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A comparison of 5-hydroxytryptamine receptors mediating contraction in rabbit aorta and dog saphenous vein: evidence for different receptor types obtained by use of selective agonists and antagonists

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1 Using recently available selective agonists and antagonists we have examined further our postulate (Apperley *et al.*, 1980) that 5-hydroxytryptamine (5-HT) mediates contraction of dog saphenous vein via a different 5-HT receptor type from that in the rabbit aorta.

2 In the rabbit isolated aorta, ketanserin and spiperone were potent, specific, competitively-acting antagonists of the contractile effects of 5-HT.

3 In contrast, in the dog isolated saphenous vein neither ketanserin nor spiperone caused any rightward displacement of concentration-response curves to 5-HT although the maximum response was reduced by about 10%.

4 In the rabbit aorta 5-carboxamidotryptamine (5-$CONH_2$-T) was a weak agonist whilst the 5-N,N-dimethyl and 5-N-ethyl derivatives were even weaker or inactive. The contractile effect of 5-$CONH_2$-T in the rabbit aorta was potently and competitively antagonized by ketanserin.

5 In contrast, in the dog saphenous vein 5-$CONH_2$-T and its 5-N,N-dimethyl and 5-N-ethyl derivatives were all potent agonists. The contractile effect of 5-$CONH_2$-T was not markedly affected by ketanserin.

6 The profile of action of ketanserin and spiperone in the rabbit aorta is consistent with the view that 5-HT_2 receptors mediate contraction in this preparation. However, the 5-HT receptor mediating contraction in the dog saphenous vein appears to be '5-HT_1-like', sharing a number of characteristics with the 5-HT_1 recognition site identified from [^{3}H]-5-HT ligand binding studies in brain tissue. tissue.

Introduction

We have previously suggested that 5-hydroxytryptamine (5-HT) receptors mediating contraction of vascular smooth muscle are heterogeneous (Apperley *et al.*, 1980). This evidence is largely based upon differences in measures of antagonist potency of the highly specific 5-HT receptor blocking drug methysergide, in preparations such as the rabbit aorta where it is a potent competitive antagonist of 5-HT, (Apperley *et al.*, 1976) and the dog saphenous vein where it is weak and appears to behave as a partial agonist (Apperley *et al.*, 1977, Curro, *et al.*, 1978; Apperley *et al.*, 1980). Similar quantitative differences in the nature of the antagonism produced by other 5-HT antagonists in the two preparations are also evident (Apperley *et al.*, 1980; unpublished observations). Clearly further studies with more selective and specific drug tool, are necessary to determine whether our postulate is correct.

More recently, by means of radiolabelled ligand binding studies, it has been shown that [^{3}H]-ketanserin and [^{3}H]-spiperone have a high affinity for a subpopulation of 5-HT recognition sites within rat brain tissue to which the term '5-HT_2 receptor' has been ascribed (Leysen *et al.*, 1981; 1982). Functional studies with ketanserin and spiperone have shown that both of these drugs are potent competitive antagonists of the contractile effects of 5-HT in many isolated vascular preparations (e.g. see Van Nueten *et al.*, 1981; Cohen *et al.*, 1983; Maayani *et al.*, 1984).

In this study we have examined the effects of these newer antagonists on contractile responses to 5-HT in the dog isolated saphenous vein and rabbit isolated

aorta. In addition we have attempted to characterize these receptors further by comparing the potencies of a number of close analogues of 5-HT including some novel 5-carboxamidotryptamines in the two preparations. A preliminary account of some of these findings has previously been presented to the British Pharmacological Society (Feniuk, *et al.*, 1981; 1983).

Methods

Preparation of vascular strips

Spirally cut strips of rabbit isolated thoracic aorta and dog isolated saphenous veins were prepared as previously described (Apperley *et al.*, 1976; 1980). Four preparations were obtained from each vascular strip and each preparation placed in a modified Krebs solution (Apperley *et al.*, 1976). Isometric contractions were recorded by use of a Statham transducing cell from an original resting tension of 0.5g. All tissues were allowed to equilibrate for a period of at least one hour and were then 'primed' with a dose of potassium chloride to give a final bath concentration of 30 mM. Agonists were not administered for periods of at least 30 min following the dose of potassium chloride.

Determination of antagonist potency—pA_2 values

Antagonist potencies were determined by calculating pA_2 values as previously described (Apperley *et al.*, 1980). Antagonism was judged to be competitive and the pA_2 value assumed to correspond to the affinity constant when the antagonist caused parallel displacement to the right of the agonist concentration-effect curve with no reduction in the maximum response and when a Schild analysis gave a linear regression with a slope not significantly different from unity. The antagonist contact time was 30 min.

Determination of agonist potencies

In these experiments phentolamine, mepyramine and atropine (all at a concentration of 1 μM) were continually present in the Krebs solution in order to prevent any action that agonists may have at α-adrenoceptors, histamine and muscarinic receptors respectively. In addition the Krebs solution contained iproniazid (50 μM) in order to prevent selective metabolism of the test compounds by monoamine oxidase enzymes.

A cumulative concentration-effect curve to 5-HT was obtained in each of the four preparations from the same vessel and the 5-HT was then washed from the bath. Sixty minutes later a cumulative concentration-effect curve to a test agonist was determined in three of the preparations whilst 5-HT was again added to the fourth preparation. The fourth preparation thus acted as a control to monitor any spontaneous change in sensitivity to 5-HT. Relative potencies were determined by dividing the EC_{50} for the test compound by the EC_{50} for 5-HT, where the EC_{50} is the molar concentration of each compound to produce 50% of its maximum effect. This value was then corrected for spontaneous change in sensitivity to 5-HT by dividing it by the ratio of the EC_{50} values for 5-HT in the control strip. This ratio varied by less than two fold during the experiment. The maximum response of each test compound was compared with the maximum response produced by 5-HT in the same preparation.

Statistics

Unless stated otherwise values given are the arithmetic mean ± s.e.mean or 95% confidence limits in parentheses.

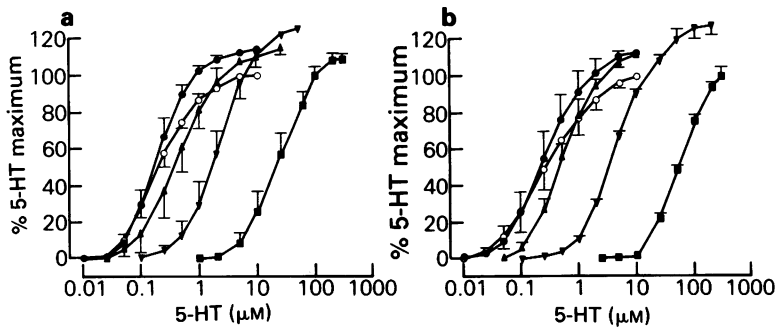


Figure 1 Rabbit isolated aorta: Effect of (a) ketanserin and (b) spiperone on contractile responses to 5-hydroxytryptamine (5-HT). In control preparations first (○) and second (●) concentration-effect curves to 5-HT were obtained in the absence of antagonist. In test preparations (second concentration-effect curves) the ketanserin and spiperone concentrations examined were 3 nM (▲), 30 nM (▼) and 300 nM (■). Ordinate scale represents the response as a percentage of the maximum response obtained to 5-HT in the first concentration-effect curve. Each value is the mean from 4 and 5 experiments for ketanserin and spiperone respectively; vertical lines show s.e.mean.

Drugs used

Atropine sulphate (Sigma), 5-hydroxytryptamine creatinine sulphate (Sigma), iproniazid phosphate (Roche), ketanserin (Janssen), mepyramine maleate (May & Baker), (±)-methoxamine hydrochloride (Wellcome), phentolamine mesylate (Ciba), spiperone (Janssen) and N-methyl-5-hydroxytryptamine oxalate (Aldrich) were used.

α-Methyl-5-hydroxytryptamine (α-Me-5-HT), 5-carboxamidotryptamine (5-$CONH_2$-T), 5-N,N-dimethyl carboxamidotryptamine (5-$CONMe_2$-T), 5-N-ethyl-carboxamidotryptamine (5-CONHEt-T) were synthesized by Dr C.F. Webb and Dr I. Coates, Chemistry Research Department, Glaxo Group Research Ltd., Ware.

Ketanserin and spiperone were initially dissolved in 0.1 M tartaric acid and diluted with 0.9% w/v sodium chloride (saline). The remaining compounds were dissolved in distilled water and diluted with saline.

Results

Effect of antagonists on the contractile responses to 5-hydroxytryptamine

Rabbit isolated aorta 5-HT produced concentration-dependent contractile responses in the rabbit isolated aorta. Both ketanserin and spiperone produced a parallel displacement to the right of the 5-HT concentration-effect curve with no apparent suppression of the maximum response (Figure 1). Analysis of the antagonistic action of ketanserin and spiperone according to the method of Arunlakshana & Schild (1959) showed that both compounds were equieffective and the antagonism appeared competitive in nature (Table 1). Both ketanserin and spiperone were also competitive antagonists at α-adrenoceptors in the rabbit isolated aorta since they competitively antagonized contractions induced by methoxamine. However, both ketanserin and spiperone were about ten times weaker as antagonists at α-adrenoceptors than at 5-HT receptors in the rabbit aorta (Table 1).

Table 1 Antagonistic potencies of ketanserin and spiperone against 5-hydroxytryptamine (5-HT)- and methoxamine-induced contractions of rabbit isolated aorta

		5-HT	*Methoxamine*
Ketanserin	pA_2	8.67 (8.38–8.95)	7.80 (7.32–8.27)
	slope	0.94 (0.84–1.03)	1.05 (0.64–1.46)
Spiperone	pA_2	8.64 (8.34–8.95)	7.76 (7.34–8.18)
	slope	1.15 (1.01–1.28)	1.14 (0.81–1.46)

pA_2 values calculated according to the method of Arunlakshana & Schild (1959). Values are mean (95% confidence limits) from at least 4 experiments.

Dog isolated saphenous vein In marked contrast to the potent antagonistic action of ketanserin and spiperone at 5-HT receptors in the rabbit aorta, neither compound in concentrations as high as 1 μM caused any displacement to the right of the concentration-effect curve to 5-HT in the dog saphenous vein. The maximum response to 5-HT was slightly reduced, but the reduction was no more than about 10% of the 5-HT maximum (Figure 2). Both ketanserin and spiperone at a concentration of 1 μM antagonized the contractile effect of the α-adrenoceptor agonist, methoxamine. The methoxamine concentration ratios were 154 ± 34 and 81 ± 27 respectively (mean ± s.e.mean) from 4 experiments.

Agonist studies

The structures of the agonists used in the present study are shown in Table 2 together with the abbreviations of the trivial names used in the text.

Rabbit aorta In the rabbit isolated aorta, 5-HT produced concentration-dependent contractions. The maximum response produced by 5-HT in the control preparations was 2.6 ± 0.2 g (mean ± s.e.mean, $n = 20$) with a geometric mean EC_{50} of 0.45 μM (95% confidence limits, 0.20–0.97 μM). The concentration-effect curve to 5-HT was highly reproducible, there being less than a two fold change in agonist sensitivity between the first and second curves. The second 5-HT maximum response was 97 ± 4% of the first. The agonist potency of 5-HT, α-Me-5-HT and N-Me-5-HT was similar, although the maximum response to N-Me-5-HT was only 71% of the 5-HT maximum (Table 3). In contrast, 5-$CONH_2$-T and its 5-N,N-dimethyl and 5-N-ethyl derivatives were all much weaker agonists than 5-HT, indeed the ethyl derivative was devoid of agonist activity in concentrations up to 300 μM (Table 3).

5-Carboxamidotryptamine produced a lower maximum response than 5-HT and its absolute potency was quite variable. Nevertheless the contractile effect of 5-$CONH_2$-T was competitively antagonized by ketanserin (10 nM–1 μM). Analysis of the antagonistic action of ketanserin according to the method of Arunlakshana & Schild (1959) yielded a pA_2 value of 8.17 (7.83–8.50), mean (95% confidence limits) and slope of 0.97 (0.54–1.41), mean (95% confidence limits) from 4 experiments.

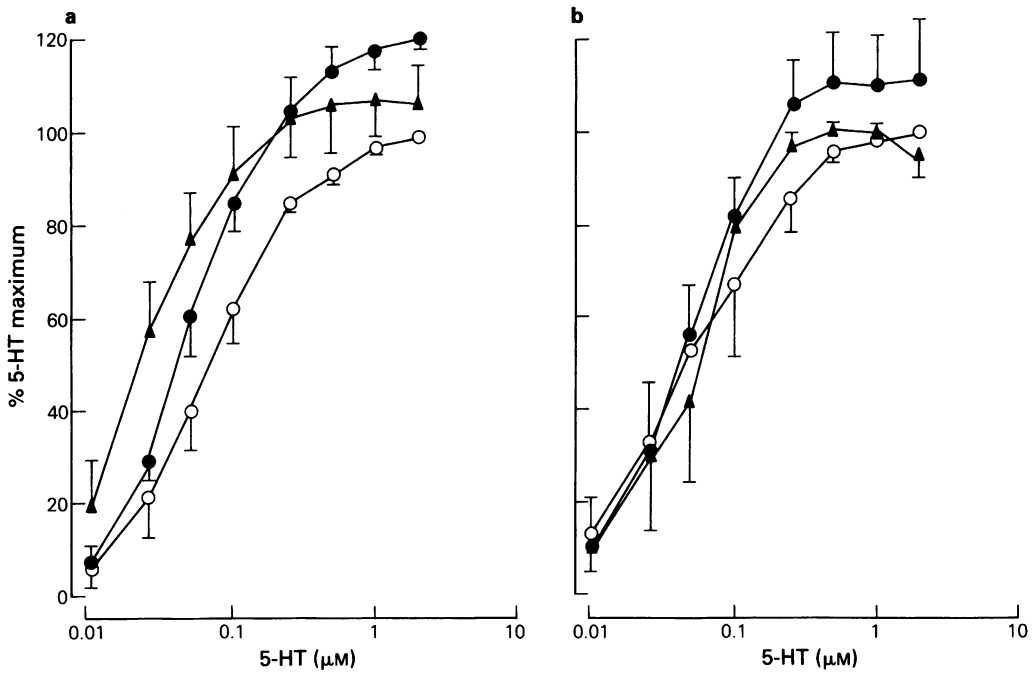
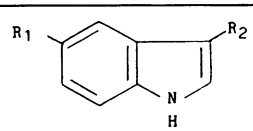


Figure 2 Dog isolated saphenous vein: effect of (a) ketanserin and (b) spiperone on contractile responses to 5-hydroxytryptamine (5-HT). In control preparations first (○) and second (●) concentration-effect curves to 5-HT were obtained in the absence of antagonist. In test preparations second concentration-effect curves to 5-HT were obtained in the presence of 1 μM ketanserin or spiperone (▲). Ordinate scale represents the response to 5-HT as a percentage of the maximum response obtained to 5-HT in the first concentration-effect curve. Each value is the mean from 4 experiments; vertical lines show s.e.mean.

Neither the 5-N,N-dimethyl nor 5-N-ethyl derivatives of 5-$CONH_2$-T antagonized the contractile effect of 5-HT in the rabbit aorta in concentrations up to 10 μM.

Dog saphenous vein In the dog saphenous vein, 5-HT produced concentration-dependent contractions. The maximum response to 5-HT in the control preparation was 1.6 ± 0.2g (mean ± s.e.mean, $n = 27$) with an EC_{50} value of 0.14 (0.09–0.22) μM (geometric mean, 95% confidence limits). The concentration-effect curves to 5-HT were highly reproducible, there being less than a two fold change in agonist sensitivity between the first and second curves. The second 5-HT maximum response was 108 ± 6% of the first. The agonist potency of N-CH_3-5-HT was similar to that of 5-HT whilst α-Me-5-HT was much weaker than 5-HT compared with its potency on the rabbit aorta (see Table 4). The greatest differences in agonist potencies between the rabbit aorta and dog saphenous vein were found with 5-$CONH_2$-T, 5-$CONMe_2$-T and 5CONHEt-T. All three compounds were highly potent agonists in the dog saphenous vein, although all three compounds produced lower maximum responses than

Table 2 Chemical structures and trivial names of agonists used in the present study



R_1	R_2	*Trivial name*	*Abbreviation*
HO-	$-CH_2CH_2NH_2$	5-Hydroxytryptamine	5-HT
HO-	$-CH_2CH(CH_3)NH_2$	α-Methyl 5-hydroxytryptamine	α-Me-5-HT
HO-	$-CH_2CH_2NHCH_3$	N-methyl 5-hydroxytryptamine	N-Me-5-HT
H_2NCO-	$-CH_2CH_2NH_2$	5-Carboxamidotryptamine	5-$CONH_2$-T
$(CH_3)_2NCO$-	$-CH_2CH_2NH_2$	5-N,N-dimethyl-carboxamidotryptamine	5-$CONMe_2$-T
C_2H_5HNCO-	$-CH_2CH_2NH_2$	5-N-ethyl-carboxamidotryptamine	5-CONHEt-T

Table 3 Agonist potencies of some structural analogues of 5-hydroxytryptamine (5-HT) for contraction of rabbit isolated aorta

	Maximum response (g)	*% 5-HT maximum*	EC_{50} (μM)	$\frac{EC_{50}\ test}{EC_{50}\ 5\text{-HT}}$	n
α-Me-5-HT	2.7 ± 0.2	99 ± 3	0.86 (0.39–1.89)	2.1 (1.1–4.1)	4
N-Me-5-HT	2.1 ± 0.2	71 ± 6	0.83 (0.34–2.03)	2.2 (1.1–4.7)	4
5-$CONH_2$-T	1.3 ± 0.4	57 ± 10	14.9 (2.6–85)	25.6 (13.5–48.5)	4
5-$CONMe_2$-T	0.6 ± 0.3	23 ± 10	89.5 (24–331)	130 (86–197)	4
5-CONHEt-T	0	0	0	> 350	4

Values are mean ± s.e.mean or geometric mean (95% confidence limits) from *n* observations. Experiments were performed in the presence of atropine (1 μM), mepyramine (1 μM), phentolamine (1 μM) and iproniazid (50 μM). For abbreviations, see Table 2.

Table 4 Agonist potencies of some structural analogues of 5-hydroxytryptamine (5-HT) for contracting dog isolated saphenous vein

	Maximum response (g)	*% 5-HT maximum*	EC_{50} (μM)	$\frac{EC_{50}\ test}{EC_{50}\ 5\text{-HT}}$	n
α-Me-5-HT	2.6 ± 0.5	120 ± 14	2.2 (0.7–7.0)	13 (5–32)	4
N-Me-5-HT	1.6 ± 0.2	82 ± 16	0.24 (0.06–0.96)	0.8 (0.7–0.90)	5
5-$CONH_2$-T	1.4 ± 0.3	75 ± 7	0.05 (0.02–0.12)	0.4 (0.1–0.9)	6
5-$CONMe_2$-T	1.3 ± 0.2	70 ± 8	0.31 (0.19–0.51)	2.1 (1.1–4.0)	6
5-CONHEt-T	0.7 ± 0.2	44 ± 9	0.10 (0.05–0.18)	1.1 (0.5–2.2)	6

Values are mean M ± s.e.mean or geometric mean (95% confidence limits) from *n* observations. Experiments were performed in the presence of atropine (1 μM), mepyramine (1 μM), phentolamine (1 μM) and iproniazid (50 μM). For abbreviations, see Table 2.

5-HT (Table 4). The contractile effect of 5-$CONH_2$-T in the dog saphenous vein was not modified by ketanserin (1 μM), the 5-$CONH_2$-T concentration-ratio being 1.9 ± 0.8 (values are mean ± s.e.mean from 5 experiments).

Discussion

General

The aim of the present study has been to characterize further the 5-HT receptors that mediate contractile responses to 5-HT in the rabbit isolated aorta and dog isolated saphenous vein. In doing so we have compared the antagonistic potencies of two 5-HT_2 receptor blocking agents, ketanserin (Van Nueten *et al.*, 1981) and spiperone (Cohen *et al.*, 1983), as well as the agonistic potencies of a series of close structural analogues of 5-HT including some novel 5-carboxamidotryptamines (Feniuk *et al.*, 1981).

Both ketanserin (pA_2 8.7) and spiperone (pA_2 8.6) were highly potent competitively acting antagonists of the contractile effect of 5-HT in the rabbit aorta, confirming the marked 5-HT receptor blocking actions of these compounds (e.g. Van Nueten *et al.*, 1981; Cohen *et al.*, 1983; Maayani *et al.*, 1984). Ketanserin and spiperone were also potent competitively acting antagonists at α-adrenoceptors but were about ten times weaker in this respect than in their ability to block 5-HT receptors. In marked contrast, neither ketanserin nor spiperone in concentrations as high as 1 μM, caused any rightward displacement of concentration-effect curves to 5-HT in the dog saphenous vein, although the maximum response was reduced by about 10%. These results provide yet more evidence to

suggest that the 5-HT receptors mediating contraction in the rabbit aorta and dog saphenous vein differ.

The fact that both ketanserin and spiperone are potent α-adrenoceptor blocking agents in the dog saphenous vein rules out an action of 5-HT on α-adrenoceptors confirming our conclusion from a previous study using phentolamine (Apperley *et al.*, 1980). One can only speculate on the mechanism by which the maximum response to 5-HT is slightly reduced by these antagonists in the dog saphenous vein, but it is possible that high concentrations of 5-HT stimulate a small proportion of receptors similar to those in the rabbit aorta. Qualitatively similar findings have previously been described by Van Nueten *et al.*, (1981). In their study, 10 nM Ketanserin caused no significant inhibition of 5-HT- induced contractions in the dog saphenous vein and concentrations as high as 10 μM caused a 50% reduction in the maximum response and only a small rightward shift of the 5-HT concentration-effect curve. The differences in this study and our own may merely reflect the presence of a variable proportion of 5-HT receptors like those occurring in the rabbit aorta.

The results of experiments with the close structural analogues of 5-HT were also consistent with the view that the 5-HT receptors mediating contraction in the rabbit isolated aorta and dog isolated saphenous vein differ. Some of the agonists (e.g. N-Me-5-HT) were non-selective, whilst α-Me-5-HT showed marginal selectivity for those 5-HT receptors mediating contraction in the rabbit aorta. The most interesting results were obtained with 5-$CONH_2$-T and its 5-N-ethyl- and 5-N,N-dimethyl-derivatives. All of these compounds were potent agonists in the dog saphenous vein whereas they were much weaker or even inactive as agonists in the rabbit aorta. It could be argued that such differences in agonist potencies in the two preparations merely reflect differences in receptor concentration or stimulus-response coupling processes. Certainly such factors have explained differences in the agonist potency of prenalterol in β-adrenoceptor containing tissues (Kenakin & Beek, 1980) and oxymetazoline in α-adrenoceptor containing tissues (Kenakin, 1984). However, neither the 5-N-ethyl- nor the 5-N,N-dimethyl-derivatives of 5 carboxamidotryptamine, which were virtually devoid of agonistic activity in the rabbit aorta, showed any antagonistic activity against 5-HT (unpublished observations), demonstrating a lack of both affinity and efficacy for the 5-HT receptor in this preparation. In contrast, the parent compound, 5-$CONH_2$-T, did appear to have activity at the 5-HT_2 receptor since its contractile action in the aorta could be competitively antagonized by ketanserin (mean pA_2 8.2 and slope 0.97) (unpublished observation), though why this pA_2 value is slightly less than that obtained with 5-HT as the agonist (mean pA_2 8.7 and slope 0.94) is not clear (Feniuk *et al.*, 1983). An action at α-adrenoceptors seems unlikely since the presence or absence of phentolamine does not appear to influence the potency of 5-$CONH_2$-T (results not shown). Whether or not this small difference in pA_2 can be accounted for by the fact that 5-$CONH_2$-T has the ability to stimulate other 5-HT receptor types remains to be determined (Feniuk *et al.*, 1984; Humphrey, 1984). However, in the rat tail artery which appears to contain a 5-HT_2 receptor like that in the rabbit aorta, 5-$CONH_2$-T produced a similar maximum response to 5-HT and was approximately twenty times weaker, (compare data in Table 2). Furthermore ketanserin antagonized the actions of 5-HT and 5-$CONH_2$-T to the same extent with pA_2 values of 9.1 and 9.2 respectively (Bradley *et al.*, 1985; Williams, unpublished observations).

Nomenclature of 5-hydroxytryptamine receptors

Characterization of 5-HT receptors in isolated smooth muscle preparations is associated with a variety of problems and is dependent upon not only the identification of both specific and selective agonists and antagonists but also upon the identification of isolated tissue preparations containing a homogeneous population of 5-HT receptors (Humphrey, 1983; 1984; Feniuk, 1984). Bearing these problems in mind, can one classify the 5-HT receptors mediating contraction in the rabbit aorta and dog saphenous vein, which on the above evidence appear to differ? The 5-HT receptor mediating contraction in the rabbit aorta would seem to be a 5-HT_2 receptor since ketanserin and spiperone were highly potent and competitive antagonists. Furthermore a comparison of the affinity constants of a wide variety of structurally dissimilar 5-HT antagonists in the rabbit aorta show a remarkable similarity to their affinities at 5-HT_2 recognition sites in ligand binding studies (Humphrey *et al.*, 1982). Although we (Apperley *et al.*, 1980; Humphrey *et al.*, 1982; Bradley *et al.*, 1983) and others (Maayami *et al.*, 1984; Peroutka, 1984) have used the term 'vascular D' receptor to describe the 5-HT receptor in the rabbit aorta and other vascular tissue, this terminology may be inappropriate (see Humphrey, 1984), since ketanserin has been claimed not to block ileal 5-HT 'D' receptors first described by Gaddum & Picarelli in 1957 (Van Nueten *et al.*, 1983). However, more detailed recent studies suggest that even in intestinal smooth muscle the 5-HT_2 and D-receptor may be the same (Engel *et al.*, 1984; 1985).

In the dog saphenous vein the 5-HT receptor mediating contraction clearly cannot be characterized as a 5-HT_2 receptor since ketanserin and spiperone were ineffective as antagonists. Peroutka (1984) has argued that the 5-HT receptors mediating contraction in certain blood vessels may be similar to 5-HT_1

recognition sites identified from ligand binding studies in brain tissue. Indeed the characteristics of the 5-HT receptor mediating contraction in the dog saphenous vein bear many similarities to the characteristics of such a binding site and may be considered to be '5-HT_1-like'. Firstly, ketanserin appears to have an extremely low affinity for 5-HT_1 recognition sites (Leysen *et al.*, 1981) and, as already mentioned, was ineffective as an antagonist at 5-HT receptors in the dog saphenous vein. Secondly, methysergide has a high affinity at 5-HT_2 receptors and a lower affinity at 5-HT_1 recognition sites (Leysen *et al.*, 1981) and we have previously demonstrated that methysergide is a much weaker 5-HT antagonist in the dog saphenous vein than in the rabbit aorta (Apperley *et al.*, 1980). Finally, the data obtained with 5-$CONH_2$-T is also consistent with the possibility that this receptor is similar to the 5-HT_1 recognition site. Engel and colleagues (1983) have demonstrated that 5-$CONH_2$-T has a high affinity for 5-HT_1 recognition sites and confirmed our observation that it is of similar potency to 5-HT in causing contraction of the dog saphenous vein (Feniuk *et al.*, 1981; present study). However, the 5-HT_1 binding site is not homogeneous and reflects the presence of at least two binding sites (Pedigo *et al.*, 1981). Since spiperone had a high affinity for the 5-HT_{1A} binding site and a low affinity for the 5-HT_{1B} binding site, the lack of antagonistic activity of spiperone on 5-HT-induced contractions in the dog saphenous vein may suggest the presence of 5-HT_{1B} sites in this preparation. Indeed, 8-OHDPAT, (8-hydroxy-2-(di-n-propylamino)tetralin), a selective ligand for the 5-HT_{1A} binding site (Middlemiss & Fozard, 1983), is inactive as an agonist or antagonist at the 5-HT-receptor in the dog saphenous vein at 1 μM (unpublished observations). However, this finding could be fortuitous since it must be realised that agonists are of little value as tools to correlate binding sites with functional receptors because of the 'efficacy factor' in studies on the latter. Thus tryptamine agonists, including 5-HT, have very low affinity for the 5-HT_2 site and, on the basis of binding data alone, appear 5-HT_1-selective (see data in Martin & Sanders-Bush, 1982).

Definitive characterization of the 5-HT receptor mediating contraction in the dog saphenous and its correlation with ligand binding sites must await the identification of a specific and selective receptor blocking drug at this site. It should then be possible to determine the nature and importance of the 5-HT receptor in the dog saphenous vein and whether it occurs in the brain. Until then it may perhaps be prudent to describe the 5-HT receptor in the dog saphenous vein as being '5-HT_1-like'.

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