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Tryptamine-induced vasoconstrictor responses in rat caudal arteries are mediated predominantly via 5-hydroxytryptamine receptors

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1 It has been suggested that tryptamine can stimulate specific receptors distinct from those for 5-hydroxytryptamine (5-HT). We have examined this possibility in the rat isolated caudal artery, paying particular attention to the involvement of monoamine oxidase metabolism and α-adrenoceptors, two factors that can complicate the quantification of antagonist potencies at 5-HT receptors.

2 5-HT and tryptamine were agonists over the concentration-ranges 3.0×10^{-8}–3.0×10^{-5} mol l^{-1} and 1.0×10^{-6}–3.0×10^{-4} mol l^{-1} respectively. The sensitivity of the caudal artery to tryptamine was increased by about 44 fold in the presence of iproniazid (5.0×10^{-5} mol l^{-1}) and about 17 fold in the presence of pargyline (1.0×10^{-5} mol l^{-1}), while responses to 5-HT and methoxamine were unaffected.

3 In the absence of iproniazid, ketanserin and methysergide were potent antagonists of responses to 5-HT with pA_2 values of 9.08 and 9.11 and slopes of the Schild regressions of 1.15 and 1.00 respectively. However, against tryptamine the antagonists were weaker such that pA_2 values were similar to those against 5-HT but the slopes of the Schild regressions were 0.47 and 0.47.

4 In the presence of iproniazid (or pargyline), the 5-HT antagonists were more potent against tryptamine such that the pA_2 values and the slopes of the Schild regressions were not significantly different from those against 5-HT. Phentolamine was a weak antagonist of responses to both 5-HT and tryptamine in the presence of iproniazid.

5 The findings in this study suggest that the contractile action of tryptamine in rat caudal artery is mediated predominantly by the same receptor as 5-HT and that the differential inactivation of tryptamine by monoamine oxidase enzymes largely accounts for the different susceptibilities of 5-HT and tryptamine to the antagonists examined.

Introduction

A number of workers have suggested that tryptamine can stimulate specific receptors distinct from those for 5-hydroxytryptamine (5-HT) both in the central nervous system (e.g. Dooley & Quock, 1976; Cox *et al.*, 1981) and on peripheral smooth muscle (Feniuk *et al.*, 1982). These claims were based on observed differences in the potencies of antagonists in inhibiting responses to the two agonists. However, in the isolated stomach fundus of the rat, the differential accessibility of tryptamine and 5-HT to intracellular monoamine oxidase (MAO) enzymes seems to account for the observed differences in antagonist potency (Handschumacher & Vane, 1967), while in the isolated aorta of the rabbit an α-adrenoceptor-mediated component present in the response to tryptamine, but not in that to 5-HT, may also be involved (Stollak & Furchgott, 1983).

Recently, it was proposed that tryptamine and 5-HT could act on different receptors to cause vasoconstriction in the perfused caudal artery of the rat (Hicks & Langer, 1983). We have investigated this situation further and have determined the effect of MAO inhibition on the potencies of antagonists in inhibiting responses to tryptamine and 5-HT. We have also examined the extent of α-adrenoceptor stimulation in the response to tryptamine. A preliminary account of these results has been presented to the British Pharmacological Society (Bradley *et al.*, 1984).

Methods

Preparation of vascular segments

Distal portions of middle caudal artery were removed from reserpine-treated male Wistar rats (220–350 g) anaesthetized with sodium pentobarbitone (90 mg kg^{-1} i.p.). After clearing extraneous tissue, four cylindrical segments, each about 5 mm long, were prepared from each artery and suspended between two L-shaped stainless steel wire supports (0.1 mm diameter) inserted into the lumen for the recording of contractile activity by a method similar to that described by Edvinsson *et al.* (1974). Each preparation was placed in a separate 10 ml organ bath containing modified Krebs-Henseleit solution at 37°C (Apperley *et al.*, 1976) which in some experiments contained iproniazid (5.0×10^{-5} mol l^{-1}) or pargyline (1.0×10^{-5} mol l^{-1}). Preparations were maintained at an applied tension of 500 mg and isometric changes in tension recorded with a Statham Microscale Accessory (model UL5) attached to a Statham Universal Transducing Cell (Model UC3) connected to a Washington MD4 oscillograph.

Preparations were allowed to equilibrate for 90 min before the start of the experiment, during which time a single dose of potassium chloride (3.0×10^{-2} mol l^{-1}) was administered.

Determination of pA_2 values

pA_2 values were determined as described by Apperley *et al.* (1976). Cumulative concentration-effect curves for a given agonist were constructed for each preparation. At each dose the response was allowed to level out (3–4 min) before adding another higher dose until a maximum response was obtained. The agonist was then washed from the baths over a 30 min period and then different concentrations of a single antagonist added to three of the baths, the fourth preparation serving as a control. After 30 min contact with the antagonist, agonist concentration-effect curves were redetermined in all four preparations. The agonist concentration-ratio (CR) was calculated as before (Apperley *et al.*, 1976) for each antagonist concentration and corrections made for spontaneous changes in sensitivity to the agonist, as judged from the control preparation. Generally any such change was less than two fold between the two consecutive concentration-effect curves.

For each experiment pA_2 values and slopes were calculated by the method of Arunlakshana & Schild (1959), each three point regression being fitted by computation using the method of least squares.

Table 1 Sensitivity of rat caudal artery to 5-hydroxytryptamine (5-HT) and tryptamine in reserpine-pretreated animals in the presence and absence of monoamine oxidase (MAO) inhibitors

Agonist	n	EC_{50} (mol l^{-1})	*CR*	*Maximum tension* (g)
5-HT	12	1.00×10^{-7} $\pm 0.08 \times 10^{-7}$	—	0.90 ± 0.07
5-HT + iproniazid	12	8.63×10^{-8} $\pm 2.19 \times 10^{-8}$	0.86	0.80 ± 0.11
Tryptamine	12	1.65×10^{-5} $\pm 0.33 \times 10^{-5}$	—	0.85 ± 0.07
Tryptamine + iproniazid	10	3.77×10^{-7} $\pm 1.08 \times 10^{-7}$	0.02	0.73 ± 0.07
Tryptamine + pargyline	5	9.60×10^{-7} 5.30×10^{-7}	0.06	0.80 0.08

All values are mean ± 95% confidence limits.
CR is the ratio of the mean agonist concentrations required to produce a 50% maximal response in preparations in the presence and absence of the MAO inhibitors, iproniazid (5×10^{-5} mol l^{-1}) and pargyline (1.0×10^{-5} mol l^{-1}).

Effects of monoamine oxidase inhibitors

The effects of MAO inhibitors on responses to 5-HT and tryptamine were determined by comparing mean values for EC_{50} (concentration to produce 50% of maximum response) and maximum response (g tension) from different preparations set up in Krebs solution either in the presence or absence of iproniazid or pargyline. In the case of methoxamine, preparations were allowed 30 min contact with the MAO inhibitor and their effects on agonist potency determined by the same method as that used for the antagonists (above).

Pretreatment with reserpine

Rats were pretreated with reserpine to abolish any indirect effects of agonists which might be mediated by catecholamine release. Reserpine was dissolved in distilled water containing 20% w/v ascorbic acid. Rats were injected (5 mg kg^{-1} i.p.) 18 h before use. This procedure has been shown to deplete the rat heart of noradrenaline completely (Paasonen & Krayer, 1959) and abolished responses of rat caudal artery to electrical field stimulation at parameters known to cause selective nerve stimulation (unpublished observations).

Drugs

The following drugs were used: 5-HT creatinine sulphate (Koch-Light), tryptamine hydrochloride (Sigma), iproniazid phosphate (Sigma), pargyline hydrochloride (Sigma), phentolamine mesylate (Ciba), ketanserin (Janssen), methysergide bimaleate (San-

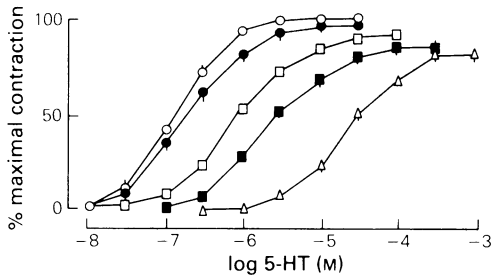

Figure 1 Rat isolated caudal artery: mean concentration-effect curves for 5-hydroxytryptamine (5-HT) in the presence of ketanserin 3.0×10^{-9} mol l^{-1} (□), 1.0×10^{-8} mol l^{-1} (■) and 1.0×10^{-7} mol l^{-1} (△). Both the first (○) and second (●) control agonist concentration effect-curves were obtained in the absence of ketanserin. Each value is the mean of 5 estimates; vertical lines show s.e.mean when this is greater than the height of the symbol.

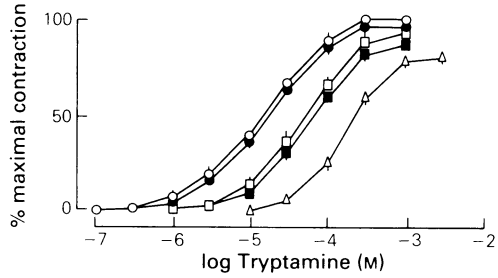

Figure 2 Rat isolated caudal artery: mean concentration-effect curves for tryptamine in the presence of ketanserin 3.0×10^{-9} mol l^{-1} (□), 1.0×10^{-8} mol l^{-1} (■) and 1.0×10^{-7} mol l^{-1} (△). Both the first (○) and second (●) control agonist concentration-effect curves were obtained in the absence of ketanserin. Each value is the mean of 6 estimates; vertical lines show s.e.mean when this is greater than the height of the symbol.

doz), methoxamine hydrochloride (Wellcome), reserpine (Sigma). All drugs were dissolved in distilled water except for ketanserin, which was dissolved in 0.1 mol l^{-1} tartaric acid and dilutions made with distilled water. All drug concentrations refer to molar concentrations of the salt.

Results

Agonists

5-HT and tryptamine produced contractions of the reserpinised caudal artery in the concentration-ranges 3.0×10^{-8}–3.0×10^{-5} mol l^{-1} and 1.0×10^{-6}–3.0×10^{-4} mol l^{-1} respectively. 5-HT (EC_{50}, 1.00×10^{-7} mol l^{-1}) was approximately 165 times more potent than tryptamine (EC_{50}, 1.65×10^{-5} mol l^{-1}) but the maximum responses to the two agonists were not significantly different (Table 1). The α_1-adrenoceptor agonist, methoxamine, contracted the preparation in the concentration range 1.0×10^{-7}–1.0×10^{-4} mol l^{-1}, with an EC_{50} of $8.45 \times 10^{-7} \pm 1.55 \times 10^{-7}$ mol l^{-1} (mean ± s.e.mean, $n = 4$) and a maximum response of 0.90 ± 0.05 g.

Ketanserin (3.0×10^{-9}–1.0×10^{-7} mol l^{-1}), methysergide (3.0×10^{-9}–1.0×10^{-7} mol l^{-1}) and phentolamine (1.0×10^{-6} mol l^{-1}) exhibited no agonistic activity.

Table 2 Agonist concentration-ratios (CR) for the antagonism by ketanserin and methysergide of contractile responses to 5-hydroxytryptamine (5-HT) and tryptamine in rat caudal artery

Antagonist	*Antagonist conc.* (mol l^{-1})	*5-HT CR*	*Tryptamine CR*	*Tryptamine (+ iproniazid) CR*	*Tryptamine (+ pargyline) CR*
Ketanserin	3×10^{-9}	5.2 (2.7–10.0)	3.3 (2.4–4.5)	3.4 (2.4–4.7)	5.6 (3.0–10.5)
	10^{-8}	15.4 (7.4–32.0)	3.4 (2.9–4.1)	10.2 (4.2–24.5)	11.3 (6.3–20.1)
	10^{-7}	212 (104–433)	9.5 (7.0–12.8)	58.8 (37.5–92.2)	78.1 (34.5–177)
Methysergide	3×10^{-9}	4.8 (4.4–5.1)	3.2 (2.2–4.7)	4.1 (2.3–7.3)	—
	10^{-8}	18.3 (8.3–40.4)	4.2 (2.5–7.1)	10.5 (3.0–37.2)	—
	10^{-7}	112 (73.9–169)	9.0 (4.9–16.6)	41.8 (18.6–94.3)	—

All values are geometric means (95% confidence limits) from 4–6 experiments. CR is the ratio of the agonist concentration required to produce 50% of the maximal response in the absence of the antagonist and the agonist concentration required to produce the same response in the presence of the antagonist.

Table 3 Effect of iproniazid (5×10^{-5} mol l^{-1}) and pargyline (1×10^{-5} mol l^{-1}) on pA_2 values for ketanserin and methysergide against tryptamine- and 5-hydroxytryptamine (5-HT)-induced contractions of rat caudal artery

	Ketanserin		*Ketanserin + iproniazid*		*Ketanserin + pargyline*	
	pA_2	*Slope*	*pA_2*	*Slope*	*pA_2*	*Slope*
Tryptamine	9.12 (8.55–9.69)	0.47 (0.34–0.60)	8.91 (8.63–9.19)	0.96 (0.77–1.15)	9.17 (8.86–9.38)	0.88 (0.80–0.96)
5-HT	9.08 (8.88–9.28)	1.15 (1.04–1.26)	9.23 (8.70–9.76)	1.08 (0.86–1.30)	—	—
	Methysergide		*Methysergide + iproniazid*			
	pA_2	*Slope*	*pA_2*	*Slope*		
Tryptamine	9.06 (8.56–9.56)	0.47 (0.44–0.50)	9.02 (8.54–9.50)	0.87 (0.73–1.01)		
5-HT	9.11 (8.97–9.25)	1.00 (0.94–1.16)	—	—		

pA_2 values and slopes were calculated by the method of Arunlakshana & Schild (1959) from the same experiments as those from which the data in Table 2 were obtained.
Each value is the mean (95% confidence limits) of 4–6 separate estimates from individual experiments (see Methods).

Effect of monoamine oxidase inhibition

Comparison of EC_{50} values and maximum responses in the presence and absence of MAO inhibitors revealed that the sensitivity of the caudal artery to tryptamine was increased about 44 times after treatment with iproniazid (5.0×10^{-5} mol l^{-1}). In contrast, there was no change in the sensitivity of the preparation to 5-HT (Table 1). In the presence of pargyline (1.0×10^{-5} mol l^{-1}) the sensitivity to tryptamine was increased by a factor of about 17. Maximum responses to the two agonists were similar both in the presence and absence of the MAO inhibitors.

Iproniazid and pargyline were without effect on responses to methoxamine (CR of 1 (0.6–1.6, geometric mean and 95% confidence limits, $n = 4$) and 0.9 (0.6–1.5, $n = 4$) respectively).

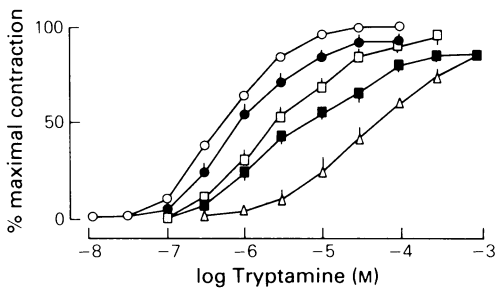

Figure 3 Rat isolated caudal artery: the effect of iproniazid (5.0×10^{-5} mol l^{-1}) on mean concentration-effect curves for tryptamine in the presence of ketanserin 3.0×10^{-9} mol l^{-1} (□), 1.0×10^{-8} mol l^{-1} (■) and 1.0×10^{-7} mol l^{-1} (△). Both the first (○) and second (●) control agonist concentration-effect curves were obtained in the absence of ketanserin. Each value is the mean of 5 estimates; vertical lines show s.e.mean when this is greater than the height of the symbol.

Antagonists

Ketanserin (3.0×10^{-9}–1.0×10^{-7} mol l^{-1}) and methysergide (3.0×10^{-9}–1.0×10^{-7} mol l^{-1}) were investigated as antagonists of 5-HT and tryptamine (Tables 2 and 3). Both antagonists produced concentration-dependent antagonism of contractile responses to 5-HT (e.g. Figure 1), causing parallel, rightward displacements of the agonist concentration-effect curves. Schild plots were linear with slopes not significantly different ($P > 0.05$) from unity (see Table 3).

Ketanserin and methysergide also caused parallel, rightward displacements of concentration-effect curves to tryptamine (e.g. Figure 2). At the lowest concentrations of methysergide and ketanserin (3.0×10^{-9} mol l^{-1}), the shifts induced by the antagonists were of similar magnitude for both 5-HT and tryptamine (Table 2). However, at the two higher concentrations, the antagonists were significantly more potent against 5-HT than against tryptamine, as reflected by their relative concentration-ratios. In consequence the pA_2 values for the two antagonists were not significantly different from those against 5-HT, but the slopes of the Schild plots were significantly less than unity when tryptamine was the agonist (Table 3).

When the antagonistic potencies of methysergide and ketanserin were redetermined against tryptamine in the presence of iproniazid, greater rightward displacements of tryptamine concentration-effect curves were seen at the higher antagonist concentrations (Figure 3 and Table 2). Although the concentration-

ratios for the higher antagonist concentrations were still significantly lower than the corresponding values for 5-HT, the slopes of the Schild plots were not significantly different from unity. Iproniazid did not affect the pA_2 values or the slopes of the Schild plots for methysergide (data not shown) or ketanserin (Table 3) against 5.HT. A similar trend was seen in the presence of MAO inhibition with pargyline. However, the slope of the Schild plot for the antagonism of tryptamine responses by ketanserin was slightly less than unity even in the presence of pargyline (Table 3).

In the presence of iproniazid, phentolamine (1.0×10^{-6} mol l^{-1}) caused rightward displacements of concentration-effect curves to both 5-HT (CR of 3.3 (1.6–6.8, geometric mean and 95% confidence limits), $n = 5$ and tryptamine (CR of 5.6 (3.6–9.1) $n = 6$). The CR for 5-HT was not statistically different from the CR for tryptamine (Student's t test at $P = 0.05$). The equivalent pA_2 values for 5-HT and tryptamine, derived from the K_i calculated from the Gaddum equation (Gaddum, 1957), were 6.4 and 6.7 respectively.

Discussion

A number of workers have shown that specific receptors for 5-HT mediating contraction exist in the rat caudal artery, which appear to be of the 5-HT_2 subtype (Van Neuten *et al.*, 1981; Bradley *et al.*, 1983). However, there have been conflicting reports as to the nature of the receptor mediating the actions of tryptamine in this preparation (Hicks & Langer, 1983; Bradley *et al.*, 1984). We have investigated the situation further, with particular regard to two factors which can complicate the analysis, namely the relative degree of MAO inactivation and the amount of α-adrenoceptor stimulation associated with the two agonists.

In the rat caudal artery, responses to 5-HT were unaffected by iproniazid and pargyline (two structurally different MAO inhibitors; see Levin & Wilson, 1977), while responses to tryptamine were markedly potentiated, indicating that MAO enzymes reduce the available concentration of tryptamine, but not 5-HT, in the tissue. This has been observed in other systems, such as the rat fundic strip, where it occurs because the cell membrane acts as a selective diffusion barrier, which excludes 5-HT but allows the less polar tryptamine molecules to gain access to intracellular MAO enzymes with subsequent breakdown (Vane, 1959).

In our study, responses to 5-HT were more potently antagonized by methysergide and ketanserin than were those to tryptamine, this difference being substantially reduced by the presence of iproniazid and pargyline. These findings are consistent with those of Handschumacher & Vane (1967) who suggested that the differential accessibilities of 5-HT and tryptamine to MAO enzymes could account for their different susceptibilities to antagonism. This postulate was supported by their observation that tryptamine could enter the cells of the rat fundic strip during the development of a contraction and be rapidly metabolised, while intracellular access by 5-HT was minimal.

An analogy may be drawn between the effects of MAO metabolism on antagonist potencies against tryptamine in this study with the effects of the saturable $uptake_1$ removal system on the potencies of antagonists in inhibiting responses to adrenoceptor agonists susceptible to $uptake_1$ (see Langer & Trendelenburg, 1969; Furchgott, 1972). For example, in the dog isolated saphenous vein, responses to noradrenaline (which is susceptible to the saturable $uptake_1$ system) are less sensitive to antagonism than are responses to methoxamine, which is unaffected by $uptake_1$ (Humphrey, 1978). By use of such an analogy, the results of this study may be explained. One can envisage that at low concentrations of tryptamine, its removal by MAO enzymes is directly proportional to its organ bath concentrations, and its concentration at the receptors is reduced by a constant proportion (see Langer & Trendelenburg, 1969). However, as the bath concentration of tryptamine increases, the active sites of the MAO enzymes approach saturation, at which point the increase in tryptamine concentration at the receptors becomes disproportionately greater than the increase in organ bath concentration. Once saturation of the enzymes is complete, one would again expect there to be direct relationship between the concentration of tryptamine at the receptor level and its concentration in the organ bath. Presumably, the concentrations of tryptamine required to produce a concentration-effect curve are normally too low to produce saturation of the enzyme, as reflected by the monophasic nature of the curve. However, the higher concentrations of tryptamine required to induce a response in the presence of a competitive antagonist saturate the enzyme and produce a disproportionate increase in the concentration of tryptamine at the receptor relative to the concentration of the antagonist, with a consequently smaller shift in the concentration-effect curve. This would be expected to lead to a low Schild plot slope (Furchgott, 1972; Kenakin, 1982). The differences in antagonist potency against tryptamine and 5-HT were most marked at the higher concentrations used, presumably reflecting saturation of MAO. In the presence of a MAO inhibitor, there should be a direct relationship between the bath concentration of tryptamine and its concentration at the receptor, leading to a Schild plot slope of unity and an estimate of pA_2 similar to the pA_2 for 5-HT, which is not subject to enzymatic inactivation.

It thus appears that the selective removal of tryptamine by MAO enzymes predominantly accounts for

its reduced susceptibility to antagonism. However, the concentration-ratios for tryptamine in the presence of the highest concentration of antagonist were smaller than those for 5-HT, even in the presence of an MAO inhibitor. A small component of α-adrenoceptor stimulation may account for the difference though this is unlikely (see below). Alternatively, it may be that some inactivation of tryptamine occurred as a result of amine oxidase activity distinct from MAO and resistant to iproniazid and pargyline (see Clarke *et al.*, 1982; Barrand *et al.*, 1984). Nevertheless, our finding that in the rat caudal artery the pA_2 value (and slope) for either ketanserin or methysergide in the presence of an MAO inhibitor is very similar whether 5-HT or tryptamine is used as the agonist indicates that the major part of the response to tryptamine is mediated by activation of the same receptor as that activated by 5-HT. Evidence has already been presented to suggest that this 5-HT receptor is of the 5-HT_2 type (Van Neuten *et al.*, 1981; Bradley *et al.*, 1983).

Stollak & Furchgott (1983) showed that responses of rabbit isolated aorta to 5-HT were more susceptible to inhibition by 5-HT receptor antagonists than were those to tryptamine, even in the presence of MAO inhibition. This difference was abolished in the presence of the α-adrenoceptor antagonist, benextramine. Both benextramine and the selective α_1-adrenoceptor antagonist, prazosin, slightly inhibited responses to tryptamine and it was proposed that while the response to 5-HT was mediated solely by a 5-HT receptor, the response to tryptamine was composed of both α-adrenoceptor-mediated and 5-HT-receptor mediated components, and that this could account for the differential potencies of the antagonists against the two agonists.

In this study, the effect of phentolamine on responses to 5-HT and tryptamine was investigated to determine the extent of α-adrenoceptor stimulation in responses to the agonists. Although in the presence of iproniazid, phentolamine caused slightly larger rightward displacements of concentration-effect curves to tryptamine than of those to 5-HT, these shifts were not significantly different. The similarity between the calculated pA_2 values for these interactions and the pA_2 value for phentolamine against 5-HT in rabbit aorta, another 5-HT_2 receptor containing preparation (Apperley *et al.*, 1976; Humphrey *et al.*, 1982), suggests that the weak potency of phentolamine reflects its affinity for 5-HT receptors rather than any α-adrenoceptor-mediated component in the response to tryptamine. Furthermore, at the highest concentrations used, ketanserin, but not methysergide, would have appreciable antagonistic actions at α_1-adrenoceptors (see Humphrey, 1984). Thus, if responses to tryptamine were mediated both by 5-HT and α-adrenoceptor activation, then it would be expected that ketanserin would be a more potent antagonist of tryptamine than 5-HT compared to methysergide, but this was not the case. It therefore appears that in this preparation, the extent of α-adrenoceptor stimulation in the response to tryptamine is non-existent or minimal. This agrees with the findings of Hicks & Langer (1983) who showed that combined treatment of the perfused rat caudal artery with selective α_1- and α_2-adrenoceptor antagonists did not modify responses to tryptamine. Even in the rabbit aorta, the α-adrenoceptor component in the response to tryptamine described by Stollak & Furchgott (1983) appears to be small, since prazosin (1.0×10^{-6} mol l^{-1}), caused only a 0.25 log unit shift of the concentration-effect curve to tryptamine, and the rabbit aorta is believed to contain only α-adrenoceptors of the α_1-subtype (Docherty & Starke, 1981).

The conclusion from this study that tryptamine acts mainly via 5-HT_2 receptors does not agree with that from a study by Hicks & Langer (1983), who found that in the perfused rat caudal artery the pA_2 value for either methysergide and ketanserin, in the presence of pargyline, was at least one unit lower against tryptamine than against 5-HT-induced vasoconstriction. It seems unlikely that this difference can be accounted for by their use of caudal arteries from non-reserpine-treated rats, particularly since they also showed that tryptamine was not acting through an α-adrenoceptor mechanism. However, they used perfused vessels and it is not clear whether in their experiments equilibrium between agonist and antagonist was achieved. The explanation for the discrepancy between their data and ours remains to be determined. It is evident that more studies in a variety of tissues are needed to clarify the controversy of whether specific tryptamine receptors exist and if so what their overall distribution is.

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