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The selective carotid arterial vasoconstrictor action of GR43175 in anaesthetized dogs

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1 GR43175 is a highly selective agonist at 5-HT_1-like receptors in the dog saphenous vein. This study describes the haemodynamic effects of GR43175 in barbitone-anaesthetized dogs.

2 GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v.) produced dose-dependent decreases in carotid arterial blood flow with little or no change in arterial blood pressure. The decrease in blood flow was associated with an increase in carotid arterial vascular resistance. In preliminary studies, the dose of GR43175 producing 50% of the maximum carotid vasoconstrictor response was $39 \pm 8\,\mu g\,kg^{-1}$, i.v.

3 In comparative regional haemodynamic studies, GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v.) had little effect on total peripheral resistance or resistance in the mesenteric, vertebral and coronary arterial vascular beds. Low doses of GR43175 decreased, whilst high doses (100 $\mu g\,kg^{-1}$, i.v. and above) increased femoral arterial vascular resistance. GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v.) had no effect on respiratory inflation pressure. In doses of 100 $\mu g\,kg^{-1}$ i.v. and above, GR43175 caused small decreases in heart rate.

4 The carotid arterial vasoconstrictor action of GR43175 was resistant to antagonism by the 5-HT_2 receptor, 5-HT_3 receptor and α-adrenoceptor blocking drugs, ketanserin, MDL72222 and phentolamine respectively, but could be antagonized by the non-selective 5-HT_1-like receptor blocking drug methiothepin. Methiothepin had no effect on the carotid vasoconstrictor action of the thromboxane A_2 mimetic, U46619.

5 The results demonstrate that GR43175 produces a selective vasoconstriction in the carotid arterial circulation of anaesthetized dogs via activation of 5-HT_1-like receptors, which appear similar to those mediating contraction of the dog isolated saphenous vein.

Introduction

GR43175, (3-[2-dimethylamino]ethyl-N-methyl-1H-indole 5 methane sulphonamide), is a highly selective agonist at 5-HT_1-like receptors mediating contraction of the dog isolated saphenous vein (Humphrey *et al.*, 1987; 1988) and isolated cerebral blood vessels from the dog and primate (Connor *et al.*, 1987). We have previously postulated that the 5-HT_1-like receptor mediating contraction of the dog isolated saphenous vein also mediates vasoconstriction of the carotid arterial circulation (see Apperley *et al.*, 1980; Feniuk *et al.*, 1985). Indeed, methysergide, which acts as a 'partial' agonist at 5-HT_1-like receptors in the dog isolated saphenous vein causes selective vasoconstriction in the carotid arterial circulation of anaesthetized dogs (Saxena, 1974; Apperley *et al.*, 1980). It has been suggested that this action of methysergide could explain its efficacy in the treatment of vascular migraine headache (Curran *et al.*, 1967; Saxena, 1974). However, methysergide is only used prophylactically (Lance, 1973) and, unlike GR43175, is not effective in the acute treatment of migraine (Doenicke *et al.*, 1988). Methysergide also has side effects which preclude its long term use clinically and which may result from the activation of a variety of receptor mechanisms including α-adrenoceptors and histamine receptors (see Curran *et al.*, 1967; Apperley *et al.*, 1976; Gunning *et al.*, 1988). GR43175 is devoid of agonistic activity at α-adrenoceptors and histamine receptors (Humphrey *et al.*, 1988).

In the present study we have investigated the haemodynamic actions of GR43175 in anaesthetized dogs and have compared the effects of a variety of 5-HT receptor blocking drugs on these actions, paying particular attention to the effect of GR43175 on the carotid arterial circulation.

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A preliminary account of these results has been presented to the British Pharmacological Society (Brittain *et al.*, 1987).

Methods

Preliminary studies

Beagle dogs (7–9 kg) of either sex were anaesthetized with barbitone (300 mg kg^{-1}, i.p.) following induction with thiopentone (25 mg kg^{-1}) and pentobarbitone (60 mg) administered intravenously (i.v.). All dogs were intubated with an endotracheal tube and artificially respired with room air using a Palmer ventilation pump at a rate of 20 strokes min^{-1} and a stroke volume of 13–16 ml kg^{-1} which was adjusted to maintain arterial pH, $Paco_2$, and Pao_2 within normal limits. Body temperature was maintained at 39–40°C. Arterial blood pressure was recorded from a cannulated femoral artery with a Bell and Howell pressure transducer (type 4-422-0001) and heart rate derived from the blood pressure signal. Blood flow in the right common carotid artery was recorded by use of a Statham electromagnetic flow probe (2.5 mm) and carotid vascular resistance was derived electronically from the mean arterial pressure and flow signals which were continuously displayed on a Devices M19 chart recorder. Vascular resistance was calculated by dividing mean arterial pressure by the mean carotid arterial flow. Respiratory inflation pressure was monitored from a side branch of the respiratory inflow circuit using a Pye Ether Pressure transducer. Cumulative doses of GR43175 (1–300 or 1000 $\mu g\,kg^{-1}$, i.v.) were administered by bolus injection at 15 min intervals.

Regional haemodynamic studies

In further studies, blood flow in the right common carotid, left femoral and superior mesenteric arteries was recorded. These animals were pretreated with saline 15 min before dosing with GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v., administered cumulatively).

In other experiments, a thoracotomy was performed and animals subjected to positive pressure ventilation (3–4 cmH_2O). Flow probes were placed around either the ascending aorta, the circumflex coronary or the vertebral artery. Aortic flow was assumed to represent cardiac output. Carotid arterial blood flow and vascular resistance was additionally monitored in all experiments as already described. Femoral, mesenteric, total peripheral, coronary or vertebral and carotid arterial vascular resistances were also calculated by dividing the mean aortic pressure by the mean respective blood flows.

Antagonist studies

In view of the long lasting carotid vasoconstrictor action of GR43175 (see below), the effect of antagonists was examined by comparing the actions of GR43175 in the carotid artery bed of saline pretreated dogs with those in dogs that had been pretreated with an antagonist.

Cumulative doses of GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v.) were administered 30 min after pretreatment with a single dose of antagonist or saline and responses measured at the peak change in carotid arterial vascular resistance. Changes in vascular resistance were determined from the basal value immediately prior to dosing with GR43175.

Specificity studies

In these studies, the right cranial thyroid artery was retrogradely cannulated and right common carotid arterial blood flow and vascular resistance calculated as already described. The thromboxane A_2-mimetic U46619 (0.01–3 $\mu g\,kg^{-1}$, i.a.) was administered by bolus retrograde injection into the common carotid artery and vasoconstrictor dose-response curves obtained before and after administration of methiothepin (1 mg kg^{-1}, i.v.). Dose-ratios were calculated from the linear portion of the U46619 dose-response curve.

Statistics

Unless otherwise stated all values shown are mean values ± s.e.mean from n observations.

Regional haemodynamics Vascular resistance before and after each dose of GR43175 was compared for statistical significance by a paired t test. Responses were considered to be significantly different when $P < 0.05$.

Effects of antagonists Carotid arterial vasoconstrictor responses (% increase in vascular resistance) to GR43175 in saline-treated animals and antagonist pretreated animals were compared by an unpaired t test. Responses were considered to be significantly different when $P < 0.05$.

Drugs used

GR43175 succinate, MDL72222 (1αH,3α,5αH-tropan-3yl-3,5 dichlorobenzoate) hydrochloride and U46619 (11, 9 epoxymethano-PGH_2) were synthesized within the Chemistry Department of Glaxo Group Research, Ware. The following compounds were purchased: phentolamine mesylate (Ciba);

methiothepin maleate (Roche). Ketanserin was a gift from Janssen pharmaceuticals.

All drugs with the exception of ketanserin and methiothepin were initially dissolved in distilled water and diluted with 0.9% w/v saline. Ketanserin was initially dissolved in 0.1 M tartaric acid and diluted with 0.9% w/v saline. Methiothepin was dissolved in 10% ethanol in distilled water.

The doses of all drugs refer to the free base.

Results

Preliminary studies of the cardiovascular and respiratory effects of GR43175

The intravenous administration of GR43175 (1–300 or 1000 $\mu g\,kg^{-1}$, i.v.) had little or no effect on arterial blood pressure or tracheal inflation pressure and produced only a small bradycardia at doses of 100 $\mu g\,kg^{-1}$ and above (Table 1). The most prominent effect produced by GR43175 was a selective, dose-dependent, long lasting decrease in carotid arterial blood flow. Since arterial blood pressure was not modified by GR43175, vascular resistance in the carotid arterial circulation increased in a dose-dependent manner. The dose of GR43175 producing 50% of its maximum response in the carotid circulation was $39 \pm 8\,\mu g\,kg^{-1}$ i.v. (values are mean ± s.e.mean from 6 dogs). An experimental recording illustrating these actions of GR43175 is shown in Figure 1. The duration of maximally effective doses of GR43175 in the carotid artery bed exceeded 2 h.

Regional haemodynamics

The effect of GR43175 on total peripheral resistance, vertebral or coronary artery vascular resistance was studied and compared with the effect of GR43175 in the carotid artery bed (Figure 2). GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v.) produced dose-dependent increases in carotid arterial vascular resistance with little or no change in either total peripheral resistance or resistance in the vertebral or coronary arterial vascular beds.

The effects of GR43175 in the femoral arterial circulation were variable. Low doses of GR43175 tended to cause vasodilatation as a consequence of a decrease in femoral vascular resistance, whilst higher doses (100 $\mu g\,kg^{-1}$, i.v. and above) caused vasoconstriction. In the mesenteric arterial bed, GR43175 (1–1000 $\mu g\,kg^{-1}$, i.v.) had no marked effect. The effects of GR43175 in the femoral and mesenteric circulations are compared with those in the carotid bed in the same experiments (Figure 3).

Effect of antagonists on the carotid arterial vasoconstrictor action of GR43175

In view of the long lasting carotid arterial vasoconstrictor action of GR43175, we have compared the carotid vasoconstrictor activity of GR43175 in saline

Table 1 Effect of GR43175 on carotid arterial vascular resistance, diastolic blood pressure, heart rate and tracheal inflation pressure in saline-pretreated anaesthetized dogs

Cumulative dose GR43175 ($\mu g\,kg^{-1}$, i.v.)		*% Δ carotid vascular resistance*	*Δ diastolic blood pressure* (mmHg)	*Δ heart rate* (beats min^{-1})	*Δ respiratory inflation pressure* (mmHg)
1	Peak	−1 ± 4	−7 ± 2	1 ± 2	0
	15 min	2 ± 1	2 ± 1	1 ± 2	0
3	Peak	10 ± 7	−8 ± 2	1 ± 3	0
	15 min	4 ± 3	1 ± 1	0 ± 3	0
10	Peak	23 ± 10	−11 ± 3	−2 ± 4	0
	15 min	17 ± 5	2 ± 1	−2 ± 3	0
30	Peak	67 ± 11	−9 ± 4	−8 ± 3	0
	15 min	43 ± 9	1 ± 2	−6 ± 3	0
100	Peak	127 ± 20	0 ± 6	−16 ± 3	0
	15 min	91 ± 14	5 ± 2	−11 ± 4	0
300	Peak	150 ± 21	3 ± 5	−21 ± 4	0
	15 min	127 ± 26	6 ± 3	−17 ± 5	0

Values are peak changes and changes 15 min after each dose of GR43175. Values stated are mean ± s.e.mean from 6 dogs. Basal values; carotid vascular resistance 0.86 ± 0.08 mmHg min ml^{-1} diastolic blood pressure 105 ± 5 mmHg, heart rate 170 ± 6 b min^{-1} and tracheal inflation pressure 5–10 mmHg (range). In 2 dogs (data not shown) the dose of GR43175 had to be increased to 1000 $\mu g\,kg^{-1}$ in order to produce the maximum carotid vasoconstrictor response. In these animals GR43175 (1000 $\mu g\,kg^{-1}$, i.v.) had no effect on respiratory inflation pressure.

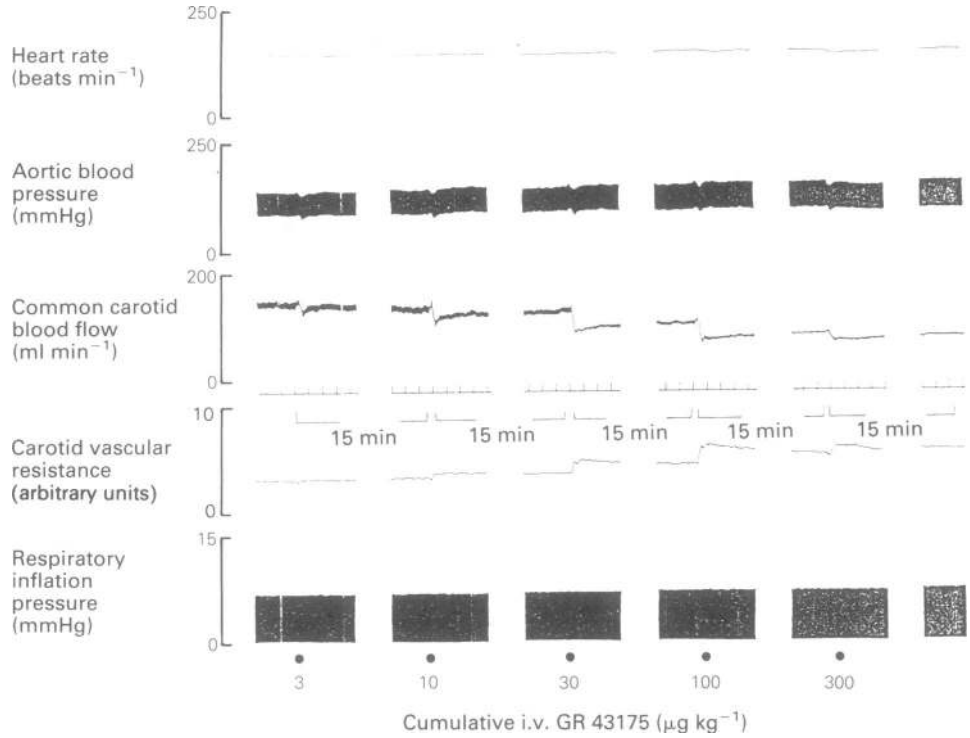

Figure 1 Experimental recording illustrating the effects of cumulatively administered GR43175 in the anaesthetized dog. Note selective vasoconstrictor action in the carotid arterial circulation with little effect on arterial blood pressure, heart rate and tracheal inflation pressure.

pretreated animals with that in animals pretreated with a receptor blocking drug.

Effect of ketanserin Pretreatment of dogs with ketanserin (0.1 mg kg^{-1}, i.v.) caused a small fall in diastolic blood pressure (113 ± 3 mmHg to 93 ± 4 mmHg) and carotid blood flow (149 ± 26 ml min^{-1} to 134 ± 25 ml min^{-1}), although carotid arterial vascular resistance was little changed by ketanserin (0.97 ± 0.17 before ketanserin and 0.92 ± 0.20 mmHg min ml^{-1} after). All values are mean ± s.e.mean from 3 dogs. Ketanserin pretreatment did not attenuate the carotid arterial vasoconstrictor activity of GR43175, indeed the vasoconstrictor action of GR43175 appeared enhanced following ketanserin pretreatment when compared with the saline pretreated dogs (Figure 4).

Effect of MDL72222 Pretreatment of dogs with MDL72222 (1 mg kg^{-1}, i.v.) had little effect on diastolic blood pressure (104 ± 8 mmHg before and 101 ± 8 mmHg after MDL72222) although a small reduction in carotid blood flow was seen (171 ± 16 ml min^{-1} to 159 ± 16 ml min^{-1}). Carotid arterial vascular resistance before and after treatment with MDL72222 was 0.74 ± 0.08 and 0.78 ± 0.10 mmHg min ml^{-1}, respectively. All values are mean ± s.e.mean from 3 dogs. Pretreatment with MDL72222 had no effect on the carotid arterial vasoconstrictor activity of GR43175 (Figure 4).

Effect of phentolamine Pretreatment of dogs with phentolamine (1 mg kg^{-1}, i.v.) reduced diastolic arterial blood pressure (98 ± 4 mmHg to 73 ± 8 mmHg), carotid arterial blood flow (131 ± 14 ml min^{-1} to 116 ± 14 ml min^{-1}) and carotid arterial vascular resistance (0.89 ± 0.08 to 0.76 ± 0.02 mmHg min ml^{-1}). All values are mean ± s.e.mean from 3 dogs. However, phentolamine had little effect on the carotid arterial vasoconstrictor action of GR43175 when compared with its effect in the saline pretreated dogs (Figure 4).

Effect of methiothepin Pretreatment of dogs with methiothepin (1 mg kg^{-1}, i.v.) reduced diastolic blood pressure (108 ± 9 mmHg to 67 ± 4 mmHg) and carotid arterial blood flow (82 ± 9 ml min^{-1} to 50 ± 3 ml min^{-1}), but had little effect on carotid

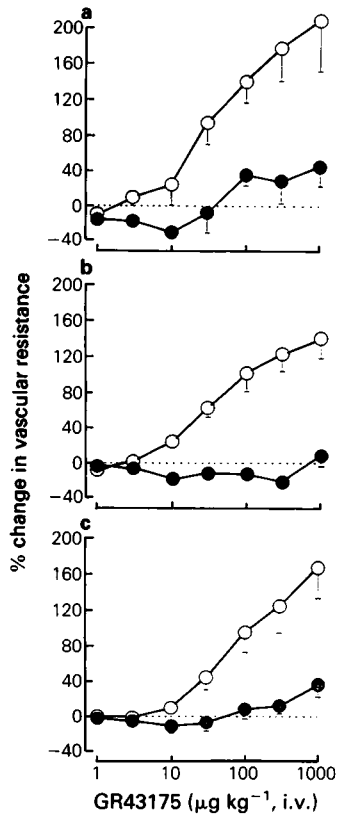

Figure 2 Comparison of the effect of GR43175 on carotid arterial vascular resistance (○) with its effect in other vascular beds (●) in anaesthetized beagle dogs. Values are mean (with s.e.mean shown by vertical bars) from 3 dogs. GR43175 was administered cumulatively and changes were measured from levels before dosing with GR43175. (a) Initial basal carotid (○) and vertebral artery blood (●) flows were 120 ± 14 and $11 \pm 3\,ml\,min^{-1}$ respectively. Initial carotid and vertebral arterial vascular resistances were 0.88 ± 0.06 and $10.81 \pm 2.30\,mmHg\ min\,ml^{-1}$ respectively. Vascular resistance was significantly increased in the carotid artery bed at doses above $30\,\mu g\,kg^{-1}$, i.v. ($P < 0.05$). The effects of GR43175 in the vertebral artery bed were not significant. (b) Initial basal carotid (○) and coronary artery blood (●) flows were 92 ± 10 and $17 \pm 1\,ml\,min^{-1}$ respectively. Initial carotid and coronary arterial vascular resistances were 1.23 ± 0.08 and $6.57 \pm 0.55\,mmHg\ min\,ml^{-1}$ respectively. Vascular resistance was significantly increased in the carotid artery bed at doses above $3\,\mu g\,kg^{-1}$, i.v. ($P < 0.05$). The effects of GR43175 in the coronary artery bed were not significant. (c) Initial basal carotid artery (○) and ascending aortic blood (●) flows were 99 ± 33 and $750 \pm 20\,ml\,min^{-1}$ respectively. Initial carotid and total peripheral arterial vascular resistances were 0.92 ± 0.22 and $0.11 \pm 0.01\,mmHg\ min\,ml^{-1}$ respectively. Vascular resistance was significantly increased in the carotid artery bed at doses above $30\,\mu g\,kg^{-1}$, i.v. ($P < 0.05$). The effects of GR43175 on total peripheral resistance were not significant.

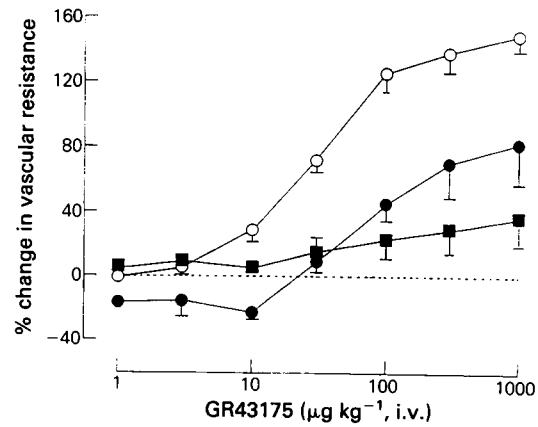

Figure 3 The effect of GR43175 on carotid (○), femoral (●) and mesenteric (■) arterial vascular resistance in anaesthetized beagle dogs. Values are mean (with s.e.mean shown by vertical bars) from 4 dogs. GR43175 was administered cumulatively and changes measured from levels before dosing with GR43175. Initial basal carotid, femoral and mesenteric arterial blood flows were 112 ± 28, 69 ± 4 and $144 \pm 2\,ml\,min^{-1}$, respectively. Initial carotid, femoral and mesenteric arterial vascular resistances were 1.14 ± 0.20, 1.65 ± 0.15 and $0.77 \pm 0.07\,mmHg\ min\,ml^{-1}$ respectively. Vascular resistance in the carotid artery bed was significantly increased at doses above $10\,\mu g\,kg^{-1}$, i.v. ($P < 0.05$). Vascular resistance in the femoral artery bed was significantly reduced at 1, 3 and $10\,\mu g\,kg^{-1}$, i.v. ($P < 0.05$) and increased at doses of $100\,\mu g\,kg^{-1}$, i.v. and above ($P < 0.05$). GR43175 had no significant effect on the mesenteric circulation.

arterial vascular resistance (1.56 ± 0.10 and $1.62 \pm 0.22\,mmHg\ min\,ml^{-1}$ before and after methiothepin treatment respectively). All values are mean ± s.e.mean from 3 dogs. Pretreatment with methiothepin caused a marked attenuation of the carotid arterial vasoconstrictor action of GR43175 when compared with the effect of GR43175 in the saline pretreated animals. This reduction in sensitivity to GR43175 in the carotid artery bed was seen both as an increase in the threshold dose of GR43175 required to cause constriction in the carotid artery bed as well as a reduction in the maximum response (Figure 4).

In three other dogs, the specificity of action of methiothepin was examined by determining its effect upon the carotid vasoconstrictor response to the local administration of the thromboxane A_2-mimetic U46619. Methiothepin ($1\,mg\,kg^{-1}$, i.v.) had no effect

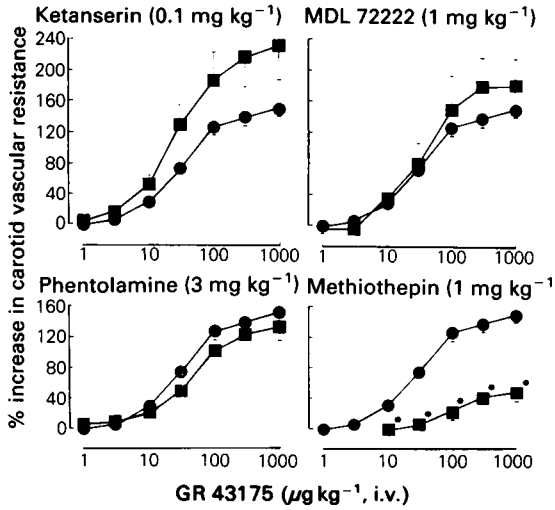

Figure 4 A comparison of the carotid arterial vasoconstrictor activity of intravenously administered GR43175 in saline pretreated anaesthetized dogs (●) and dogs pretreated with a variety of receptor blocking drugs (■). Note the marked attenuation of the carotid arterial vasoconstrictor activity of GR43175 in animals which had been pretreated with methiothepin (1 mg kg^{-1}, i.v.). Values are mean (with s.e.mean shown by vertical bars) from 3 dogs. * Vasoconstrictor responses significantly different from those in saline pretreated animals ($P < 0.05$).

on the carotid vasoconstrictor response to U46619, the U46619 dose-ratios in the presence of methiothepin being 0.70, 0.24 and 1.00.

Discussion

This study is the first detailed description of the haemodynamic actions of the selective 5-HT$_1$-like receptor agonist, GR43175 (Humphrey *et al.*, 1987), a compound which has been shown to be efficacious in the acute treatment of migraine (Doenicke *et al.*, 1988). The aims of the study were two fold. Firstly, to investigate the effect of GR43175 on a variety of different vascular beds and secondly, to characterize the receptor mechanisms involved in its carotid vasoconstrictor action in anaesthetized dogs.

The intravenous administration of GR43175 produced a dose-dependent increase in carotid arterial vascular resistance with little or no change in mesenteric, vertebral, coronary or total peripheral vascular resistance. Furthermore, GR43175 produced little or no change in blood pressure or tracheal inflation pressure. However, high doses of GR43175 (100 μg kg^{-1}, i.v. and above) did produce a small bradycardia which may be centrally mediated (Coote *et al.*, 1987). The most prominent effect of GR43175 was to produce a highly selective vasoconstriction within the carotid arterial circulation, an action which is shared by the antimigraine drugs, ergotamine and methysergide (Saxena, 1974; Saxena & de Vlaam-Schluter, 1974). However ergotamine, unlike GR43175, also causes marked increases in blood pressure, total peripheral, mesenteric, vertebral and coronary vascular resistance (Saxena & de Vlaam-Schluter, 1974). Indeed, the non-selective nature of the vasoconstrictor action of ergotamine probably accounts for many of the unwanted vascular effects associated with ergotamine therapy.

Although GR43175 produced a selective vasoconstriction in the carotid artery bed of anaesthetized dogs, its effects in the femoral circulation were more complex. Low doses of GR43175 tended to cause vasodilatation in the femoral circulation whilst higher doses caused vasoconstriction, which was less than that seen in the carotid artery bed. It seems likely that the overall haemodynamic response to GR43175 in the femoral circulation of the dog depends upon a balance between two opposing actions. We have previously shown that similar changes occur in the femoral circulation of dogs following methysergide administration (Feniuk *et al.*, 1981). Methysergide, like GR43175, is an agonist at 5-HT$_1$-like receptors in the dog isolated saphenous vein, albeit a partial agonist (Apperley *et al.*, 1980; Apperley & Humphrey, 1986; Humphrey *et al.*, 1988). We have shown that the vasomotor actions of methysergide in the femoral circulation are highly dependent upon the inherent degree of sympathetic tone (Feniuk *et al.*, 1981). Vasodilatation appears to be produced by an inhibition of sympathetic neurotransmission and vasoconstriction by a direct effect on the vasculature (Feniuk *et al.*, 1981), the same 5-HT$_1$-like receptor being involved in both actions and existing both pre- and post-junctionally as is the case in the dog isolated saphenous vein (Watts *et al.*, 1981). Furthermore, GR43175 is equiactive at both pre- and post-junctional 5-HT$_1$-like receptors in the dog isolated saphenous vein (Humphrey *et al.*, 1988). It therefore seems likely that the overall haemodynamic effect of GR43175 in the femoral circulation, like that of methysergide, is dependent upon the degree of sympathetic tone. Thus low doses may produce vasodilatation via an inhibition of sympathetic neurotransmission and high doses produce vasoconstriction via a direct effect on the vasculature. This suggests that in the dog at least, 5-HT$_1$-like receptors which mediate vasoconstriction exist not only in the carotid circulation but also in the femoral circulation. This is supported by the observation that 5-HT-induced vasoconstriction of the dog forelimb circulation is not modified by

5-HT_2 receptor blockade (Jandhyala & Kivlighn, 1987), thus by exclusion implicating 5-HT_1-like receptors. Interestingly canine foot pads, like the carotid circulation are known to contain arteriovenous anastomoses or shunt vessels (Delaney & Scarpino, 1973). It may be that 5-HT_1-like receptors, like those in the dog saphenous vein, are mainly localised to shunt vessels.

Saxena *et al.* (1983) have shown that in anaesthetized dogs approximately 40% of carotid arterial blood flow is shunted to the venous circulation by arteriovenous anastomoses. Interestingly, dilatation of arteriovenous shunts has been implicated in the pathogenesis of migraine headache (Heyck, 1969). It is tempting to speculate that the carotid vasoconstrictor action of GR43175 in anaesthetized dogs is due to a decrease in arteriovenous shunt flow. We have recently shown in anaesthetized cats that GR43175 has a marked vasoconstrictor action on arteriovenous shunts (Feniuk *et al.*, 1987) and we are currently examining this action in more detail.

The aim of the second part of this study was to characterize the receptors involved in the carotid arterial vasoconstrictor action of GR43175. We have previously shown that in the dog isolated saphenous vein, the contractile effect of GR43175 is resistant to antagonism by 5-HT_2 and 5-HT_3 receptor blocking drugs, such as ketanserin and MDL72222 but is specifically antagonized by methiothepin, suggesting the activation of 5-HT_1-like receptors (Humphrey *et al.*, 1988). Similar effects were seen in the present study *in vivo*. Neither ketanserin nor MDL72222 attenuated the carotid vasoconstrictor action of GR43175 thereby excluding an action involving 5-HT_2 and 5-HT_3 receptors. Indeed, following ketanserin pretreatment, the carotid vasoconstrictor action of GR43175 appeared enhanced. The mechanism of this enhancement is not known. Nevertheless, GR43175 is devoid of agonist effects in a range of isolated tissue preparations containing 5-HT_2 receptors, including the rabbit aorta, dog femoral artery and pig and dog coronary arteries (Humphrey *et al.*, 1988). An action of GR43175 on α-adrenoceptors can also be excluded since phentolamine had little or no effect on the carotid vasoconstrictor action of GR43175. In marked contrast, following pretreatment with methiothepin, the carotid arterial vasoconstrictor action of GR43175 was markedly attenuated, suggesting an action involving the stimulation of 5-HT_1-like receptors similar to those mediating contraction of the dog isolated saphenous vein (Apperley & Humphrey 1986). Although methiothepin itself had marked cardiovascular effects, its antagonism of the GR43175-induced carotid vasoconstrictor response was specific in nature since it had no effect on the carotid vasoconstrictor response produced by the thromboxane A_2 mimetic, U46619.

In summary, the results from the present study have clearly demonstrated the selective carotid vasoconstrictor action of GR43175, an effect which involves the activation of 5-HT_1-like receptors in the vasculature. Such an action of GR43175 could explain the mechanism by which GR43175 is useful in the treatment of acute migraine headaches (Doenicke *et al.*, 1988).

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