The antimigraine drug, sumatriptan (GR43175), selectively blocks neurogenic plasma extravasation from blood vessels in dura mater

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1 We describe the actions of GR43175, a 5-hydroxytryptamine₁ (5-HT₁)-like receptor agonist, on neurogenically-mediated plasma protein extravasation within an important pain-sensitive intracranial tissue, the dura mater.

2 GR43175 markedly attenuated extravasation of ¹²⁵I-albumin from blood vessels within ipsilateral dura mater when administered to rats (100 µg kg⁻¹) fifteen minutes before unilateral electrical trigeminal stimulation (1.2 mA, 5 Hz, 5 ms, 5 min.); the ratio (stimulated/unstimulated sides) decreased from 1.81 to 1.23, *P* < 0.005).

3 GR43175 (100 µg kg⁻¹, i.v., rats; 30 µg kg⁻¹, i.v., guinea-pigs) decreased the leakage of radiolabelled albumin from 163% to 119% (*P* < 0.005, guinea-pig) or from 174 to 118% (*P* < 0.05, rat) above vehicle-treated controls when injected ten minutes before systemic capsaicin treatment (0.5 or 1 µmol kg⁻¹, i.v.).

4 GR43175 (30–300 µg kg⁻¹) did not block plasma protein extravasation within extracranial tissues of rats and guinea-pigs innervated by the trigeminal nerve (conjunctiva, eyelid and lip).

5 The protein leakage which followed the i.v. administration of 5-HT (1 µmol kg⁻¹) or neuropeptides which mediate neurogenic plasma extravasation, substance P (0.3 nmol kg⁻¹ or 1 nmol kg⁻¹) and neurokinin A (1 nmol kg⁻¹), was not blocked by GR43175 (100, 300 µg kg⁻¹) despite the presence of leakage in amounts equivalent to that following neurogenic stimulation.

6 GR43175 (100 µg kg⁻¹) decreased bradykinin (10 µmol kg⁻¹)-induced extravasation from 142 to 115% above vehicle-treated animals (*P* < 0.05).

7 These results demonstrate an important action of GR43175 on neurogenic mechanisms in dural blood vessels. Since the ergot alkaloids possess a similar profile of drug activity, it is suggested that drugs useful in the treatment of acute vascular headaches may share a similar mechanism of action.

Introduction

Neurogenic inflammation (vasodilatation and plasma protein extravasation) within cephalic tissues has been proposed as a possible mechanism in headache pathogenesis (Moskowitz *et al.*, 1979; Mayberg *et al.*, 1981; Moskowitz, 1984; Hardebo, 1984). Neurogenic inflammation is mediated by release of vasoactive neuropeptides, substance P (SP) (Lembeck & Holzer, 1979), neurokinin A (NKA) and calcitonin gene-related peptide (CGRP), from sensory fibres innervating blood vessels (Saria *et al.*, 1985; 1986). Receptors located on the endothelium mediate both the endothelium-dependent vasodilatation and enhanced permeability induced by the tachykinins. Receptors on vascular smooth muscle mediate the vasodilatation produced by CGRP (Brain *et al.*, 1985).

The dura mater, an important source of headache pain (Ray & Wolff, 1940), provides a thick covering for the brain and contains blood vessels with fenestrated capillary endothelium (Andres *et al.*, 1987). The dura and its attendant blood vessels are innervated by trigeminal and upper cervical sensory nerve fibres which contain the vasoactive peptides, SP, NKA and CGRP (Edvinsson & Uddman, 1982; Mayberg *et al.*, 1984; Jansen *et al.*, 1986; Saito *et al.*, 1987). Perivascular sensory axons are unmyelinated and small and reside within the adventitial layer. Neurogenic plasma protein extravasation develops within the dura mater during electrical trigeminal ganglia stimulation or after intravenous administration of capsaicin (Markowitz *et al.*, 1987). Its development is markedly attenuated in animals in which perivascular afferent fibres were destroyed by capsaicin treatment during the neonatal period. In these same animals, the systemic administration of SP or NKA produces the same amount of leakage as in vehicle-treated controls.

We have shown that the antimigraine drugs, ergotamine tartrate, dihydroergotamine and methysergide (given chronically) selectively block neurogenic plasma protein extravasation within dura mater without affecting leakage within extracranial vascular tissues, or the extravasation following systemic administration of SP or NKA (Saito *et al.*, 1988). These antimigraine drugs readily pass the blood brain barrier (Ala-Hurula *et al.*, 1979) and exhibit activity at 5-hydroxytryptamine (5-HT) receptors. Recently, it was found that the 5-HT₁-like receptor agonist, GR43175 alleviates the pain of migraine headaches (Doenicke *et al.*, 1988). GR43175 passes the blood brain barrier poorly (Humphrey, personal communication) and like the ergot alkaloids, exhibits vasoconstrictor actions on cephalic blood vessels.

The studies described in this paper examine the possibility that GR43175 and the ergot alkaloids share a similar mechanism of action, which may explain their therapeutic effectiveness in acute migraine headaches. Based on the dose-response, temporal characteristics and pharmacological profile of GR43175 against electrical stimulation, capsaicin, 5-HT and the tachykinins, we conclude that GR43175 exhibits an ergot-like effect within the dura mater which appears to be primarily neurogenically-mediated. Whether the therapeutic effects of GR43175 and the ergot alkaloids are also related to their potent vasoconstrictor properties in cephalic blood vessels requires further study.

Methods

Male Sprague-Dawley rats (150–200 g) and male Hartley guinea-pigs (250–300 g) were housed under diurnal lighting conditions and allowed food and water *ad libitum*.

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Electrical stimulation of the rat trigeminal ganglion

Anaesthetized animals (pentobarbitone 60 mg kg^{-1} i.p.) were placed in a stereotaxic frame (Kopf Instruments, Tujunga, CA) and the calvarium exposed by a mid-sagittal incision. A 2 mm diameter hole was drilled 3.2 mm posterior to the bregma and 2.5 mm laterally on each side of the sagittal suture for electrode placement. The left femoral vein was then exposed and ^{125}I -BSA (New England Nuclear, Boston, MA) $50 \mu\text{Ci kg}^{-1}$ (diluted in 0.9% saline) injected as a bolus. After five minutes, bipolar electrodes (Kopf Instruments, Tujunga, CA) were lowered into both trigeminal ganglion to a depth of 9.2 mm below the calvarium. A shock stimulus (1.2 mA, 5 Hz, 5 ms duration) was delivered for 5 min to the right trigeminal ganglion (IsoLinear, World Precision Instruments, San Carlos CA). These parameters were sufficient (by electrophysiological criteria) to discharge small unmyelinated C fibres in the trigeminal nerve (unpublished data). Animals were perfused via the left cardiac ventricle with 0.9% saline at a constant pressure of 110 mmHg for 3 min immediately after stimulation. The skull was opened and dura mater was dissected as previously described (Markowitz *et al.*, 1987). The large dural sinuses, the region of dura through which the electrodes penetrated, and the dura covering the trigeminal ganglia were excluded from analysis. In some of the experiments, specimens of conjunctiva, eyelid and lip were also dissected. Samples were weighed and counted for radioactivity (Micromedex Systems Inc, Huntsville, AL). Radioactivity (c.p.m. mg^{-1} wt) was compared between the stimulated and the unstimulated sides. Data are expressed as the ratio between the two sides.

Chemically-induced plasma protein extravasation

To examine the effects of the various agents on plasma extravasation within the dura mater, the right femoral vein was exposed and ^{125}I -BSA ($50 \mu\text{Ci kg}^{-1}$) was injected as a bolus. After 5 min, drug or vehicle was injected into the left femoral vein. CGRP (10 nmol kg^{-1}) was administered 5 min after SP (0.1 or 1 nmol kg^{-1}) injection. In the experiments on guinea-pigs, capsaicin ($0.5 \mu\text{mol kg}^{-1}$) or 5-HT ($1 \mu\text{mol kg}^{-1}$) was administered via the jugular vein. Ten minutes later, animals were perfused via the left cardiac ventricle with 0.9% saline. The dura mater on the right side was dissected as described above. In some experiments, samples of conjunctiva, eyelid and lip were also collected. Samples were weighed and counted for radioactivity. Data are expressed as c.p.m. mg^{-1} wt and as % of extravasation between vehicle- and drug-treated animals.

GR43175 pretreatment

GR43175 ((3-[2-diethylamino]ethyl-N-methyl-1H-indole-5-methane sulphonamide, Glaxo, Ware, UK) 10 , 30 , 100 or $300 \mu\text{g kg}^{-1}$ (diluted in 0.9% saline) was injected via the left femoral vein (rat) 15 min before electrical stimulation of the right trigeminal ganglion or via the jugular vein 10 min before capsaicin (guinea-pigs). GR43175 (10 , 30 , 100 or $300 \mu\text{g kg}^{-1}$) was injected 10 min before capsaicin, SP, NKA, 5-HT or bradykinin. Control animals received the same volume of saline. The amount of ^{125}I -albumin within dura mater and other tissues was compared between GR43175- and saline-treated animals.

Intra-arterial blood pressure monitoring

Aortic blood pressures (mean) were obtained in separate groups of Sprague-Dawley rats (250 – 300 g) anaesthetized with pentobarbitone (60 mg kg^{-1} i.p.). A 22 gauge catheter was advanced to the aorta via the left femoral artery and connected to a blood pressure monitor (Winston Electronics Co, Millbrae, CA). Blood pressure was recorded continuously from 20 min before (baseline) to 20 min after i.v. capsaicin

($1 \mu\text{mol kg}^{-1}$), bradykinin (1 or $0.1 \mu\text{mol kg}^{-1}$), or SP (0.3 or 1 nmol kg^{-1}) administration in the presence and absence of GR43175 ($100 \mu\text{g kg}^{-1}$).

Drugs

The following drugs and chemicals were used: capsaicin (Polyscience Inc., Willmington, PA) ($0.5 \mu\text{mol kg}^{-1}$ or $1 \mu\text{mol kg}^{-1}$), SP (0.3 or 1 nmol kg^{-1}), NKA (1 nmol kg^{-1}), bradykinin (0.1 or $1 \mu\text{mol kg}^{-1}$), CGRP (10 nmol kg^{-1}) (Peninsula Lab, San Carlos, CA); 5-HT ($1 \mu\text{mol kg}^{-1}$) (Sigma Chemical Co., St. Louis, MO). The doses injected approximated the EC_{50} as determined in separate experiments. Capsaicin was diluted in saline:ethanol:Tween 80, 8:1:1, SP, 5-HT and CGRP in normal saline, and bradykinin and NKA in phosphate buffered saline, pH 7.4. Animals were injected with vehicle for each experiment and at each drug concentration to control for variability in albumin leakage noted in the perfused tissues from week-to-week. Drug or vehicle injections were performed alternately, and tissues processed accordingly. All drugs were administered intravenously.

Data analysis

Each group contained a minimum of 3–5 animals and each experiment was repeated at least twice. Student's *t* test was used for statistical analysis except for blood pressure data (ANOVA). Data are expressed as mean $\pm$ s.e.mean. $P < 0.05$ was considered significant.

Results

Trigeminal stimulation studies

Electrical trigeminal stimulation increased the leakage of ^{125}I -albumin within rat dura mater from 16 ± 1 to

Figure 1 GR43175 significantly reduced plasma protein extravasation (^{125}I -albumin) following electrical stimulation of the right trigeminal ganglion in the rat ipsilateral dura mater. Animals were injected (i.v.) with 30 (hatched column), 100 (cross-hatched column) or 300 (solid column) $\mu\text{g kg}^{-1}$ GR43175 15 min before electrical stimulation (1.2 mA, 5 ms, 5 Hz) and 5 min before ^{125}I -albumin ($50 \mu\text{Ci kg}^{-1}$). Five minutes after stimulation, animals were perfused with saline via the left cardiac ventricle (see Methods). When administered 15 min before electrical trigeminal stimulation, GR43175, 100 and 300 but not 30 $\mu\text{g kg}^{-1}$ decreased the ratio of c.p.m. mg^{-1} wt on the stimulated vs unstimulated sides as compared to vehicle-treated stimulated animals (open column). GR43175 did not change the c.p.m. mg^{-1} wt on the non-stimulated side (data not shown) ($n = 4$ – 15 in each group). *** $P < 0.005$, * $P < 0.05$. Vertical bars show s.e.mean.

28 ± 2 c.p.m. mg^{-1} wt on the side ipsilateral to the stimulation ($P < 0.001$). The ratio (stimulated/unstimulated sides) increased to 1.81 ± 0.10 (dura mater), 9.3 ± 1.1 (conjunctiva), 8.8 ± 1.2 (eyelid) and 7.2 ± 1.2 (lip). When administered i.v. at a dose of $100 \mu\text{g kg}^{-1}$, GR43175 decreased this ratio in dura mater from 1.81 ± 0.10 to 1.23 ± 0.10 ($P < 0.005$) (Figure 1), but did not change significantly the leakage in the conjunctiva, eyelid or lip (9.3 ± 1.1 – 8.8 ± 1.1 , 8.8 ± 1.2 – 10.8 ± 1.9 , and 7.2 ± 1.2 – 7.1 ± 1.2 , respectively). Similar results were obtained with $300 \mu\text{g kg}^{-1}$. A lower concentration ($30 \mu\text{g kg}^{-1}$) did not block the response in any of the tissues studied (Figure 1). GR43175 administration by itself (30, 100 or $300 \mu\text{g kg}^{-1}$) did not alter the content of ^{125}I -albumin within the dura mater of unstimulated animals. The drug did not increase radiolabelled albumin leakage on the side contralateral to the electrical trigeminal stimulation (data not shown).

Capsaicin stimulation studies

Capsaicin increased the leakage of iodinated albumin within rat dura mater (20 ± 1 c.p.m. mg^{-1} wt) as compared to vehicle-treated controls (11 ± 1 c.p.m. mg^{-1} wt) ($P < 0.05$). (Figure 2). Capsaicin-induced extravasation was also found in the dura mater of guinea-pigs (26 ± 2 c.p.m. mg^{-1} wt vs 16 ± 1 c.p.m. mg^{-1} wt of control group, $P < 0.05$). The administration of GR43175 $100 \mu\text{g kg}^{-1}$ i.v. decreased the capsaicin-induced radiolabelled albumin leakage in rat dura mater from 20 ± 1 c.p.m. mg^{-1} wt to 14 ± 2 c.p.m. mg^{-1} wt ($P < 0.05$). Thirty $\mu\text{g kg}^{-1}$ decreased the values in guinea-pig dura mater (26 ± 2 to 19 ± 1 c.p.m. mg^{-1} wt, $P < 0.05$), but did not block the response in the rat. GR43175 did not block extravasation in extracranial tissues at any of the above doses tested.

Sensory peptides

Substance P (1 nmol kg^{-1}) increased the amount of iodinated albumin within the dura mater from 12 ± 1 to

Figure 2 (a) GR43175 significantly reduced plasma protein extravasation (^{125}I -albumin) following capsaicin administration ($1 \mu\text{mol kg}^{-1}$, i.v., solid columns) in rat dura mater. One hundred (wide diagonally-hatched column) but not 30 (narrow diagonally-hatched column) $\mu\text{g kg}^{-1}$, i.v., were effective. Data are expressed as % of c.p.m. mg^{-1} wt of vehicle-treated animals (open columns). (b) GR43175, 30 (narrow diagonally-hatched column) but not 10 (cross-hatched column) $\mu\text{g kg}^{-1}$, i.v., significantly reduced ^{125}I -albumin extravasation following capsaicin administration ($0.5 \mu\text{mol kg}^{-1}$, i.v., solid columns) in guinea-pig dura mater as compared to vehicle-treated animals (open columns). Data are expressed as described above ($n = 3$ – 8 in each group). * $P < 0.05$, ** $P < 0.01$ as compared to vehicle-treated animals. † $P < 0.05$ as compared to capsaicin-injected animals.

Figure 3 GR43175 did not block plasma extravasation within dura mater induced by substance P administration. (a) One hundred $\mu\text{g kg}^{-1}$ GR43175 was administered ten minutes before substance P (SP), 1 nmol kg^{-1} . (b) GR43175 100 or (c) $300 \mu\text{g kg}^{-1}$ was administered 10 min before substance P, 0.3 nmol kg^{-1} . Open columns, vehicle-treated group; solid columns, SP treatment; hatched columns, SP + GR43175 treatment. Data are expressed as described in Figure 2 ($n = 5$ – 8 in each group). ** $P < 0.01$ as compared to vehicle-treated animals.

20 ± 2 c.p.m. mg^{-1} wt ($P < 0.01$) (Figure 3). Within the conjunctiva, eyelid and lip, values increased from 28 ± 4 to 71 ± 9 ($P < 0.05$), from 22 ± 4 to 46 ± 4 ($P < 0.05$) and from 28 ± 5 to 47 ± 3 c.p.m. mg^{-1} wt, respectively. When SP was given at a concentration of 0.3 nmol kg^{-1} , the c.p.m. mg^{-1} wt in dura mater increased from 8 ± 1 to 12 ± 1 ($P < 0.01$) (Figure 3). Lower concentrations of SP were not effective. GR43175 $100 \mu\text{g kg}^{-1}$ did not block SP-induced extravasation in dura mater or in the extracranial tissues at either of the above SP concentrations (Figure 3).

The administration of CGRP (10 nmol kg^{-1} i.v.) did not by itself increase the amount of iodinated albumin in dura mater (Markowitz *et al.*, 1987) nor did it further increase leakage when given 5 min after SP (0.3 or 1 nmol kg^{-1} ; $n = 3$ – 4 in each group) administration (18 ± 4 c.p.m. mg^{-1} wt to 18 ± 3 c.p.m. mg^{-1} wt).

Neurokinin A (1 nmol kg^{-1} ; $n = 5$) increased c.p.m. mg^{-1} wt in dura mater (21 ± 1 as compared to 16 ± 1 in vehicle-treated animals; $n = 4$, $P < 0.01$). This response was not modified by administration of GR43175 $100 \mu\text{g kg}^{-1}$ (23 ± 1 c.p.m. mg^{-1} ; $n = 5$).

Bradykinin

Bradykinin $0.1 \mu\text{mol kg}^{-1}$ or $1 \mu\text{mol kg}^{-1}$ increased radioactive albumin in rat dura mater (22 ± 2 vs 17 ± 1 c.p.m. mg^{-1} wt in vehicle-treated animals, $P < 0.05$) (Figure 4). The extravasation induced by $0.1 \mu\text{mol kg}^{-1}$ was significantly reduced by both 30 and $100 \mu\text{g kg}^{-1}$ GR43175 ($P < 0.05$) (Figure 4).

5-HT

A dose of $1 \mu\text{mol kg}^{-1}$ 5-HT but not lower, increased leakage of ^{125}I -albumin in guinea-pig dura mater (23 ± 1 ($n = 8$) versus 17 ± 1 c.p.m. mg^{-1} wt ($n = 6$) in vehicle-treated animals, $P < 0.01$). Extravasation was also noted in conjunctiva (22 ± 1 c.p.m. mg^{-1} as compared to 12 ± 1 c.p.m. mg^{-1} in vehicle-treated animals, $P < 0.05$). Lip and eyelid were not tested. The administration of GR43175 (100 or $300 \mu\text{g kg}^{-1}$; $n = 3$ in each group) did not block the response in either tissue. The same concentration of 5-HT did not increase the content of ^{125}I -albumin in dura mater or extracranial tissues in rats.

Figure 4 GR43175 blocked bradykinin-induced plasma extravasation within rat dura mater. GR43175 (hatched columns), 30 and 100 $\mu\text{g kg}^{-1}$, i.v., but not 10 $\mu\text{g kg}^{-1}$ administered 10 min before bradykinin (0.1 $\mu\text{mol kg}^{-1}$, solid columns), blocked ^{125}I -albumin leakage into the dura mater. Open columns represent vehicle-treated groups. Data are expressed as described in Figure 2 ($n = 4-10$ in each group). * $P < 0.05$, ** $P < 0.01$ as compared to vehicle-treated animals. † $P < 0.05$ as compared to bradykinin-treated animals.

Arterial blood pressure monitoring

Mean arterial blood pressure ranged from 120 to 97 mmHg (108 ± 2) in control animals ($n = 4$), and was not lowered by either bradykinin (0.1 or 1 $\mu\text{mol kg}^{-1}$; $n = 3$ in each group) or SP (0.3 or 1 nmol kg^{-1} ; $n = 3$ in each group) administration. Mean blood pressure decreased from 107 ± 7 mmHg to 89 ± 5 mmHg ($P < 0.05$) when capsaicin (1 $\mu\text{mol kg}^{-1}$) was administered intravenously ($n = 3$). GR43175 (100 $\mu\text{g kg}^{-1}$) did not alter the mean systemic arterial blood pressure and did not change the blood pressure response to injections of a drug that lowered blood pressure (capsaicin 1 $\mu\text{mol kg}^{-1}$; $n = 3$) or to those with no effects on blood pressure (substance P, 1 nmol kg^{-1} and bradykinin 0.1 or 1 $\mu\text{mol kg}^{-1}$; $n = 3$ in each group).

Discussion

Our findings indicate that the 5-HT₁-like receptor agonist, GR43175, blocks plasma extravasation selectively within dura mater of the rat and guinea-pig when administered before neurogenic stimulation of the trigeminovascular system (electrical or capsaicin stimulation). In the doses used, GR43175 did not increase systemic arterial blood pressure or modify the pressure responses to capsaicin, substance P or bradykinin administration, GR43175 did not promote extravasation within dura mater when given alone, or enhance the ability of 5-HT in this regard. Furthermore, GR43175 did not reduce the extravasation caused by systemic SP, or NKA administration, but did attenuate the leakage which followed bradykinin administration. Hence, the blockade by GR43175 appears specific to extravasation induced by neurogenic mechanisms.

Like the ergot alkaloids (Saito *et al.*, 1988), GR43175 blocked the extravasation within the dura mater and not within extracranial tissues. This apparent selectivity may suggest the presence of receptor populations on meningeal blood vessels which are not expressed on extracranial tissues. Alternatively, the lack of drug response at the doses tested may reflect the more marked leakage which was measured in the lip, conjunctiva and eyelid. Additional studies will be needed to clarify this point.

Among the peptides identified within the trigeminovascular system, SP and NKA are the most important mediators of

Table 1 Antimigraine drugs block neurogenic plasma extravasation in dura mater

Pretreatment	Inducing agent			
	ES	Capsaicin	SP/NKA	BK
GR43175	+	+	-/-	+
Ergots (Saito <i>et al.</i> , 1988)	+	+	-/-	-
Indomethacin (Buzzi <i>et al.</i> , 1989)	+	?	+/?	?
Aspirin (Buzzi <i>et al.</i> , 1989)	+	?	+/?	?

Ergots: ergotamine, dihydroergotamine, methysergide (chronic).

ES: electrical stimulation of the trigeminal ganglion.

SP: substance P; NKA: neurokinin A; BK: bradykinin.

+ blockade; - no effect; ? unknown.

neurogenic plasma extravasation within the dura mater. Although CGRP dilates cephalic blood vessels, it does not cause leakage in dura mater or extracranial tissues (Markowitz *et al.*, 1987). Furthermore, CGRP did not enhance the leakage induced by SP when tested over a range of doses. Since CGRP and SP are mild constrictors of pial venules but arteriolar vasodilators, the tachykinins must exhibit specific effects on endothelial leakage not shared by CGRP. In our model, leakage of albumin probably takes place in the fenestrated endothelium of post-capillary venules (Andres *et al.*, 1987).

Table 1 compares the actions of GR43175 with other drugs used in alleviating migraine headaches, the ergot alkaloids as well as aspirin and indomethacin. Like the ergot alkaloids (Saito *et al.*, 1988), aspirin and indomethacin (Buzzi *et al.*, 1989), the responses to GR43175 were selective for leakage within dura mater; extravasation in the conjunctiva, eyelid and lip were not blocked. The three ergot preparations (ergotamine tartrate, dihydroergotamine and methysergide given chronically), as well as aspirin and indomethacin, were effective against the responses to either trigeminal electrical stimulation or capsaicin administration. If the GR43175 response was mediated by vasoconstriction alone, then blockade of leakage caused by the intravenous injections of the tachykinins, SP and NKA (EC_{50} concentrations), or even 5-HT would have been anticipated. This was not observed. GR43175 blocked the leakage caused by systemic bradykinin administration, which may be related to the ability of bradykinin to depolarize unmyelinated C fibres (Armstrong *et al.*, 1953). As yet, there is no apparent explanation for why the ergot alkaloids did not decrease the response to bradykinin (unpublished data). Perhaps this is due to the alkaloid-induced mild systemic arterial hypertension and increased perfusion pressure. Based on the observed profile of activity, we suggest that GR43175 exhibits a peripheral blockade of small fibre (C- and A-delta) dependent neurogenic plasma extravasation within the dura mater. Neurogenic blockade has been observed in another tissue derived from neural crest—sympathetic nerves. GR43175 blocked sympathetically-mediated contractions in the dog isolated saphenous vein induced by electrical field stimulation, presumably by acting at prejunctional sympathetic 5-HT receptors (Humphrey *et al.*, 1988). Whether the proposed action on perivascular afferent neurones is mediated by a 5-HT₁-like receptor mechanism remains to be determined.

Since GR43175 and the ergot alkaloids are potent constrictors of cephalic blood vessels, an additional therapeutic action based on the postjunctional effects of these drugs on dural blood vessels cannot be ruled out at the present time. The mechanism by which such an action may decrease headache is unknown, since vasodilatation is apparently not responsible for the headache pain (see Olsen & Olesen, 1988). Vasoconstriction might increase the threshold for depolarizing perivascular afferent fibres (Moskowitz, 1986) or decompress oedematous pain-sensitive tissues in a small fixed, rigid com-

partment (Ekbohm *et al.*, 1988). Additional studies will be needed to clarify this point.

We suggest that the above findings may be relevant to the therapeutic action of GR43175 in migraine. GR43175 alleviates migraine headaches in several clinical trials when administered subcutaneously, i.v. or orally. Twenty-four $\mu\text{g kg}^{-1}$ i.v. was the most effective dose and the onset of action was within minutes (Doenicke *et al.*, 1988). Doses of 30–100 $\mu\text{g kg}^{-1}$ blocked neurogenic inflammation in our rodent model when the drug was administered 15 min before

electrical trigeminal stimulation or 10 min before chemical stimulation. A similarity between the blocking effects of GR43175 and the ergot alkaloids, as well as the anti-inflammatory drugs indomethacin and aspirin, also suggests the relevance to its therapeutic actions.

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