe was used to assess cortical blood flow and to detect the presence or absence of prior cortical spreading depression. The methods to monitor cortical blood flow have been described previously (Piper et al., 1991b).

The carotid arteries were exposed bilaterally and stripped of their fascia for a length of several centimetres. Common carotid blood flows were monitored with electromagnetic flow probes (0.15 cm opening) placed around each artery and the signal recorded on EMI flowmeters (EMI Australia, Homebush, NSW, Australia) (Lambert et al., 1988).

Subsequent preparatory surgical procedures were carried out under supplementary 1.5% halothane anesthesia to prevent the initiation of cortical spreading depression (Piper et al., 1991a). Cortical vasodilatation produced by arterial hypercapnia was used as a measure of cerebral vascular reactivity, to check whether insertion of the electrodes into the trigeminal ganglion led to spreading cortical depression, which is characterised by loss of reactivity to carbon dioxide. Reactivity was measured by supplementing the inhaled gas mixture with CO_2 to achieve a final CO_2 concentration of 8%, for 5 min. Cortical blood flow was measured before, during and after the CO_2 inhalation, and the change in flow was calculated. This standard stimulus resulted in a rise of pCO_2 from about 40 to 80 mm Hg and a rise of approximately 30% in cortical blood flow. Animals in which cortical spreading depression had occurred were rejected from the study.

Parallel bipolar stainless steel stimulating electrodes, tip diameter 0.2 mm, exposed tip length 0.5 mm and tip separation 0.5 mm (NEX-200; David Rhodes, CA, USA) were placed stereotaxically in each trigeminal ganglion, near the entry point of the first and second divisions of the nerve (A/P = +9.0, L = 7.0) according to the stereotaxic atlas of Schneider et al. (1981), at a horizontal coordinate in the ganglion corresponding to the location of cell bodies with fibres projecting to the dural supplied by the meningeal artery. Occurrence of a trigeminal depressor response was used as an additional test criterion for determining placement within the ganglion. The location used is at the spot equidistant from points 'b', 'c', 'd' and 'e' in the ganglion axis of Schneider et al. (1981) and was chosen in conjunction with the stimulus parameters to encompass first and second division neurons with axons projecting to the dura and middle meningeal artery (Steiger and Meakin, 1984; Mayberg et al., 1984). At this point, the ganglion is approximately 1.2 mm in depth. Accordingly, the ganglion was penetrated cautiously with the stereotaxic manipulator until the electrode made contact with the skull surface, after which it was withdrawn 0.8 mm, to place it slightly above the dorso-ventral mid-point of the ganglion. Stimuli were delivered to one or the other trigeminal ganglion from a Grass S88 stimulator (Grass Instrument, Quincy, MA, USA) through Grass stimulus isolation and constant current units (100–250 μA, 250 μs for 30 s). These stimulus parameters were chosen according to criteria recommended by Ranck (1975), so that cell bodies within an approximate 0.7 mm radius only were stimulated. With these electrodes and the currents used (250 μA), the volume of ganglion stimulated should approximate an

Table 1
Mean and S.E. values of vascular parameters

	mma			Right carotid (ml/min)	Left carotid (ml/min)	Blood pressure (mm Hg)
	Velocity (kHz)	Volume (*a*)	Flow (*b*)			
Mean	5.1	0.39	109	23.7	23.7	115
S.E.	0.3	0.03	7	1.8	1.6	3

There was no significant difference between left and right carotid blood flow: $F(8,8) = 1.27$, $P > 0.05$, one-way analysis of variance ($n = 9$).
a, mean number of scatterings per photon, proportional to red blood cell number.
b, unspecified flow units, proportional to flow in ml min^{-1} 100 g^{-1}, ≈ velocity · volume · 60.

oblate ellipsoid 2.1 mm diameter and 1.4 mm high. This should have resulted in all ganglion cells and fibres of the first and second divisions being activated, without activation of structures outside the ganglion. Frequency-response curves for blood pressure, flows and resistances were constructed for 9 geometrically spaced frequencies between 0.1 and 50 s^{-1}. At the conclusion of the experiments, a small cathodal DC current (20 μA for 20 s) was passed through both poles of each electrode to produce a lesion at the site of stimulation. The ganglia and roots were examined after death to verify the placement of stimulating electrodes and the success of the rhizotomy. Observations on the rhizotomy and electrode placements were recorded on drawings.

Expired CO_2, blood pressure, heart rate, common carotid blood flows and Laser-Doppler flows were recorded on line with an A/D card (DT2821F; Data Translation, Marlboro, MA, USA) in an IBM-compatible computer running GlobalLab (GlobalLab, Marlboro, MA, USA) data acquisition software. Each signal was recorded at 10 samples per s. For post-experimental processing, the signals were averaged over 2-s epochs to eliminate short-duration changes associated with respiration and pulse. Since blood flow measured by Laser-Doppler flowmetry may not give an absolute measure of flow in ml min^{-1} 100 g^{-1}, changes in flow were calculated as percentage changes from baseline flow and therefore, for consistency, all other parameters were similarly treated. This method has been described previously (Piper et al., 1991b). In brief, meter readings for the 30 s prior to electrical stimulation were averaged over 15 of the 2-s epochs. All signals during and after stimulation were then recalculated as percentage deviations from these averages – again for each 2-s epoch. Responses to trigeminal stimulation in this paper are all presented in such form. Absolute baseline values, in instrumental units, appear in Tables 1 and 2.

The vascular resistance of either arterial bed was calculated from the relationship *resistance = perfusion pressure / flow*. Since carotid perfusion pressure is almost identical to systemic blood pressure (Welch et al., 1974), the latter was used in the calculation of carotid bed resistance. A similar assumption was made for the middle meningeal arterial blood flow measurements.

After surgery, animals were allowed to stabilise for 1 h. Frequency-response curves for trigeminal stimulation were then obtained. Left and right trigeminal ganglia were stimulated in fully random order, at 3-min intervals, 9 stimulus frequencies on each side requiring 54 min. A second frequency-response curve was then obtained. The drug being tested was then administered intravenously and responses recorded for 30 min or until blood pressures and flows had stabilised. A test frequency-response curve was commenced 30 min after drug injection or when parameters had stabilised, whichever was the later. Two animals

Table 2
Baseline levels of blood pressure and arterial flows before after sumatriptan or dihydroergotamine treatment

	Blood pressure	Carotid flow	Carotid resistance	Meningeal flow	Meningeal resistance
Dihydroergotamine					
Control	120 ± 4	19.9 ± 1.5	6.58 ± 0.54	141 ± 33	1.30 ± 0.31
After treatment	132 ± 4[a]	18.6 ± 2.0	8.32 ± 0.82[a]	136 ± 33	1.40 ± 0.31
$n = 5$					
Sumatriptan					
Control	124 ± 4	18.8 ± 1.5	7.43 ± 0.80	169 ± 26	0.95 ± 0.22
After treatment	123 ± 4	16.4 ± 1.6[a]	8.50 ± 0.81	164 ± 27	1.05 ± 0.28
$n = 6$					

Values shown are mean ± S.E. values. Each animal served as its own control. a = parameters that are significantly different from their controls ($P < 0.05$, Student's paired *t*-test). Measurements were made immediately before administration of drugs and approximately 30 min following drug administration, immediately prior to repeating trigeminal stimulation. At this stage, the initial vascular changes produced by the drugs had stabilised. There was no effect of bolus intravenous injections of normal saline (0.1–1 ml).

received both sumatriptan and dihydroergotamine. The former was given first and a period of 6 h (3 half-lives) elapsed between the 2 administrations.

In this report, all error ranges associated with mean values are given as the S.E.M. Baseline levels of blood pressure, flows and resistances were compared with a Student's paired *t*-test. Frequency-response curves were analysed according to the non-parametric method of Krauth (1980). The first 4 orthogonal polynomial coefficients (a_0 to a_3) were calculated for each response curve in each cat and the coefficients were tested for differences between the groups with a contingency table test or the exact Irwin-Fisher test. Coefficient a_0 represents the average level of the response and a_1 to a_3 are related to the first- to third-order polynomial coefficients of the frequency-response relationship. Based on previous experience, we chose, a priori, to analyse the pattern of only the first 2 coefficients a_0 and a_1 (Lambert and Michalicek, 1994). Significance was accepted at the $P < 0.05$ level.

The following drugs were used in the experiments: α-chloralose (Calbiochem), gallamine tri-ethiodide (May and Baker), dihydroergotamine mesylate (Sandoz), sumatriptan succinate (Glaxo). Sumatriptan succinate pure substance was dissolved in normal saline and injected intravenously at a dose of 80 μg/kg, approximately the human subcutaneous dose for this drug. Dihydroergotamine mesy-

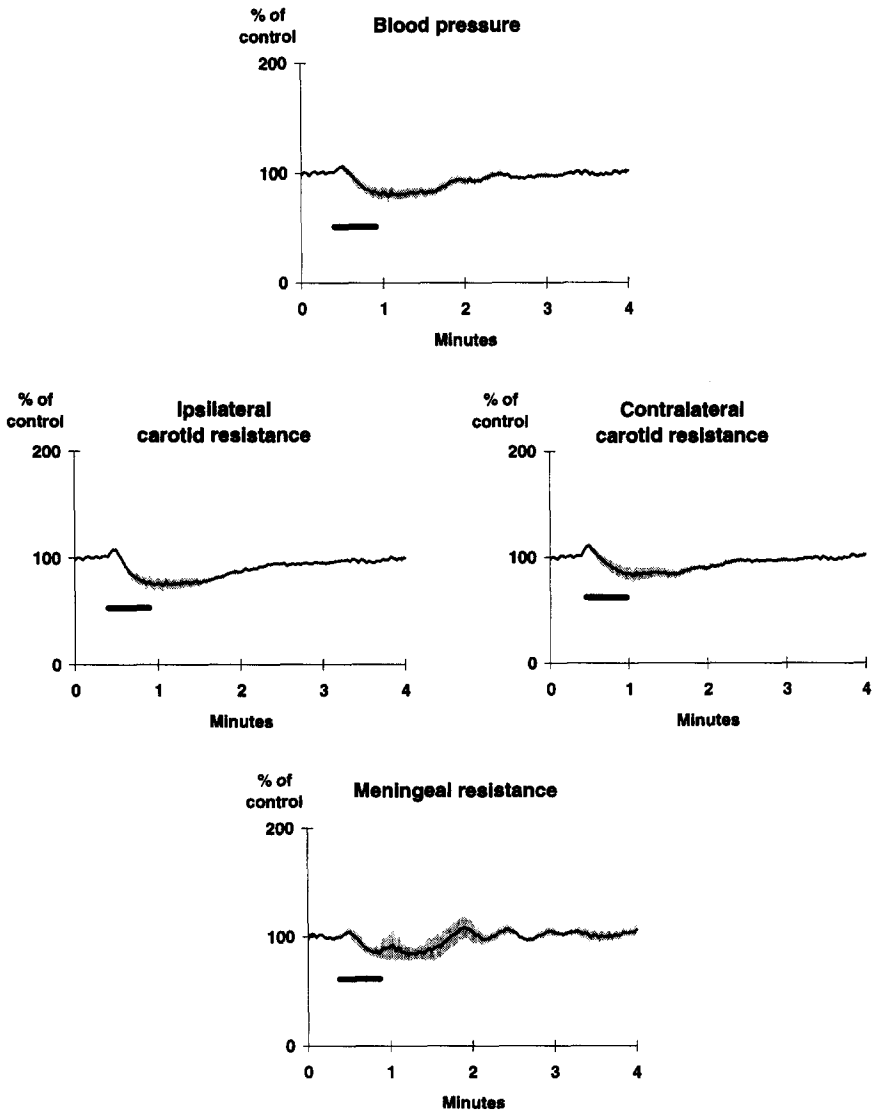

Fig. 1. Mean responses of carotid and meningeal circulations to stimulation of the trigeminal ganglion near the exit point of the first and second trigeminal divisions, at a frequency of 2 s^{-1}. Stimulation of the trigeminal ganglion produced a fall in blood pressure ('trigeminal depressor response', top), and dilatation in both the carotid (middle) and meningeal (bottom) vascular beds. Responses are expressed as percentage deviations from baseline levels which were averaged over the 15 s prior to stimulation (Table 1) and are shown as mean values with S.E. envelopes (shading). For most points on the graphs, $n = 9$. Sample rate plotted = 0.5 s^{-1}, aggregated from an original 10 s^{-1} sample rate (see text). The 30-s period of stimulation is indicated by the horizontal bars.

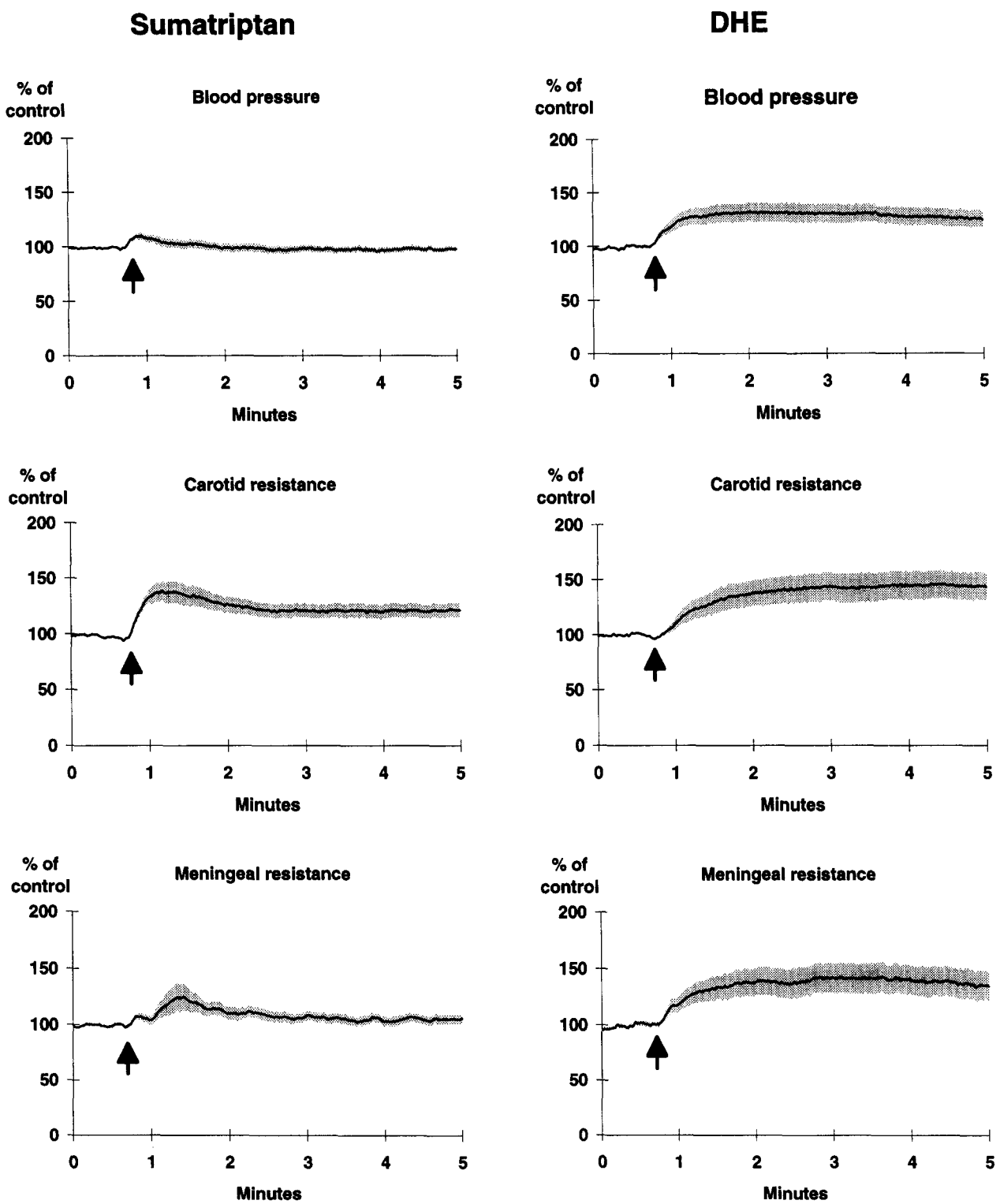

Fig. 2. Left: Effects of an intravenous injection of sumatriptan 80 μg/kg inv. on baseline blood pressure, carotid vascular resistance and meningeal vascular resistance. Sumatriptan caused a biphasic vasoconstriction in the carotid circulation. There was a transient rise in resistance in the middle meningeal arterial bed. Right: Effects of an intravenous injection of dihydroergotamine 40 μg/kg inv. on baseline blood pressure, carotid vascular resistance and meningeal vascular resistance. The predominant effect was a constriction in the general carotid circulation. There was also a constriction of the middle meningeal artery. The traces show mean responses, expressed as a percentage of the baseline levels averaged over the 30 s prior to drug administration, with their S.E. envelopes. $n = 5$ (sumatriptan) or 6 (dihydroergotamine).

late (Dihydergot ampules 1 mg/ml) was diluted 1 : 100 in normal saline and injected intravenously in a dose of 40 μg/kg, equivalent to about twice the usual human dose by this route.

All experiments described in this report were approved by this university's Animal Ethics Committee and conformed to its Guidelines.

3. Results

Mean baseline blood pressure, blood gas parameters, carotid flows (23.7 ± 1.7 ml min^{-1}) and Laser-Doppler estimates of meningeal blood 'flow' (109 ± 7 Laser-Doppler units) were within normal limits in the cats studied. There was no significant difference between resting levels

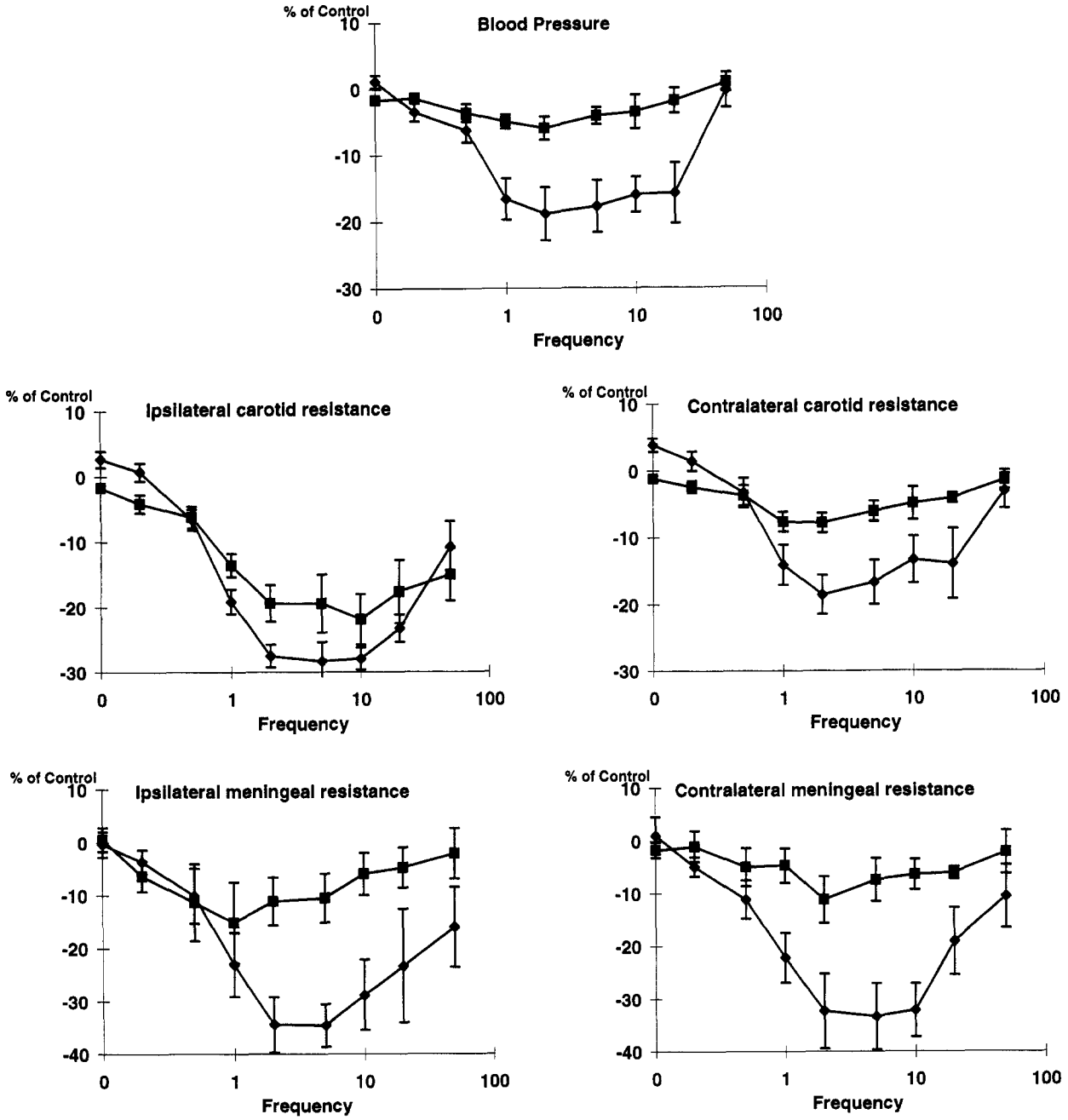

Fig. 3. Frequency-response curves for the responses of carotid and middle meningeal arterial circulations to stimulation of the trigeminal ganglion before (diamonds) and after (squares) administration of dihydroergotamine, 40 μg/kg. Responses are expressed as percentage deviations from control values and are shown as mean ± S.E. values. Blood pressure responses and responses in the meningeal arterial bed and the carotid bed contralateral to the stimulated site were significantly reduced by prior dihydroergotamine treatment. Responses in the carotid bed ipsilateral to the stimulated side were not affected. Responses are expressed as percentage deviations from control values and are shown as mean ± S.E. values. Significance tests conducted according to the method of Krauth (1980). In most cases, $n = 9$.

of carotid blood flow between the left and right sides (Table 1). Bolus intravenous injections of normal saline had no effect on any of these measures.

3.1. Trigeminal stimulation

Stimulation of the trigeminal ganglion near the origin of the 1st and 2nd divisions of the trigeminal nerve produced a frequency-dependent fall in blood pressure and a rise in carotid blood flow, as described previously (Lambert et al., 1991a). In some animals, at some frequencies, especially where the blood pressure fall was large, flow in the carotid arteries actually decreased, but always less proportionately than the fall in blood pressure. Blood pressure and flow responses were maximal at 2–5 s^{-1} and declined at higher frequencies, producing a bell-shaped frequency-response curve. Calculated carotid vascular resistance fell in a frequency-dependent manner. The resistance responses were

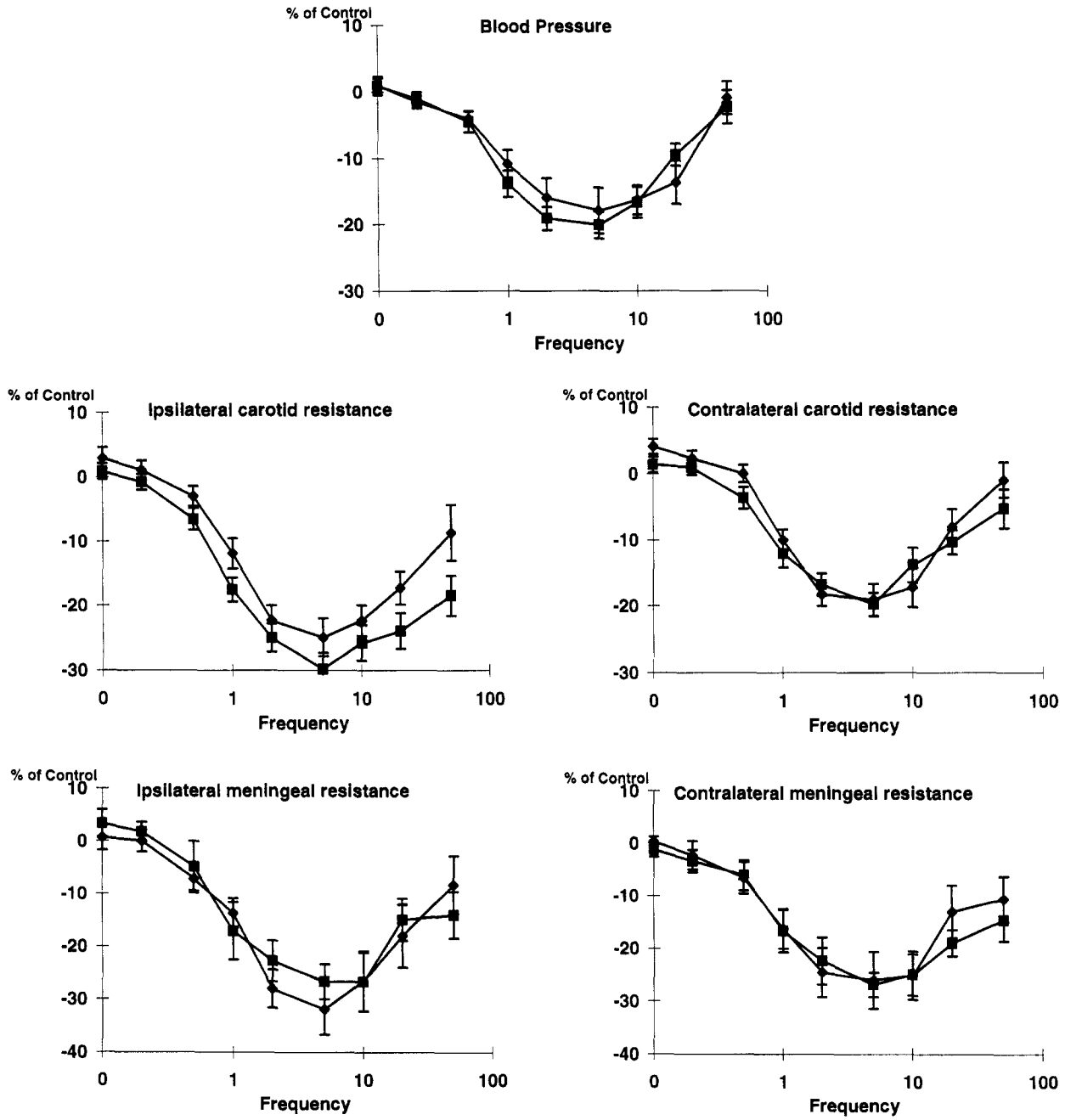

Fig. 4. Frequency-response curves for the responses of carotid and middle meningeal arterial circulations to stimulation of the trigeminal ganglion before (diamonds) and after (squares) administration of sumatriptan, 80 μg/kg. Responses are expressed as percentage deviations from control values and are shown as mean ± S.E. values. No components of the response to stimulation of the trigeminal system were affected by prior treatment with sumatriptan. Significance tests conducted according to the method of Krauth (1980). In most cases, $n = 9$.

65% greater in magnitude in the carotid vascular bed ipsilateral to the stimulated trigeminal root. These differences were significant, when analysed according to the method of Krauth (1980). The orthogonal coefficients of the carotid artery resistance response curves were significant for coefficients a_0 and a_1. χ^2 for these 2 coefficients in a comparison between the contralateral and ipsilateral carotid circulations was 9.5 (df = 3, $P < 0.05$).

Stimulation of the first and second divisions of the trigeminal nerve also produced decreases in meningeal vascular resistance, maximal at 2–5 s^{-1} (30% decrease). Depending on the changes in blood pressure produced by the stimulation, flow in the middle meningeal artery could either rise or fall, but resistance always fell. There was little difference between the response of the middle meningeal artery induced by trigeminal stimulation ipsilateral to the artery and that induced by stimulation contralateral to it. At a stimulus frequency of 2 s^{-1}, the blood flow in the middle meningeal artery increased by 18% of control on the ipsilateral side and 15% of control on the contralateral side. The corresponding resistance changes were a 35% fall and a 30% fall. There was no significant difference in the frequency-resistance response curves on the 2 sides. χ^2 for the difference between the first 2 coefficients a_0 and a_1 for ipsilateral vs. contralateral stimulation was 0.92 (N.S.). The changes in blood flow in the middle meningeal artery occurred mainly as a result of an increase in the 'volume' signal, representing cross sectional area of the blood vessel. Laser-Doppler velocity either remained constant or, in those cases where systemic blood pressure itself fell, also fell slightly.

Mean responses of the carotid and meningeal circulations to a stimulus frequency of 2 s^{-1} are shown in Fig. 1. Resting levels of blood pressure and flows, upon which the frequency-response curves are based, are shown in Fig. 2. Frequency-response curves are shown in Figs. 3 and 4 (open circles).

3.2. Effect of dihydroergotamine or sumatriptan injections on baseline values of blood pressure and vascular parameters

Intravenous injections of 40 $\mu g\ kg^{-1}$ dihydroergotamine (Fig. 2) produced a rise in blood pressure of 31.6 ± 8.5% (Student's $t = 3.8$, $P < 0.005$) of control, which peaked at 25–30 s after administration and only slowly returned to normal levels (≥ 30 min). Carotid artery blood flow also rose (but to a smaller extent) and then declined in a similar manner. Calculated carotid bed vascular resistance also rose after dihydroergotamine injection reaching a peak of 146 ± 12% ($t = 3.6$, $P < 0.01$) at 3 min after injection and remained elevated for nearly 2 h. There was no difference in the degree of vasoconstriction on the 2 sides of the head, although there was a slight difference in the time courses. Mean middle meningeal blood flow did not change significantly (93 ± 3%, $t = 2.4$, N.S.) but middle meningeal resistance increased to 142 ± 3.2% of control ($t = 3.2$, $P < 0.05$). Meningeal blood flow and resistance had returned to normal within 30 min, at the time when the arterial beds were again tested for their responses to stimulation of the trigeminal ganglion (Table 2, Fig. 2).

Intravenous injection of 80 $\mu g/kg$ sumatriptan produced an initial rise in blood pressure to 109.6 ± 2.2% of control ($t = 4.4$, $P < 0.005$), which peaked at 25–30 s after administration, with a consequent recovery to normal and sometimes a further decline to below baseline levels. Carotid resistance increased initially to 138 ± 9.8% of control ($t = 8.6$, $P < 0.001$) and slowly recovered, to settle about 30% above baseline level, resulting in a carotid blood flow which was approximately 87% of control (Ta-

Table 3
Orthogonal regression coefficients for the log(frequency)-response curves for blood pressure, meningeal resistance and carotid resistance before and after sumatriptan or dihydroergotamine treatment

	Blood pressure	Meningeal resistance	Ipsilateral carotid resistance	Contralateral carotid resistance
Dihydroergotamine				
Control	a_0 −10.13, a_1 4.36	a_0 −19.20, a_1 −9.23	a_0 −15.68, a_1 −9.71	a_0 −9.48, a_1 −5.55
After treatment	a_0 −3.29, a_1 0.00	a_0 −6.67, a_1 −1.06	a_0 −13.47, a_1 −6.93	a_0 −4.55, a_1 −0.66
χ^2	17.06, $P < 0.001$	10.44, $P < 0.02$	5.56 N.S.	8.72, $P < 0.05$
Sumatriptan				
Control	a_0 −10.67, a_1 −4.45	a_0 −16.35, a_1 −7.97	a_0 −13.78, a_1 −8.53	a_0 −7.46, a_1 −5.04
After treatment	a_0 −10.14, a_1 −4.03	a_0 −14.73, a_1 7.75	a_0 −16.74, a_1 −9.88	a_0 −8.88, a_1 −4.08
χ^2	0.50, N.S.	1.22, N.S.	3.17, N.S.	1.29, N.S.

Values shown are the averages of the individual first and second orthogonal coefficients of the log(frequency)-response curves in each case. χ^2-test for individual coefficients (not the averages) was carried out by contingency table analysis of patterns of paired coefficients, a_0 and a_1, according to the method of Krauth (1980). Carotid resistance figures before and after drug treatment contain pooled data from both left and right trigeminal stimulation, with the response always being recorded from the carotid artery ipsilateral (column 3) or contralateral (column 4) to the stimulus. Meningeal resistance figures contain pooled data from ipsilateral and contralateral stimulations, since these have been shown to be not significantly different and are mediated via non-somatotopic mechanisms.

ble 2). Middle meningeal arterial resistance rose within 1 min of injection to 124 ± 12.2%) of baseline ($t = 2.0$, N.S.) and after 3 min stabilised at about 10% above the previous baseline levels (Table 2, Fig. 2).

Responses to trigeminal stimulation were tested approximately 30 min after sumatriptan or dihydroergotamine injection, at which point blood pressure, carotid artery flow and middle meningeal artery flow had stabilised. A typical complete bilateral frequency-response curve required about 54 min to perform, thus the post-drug test responses occurred from 30 to 84 min post-drug (median 57 min, or approximately 1 h).

3.3. Effect of dihydroergotamine and sumatriptan on dilatation produced by stimulation of the trigeminal ganglion

Dihydroergotamine significantly reduced most components of the trigeminovascular response to stimulation of the trigeminal ganglion. Blood pressure, meningeal and contralateral carotid vascular responses were all significantly reduced, but the responses in the carotid artery ipsilateral to the electrical stimulus were not reduced (Table 3, Fig. 3)

Sumatriptan had no effect on the responses of any of the vascular beds examined to stimulation of either trigeminal ganglion (Table 3, Fig. 4).

4. Discussion

The results reported here extend previous findings on the influence of trigeminal activity on cranial and extracranial carotid blood flow (Goadsby et al., 1986; Lambert et al., 1984) which suggest that the greater part of the carotid bed vasodilatation produced by stimulation of the trigeminal ganglion takes place in the extracerebral circulation. It involves a central mechanism which produces the vascular changes by activation of the parasympathetic component of the facial nerve (Goadsby et al., 1986; Lambert et al., 1984). In another report, we have demonstrated that the dilatation which occurs in the middle meningeal artery in response to trigeminal stimulation is produced by a mixture of autoregulation and a lowering of the circulating levels of catecholamines (Lambert et al., 1993) and not through orthodromic mechanisms. Thus, even from the outset of our experiments, it seemed unlikely that dihydroergotamine could act to modify dural vasodilatation by preventing antidromic vasodilatation at the peripheral ends of dural sensory nerves. This has been confirmed in our laboratory for the carotid and cortical vascular beds by experiments similar to those described here but in animals in which one trigeminal root had been sectioned distal to the ganglion. In these experiments, sumatriptan did not alter the already very small response to trigeminal stimulation on the lesioned side and dihydroergotamine produced only a small blockade only at very high stimulus frequencies and only in the cortical circulation (Lambert et al., 1991a).

The stimulus parameters chosen for this study were designed to ensure activation of C-fibres. The intensities used (250 μA) are only 15–20% of those used by Buzzi and Moskowitz (1990), but are sufficient to activate a-δ and C-fibre afferents from the dura (Lambert et al., 1991b). These intensities would also have activated the complete range of trigeminal fibres passing through the ganglion. However, we have shown elsewhere (Lambert et al., 1988) that responses to stimulation of trigeminal ganglion and dural sensory nerves are qualitatively similar, although the latter are larger. We believe that the method of stimulation used in the present experiments satisfactorily mimics noxious activation of dural afferents and parallel and both orthodromic and antidromic activity.

The currently most clinically successful antimigraine drugs, dihydroergotamine and sumatriptan, interact strongly and predominantly with 5-HT receptors as antagonists or agonists (Humphrey et al., 1990a). Both constrict some components of the cranial circulation and their efficacy in migraine is often attributed to this action. In the current experiments, although dihydroergotamine and sumatriptan produced vasoconstriction in the both the carotid and middle meningeal arteries, the constriction in the latter was not maintained. The meningeal circulation therefore seems to be more akin to the cortical microcirculation, where the action of dihydroergotamine, although significant, is also fairly short-lived. Although the middle meningeal artery in cats arises from the external carotid circulation, it nevertheless shares with the internal carotid circulation many of its properties, such as its ability to autoregulate its flow (Michalicek et al., 1996). It has a very complex vascular anatomy with 6 distinct types of blood vessel (Kerber and Newton, 1973) and may be better able to adjust in the face of imposed pharmacological changes than is the external carotid circulation.

Sumatriptan produced only a small and evanescent vasoconstriction in the middle meningeal artery. This seems to be at variance with the results of Whalley et al. (1991 and Edvinsson et al. (Jansen et al., 1992), who showed that sumatriptan was a potent vasoconstrictor agent in isolated human meningeal arteries. Sumatriptan is also a potent constrictor of pial arterioles (Connor et al., 1992; Humphrey et al., 1991), but apparently only when applied perivascularly (Humphrey et al., 1991). Until now, its constrictor effect on dural arteries in situ has not been tested. Species differences might account for its relatively weak constrictor effect seen in our experiments, but it seems more reasonable to attribute them to the fact that our experiments were carried out in vivo, rather than in vitro. Our results in the middle meningeal artery agree with those found in large cerebral arteries and arteriovenous anastomeses by Caekebeke et al. (1992) and Friberg et al. (1991), who studied the craniovascular effects of

sumatriptan in humans. Friberg et al. (1991) reported that sumatriptan increased blood velocity in large arteries without changing cerebral perfusion. They attributed this observation to vasoconstriction being confined to large-diameter, non-resistance vessels, with no effect on resistance vessels. Other investigators have reported that sumatriptan constricts dural arteriovenous anastomoses (Den Boer et al., 1991). Constriction of arterio-venous anastomosess could easily decrease flow measured in the trunk of the middle meningeal artery, although this presupposes that the arterio-venous anastomosess were open to start with, a supposition which we were unable to test in our experiments.

After administration of dihydroergotamine, the depressor effects of trigeminal ganglion stimulation were significantly reduced. Kumada et al. (1977) have shown that the 'trigeminal depressor response' arises mainly through a withdrawal of sympathetic tone. The blockade of the trigeminal depressor response by dihydroergotamine is therefore most likely to be due to its known α-adrenoceptor blocking effect (Muller-Schweinitzer and Wiedmann, 1978). The inherent vasoconstrictor activity of dihydroergotamine, which was greater in these experiments than that of sumatriptan may also have contributed to a diminution in the response to trigeminal stimulation by antagonising physiologically the dilator effect of stimulation.

We have shown elsewhere that dihydroergotamine can significantly reduce the dilator response of the carotid artery produced by stimulation of the main body of the trigeminal ganglion (Lambert and Michalicek, 1992). The failure of dihydroergotamine to block the response when only part of the ganglion was stimulated differs from the previous results. There may be a different mechanistic 'mix' of the resulting response in the carotid bed when only the first and second divisions are stimulated. Both our previous work (Lambert et al., 1984) and that of Gonzalez et al. (1975) showed that the degree of vasodilatation in response to trigeminal stimulation varies from division to division, with the first producing the most powerful effect.

The α-adrenoceptor blocking effect of dihydroergotamine (Muller-Schweinitzer and Wiedmann, 1978) may account for the blockade of the dilator responses of the middle meningeal artery to trigeminal stimulation, since this response is at least partly due to a change in circulating levels of catecholamines (Lambert et al., 1993).

Studies have shown that dihydroergotamine blocks neuronal activation induced in the spinal cord and trigeminal nucleus by electrical or mechanical stimulation of the superior sagittal sinus, a dural vessel (Hoskin et al., 1994; Lambert et al., 1992). Although such an action could conceivably block a stimulus-induced vasodilatation, it does not appear to have been responsible for the block seen here. We believe that this indicates that the trigeminal or spinal pathways responsible for the trigeminal depressor response may be distinct, or at least pharmacologically different from, those examined in the 2 previous studies.

Sumatriptan administration did not block dilatation in the carotid and meningeal arteries in response to stimulation of the trigeminal ganglion, not even through orthodromic mechanisms. Sumatriptan shares many of its serotonin receptor agonist and binding properties with dihydroergotamine, but it does not have the α-adrenoceptor blocking properties of dihydroergotamine (Eltze et al., 1991). In addition, sumatriptan is a relatively more polar and basic compound than dihydroergotamine and apparently does not penetrate the blood–brain barrier as readily (Humphrey et al., 1990b; Sleight et al., 1990). We have shown that sumatriptan, administered intravenously, is less active than dihydroergotamine in its ability to block processing at second-order craniovascular sensory neurons (Boers and Lambert, 1990), an observation that has recently been confirmed with c-*fos* studies (P.J. Goadsby, personal communication).

In conclusion, these experiments suggest that dihydroergotamine and sumatriptan have a different spectrum of activity on dural arteries, but that neither of them produces vasoconstriction by blockade of antidromic vasodilatation. Both these compounds are effective antimigraine drugs, and are supposed to act because of their actions at vascular or neuronal 5-HT receptors, most probably of the 5-HT_{1D} type. The differentiation in effect seen in these experiments therefore argues against vasoconstriction or antagonism of vasodilatation in the dural vasculature being the critical path of action of both drugs. Other mechanisms of action, such as antagonism of trigeminal-induced plasma extravasation or an equivalent antagonism at the central ends of these same nerves, remain as possibilities, however.

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