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Evidence for the existence of 5-hydroxytryptamine receptors, which are not of the 5-HT_2 type, mediating contraction of rabbit isolated basilar artery

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In the rabbit isolated basilar artery the contractile action of 5-hydroxytryptamine (5-HT) was little affected by high concentrations of ketanserin (1.0×10^{-6} M) indicating that 5-HT-receptors other than those of the 5-HT_2-type were involved. The contractile action of 5-HT was mimicked by methysergide and 5-carboxamidotryptamine (5-CT) with equipotent concentration ratios (5-HT = 1) of about 22 and 0.6 respectively. This profile is characteristic of that in the dog saphenous vein which contains a 5-HT receptor type that may be described as '5-HT_1-like'.

Introduction In many peripheral vascular preparations 5-hydroxytryptamine (5-HT) produces contractions via 5-HT_2-receptors (Van Nueten *et al.*, 1981). However, 'non-5-HT_2' receptors which are not blocked by ketanserin are involved in the 5-HT-mediated contraction of some vascular preparations such as the dog saphenous vein (Feniuk *et al.*, 1985). In this study we have attempted to characterize the 5-HT receptor in the rabbit isolated basilar artery by using 5-carboxamidotryptamine (5-CT), which is a potent agonist at the 5-HT receptor type in the dog saphenous vein (Feniuk *et al.*, 1981).

Methods The whole brain was removed from rabbits (New Zealand White, 2.0–3.5 kg of either sex) under pentobarbitone anaesthesia (60 mg kg^{-1}, i.p.). The basilar artery was dissected from the brain and four segments (4–5 mm long) prepared for recording of isometric tension changes by a recently described method (Bradley *et al.*, 1985).

After equilibration each preparation was dosed with potassium chloride (3×10^{-2} M) and then washed and 30 min later a cumulative concentration-effect curve to 5-HT (or methysergide or 5-CT) constructed. In some experiments the preparations were dosed with a single concentration of antagonist (or vehicle) 30 min before dosing with agonist. Concentration-effect curves in the presence of antagonist were compared with that in the control preparation in the presence of vehicle alone and agonist concentration-ratios (expressed as geometric means (range) of 3–5 observations) measured at the level of 50% maximum response in each experiment.

Results 5-HT potently contracted the vessels producing a maximum tension change equivalent to 70.7 ± 14.3% ($n = 11$) of the potassium chloride response (0.34 ± 0.08 g, mean ± s.e.mean, $n = 28$ animals). Methysergide and 5-CT also potently contracted the basilar artery with maximum responses equivalent to 45.6 ± 11.7% ($n = 8$) and 58.4 ± 10.1% ($n = 6$), respectively, of the potassium chloride response (Figure 1). Equipotent concentration-ratios (5-HT = 1) estimated at the level of the 50% response to 5-HT were 22.2 and 0.6 for methysergide and 5-CT, respectively. Concentration-effect curves to 5-HT, methysergide and 5-CT were shifted slightly rightward, or not at all, by ketanserin, 1.0×10^{-6} M (agonist concentration-ratios of 2.4 (0.7–6.7), 2.9 (1.2–8.1) and 2.5 (1.1–6.4), respectively) or by phentolamine, 1.0×10^{-6} M (agonist concentration-ratios

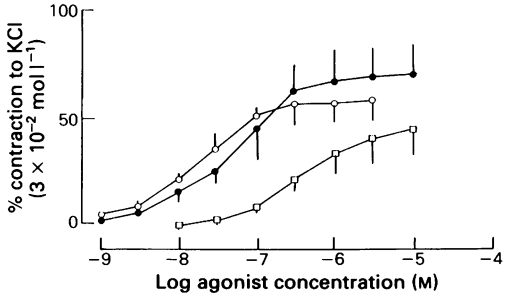

Figure 1 Rabbit isolated basilar artery: mean concentration-effect curves to 5-carboxamidotryptamine (○), 5-hydroxytryptamine (●) and methysergide (□). Each value is the mean of 6–11 estimates; vertical lines show s.e.mean when this is greater than the height of the symbol.

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of 4.3 (1.5–12.0), 2.7 (1.3–4.6) and 2.6 (0.9–5.0), respectively.

Discussion It appears that at least two types of 5-HT receptor mediate the 5-HT induced contraction of vascular smooth muscle. One type is commonly found in peripheral vessels like the rat caudal artery and is potently and competitively blocked by ketanserin and methysergide (Van Nueten *et al.*, 1981; Bradley *et al.*, 1985). This 5-HT receptor type is very similar to the 5-HT_2 ligand binding site identified in the brain, is widely distributed and appears to mediate many of the effects of 5-HT (see Humphrey, 1984). In contrast, the dog saphenous vein contains 'non-5-HT_2' receptors that are not blocked by ketanserin or other classical 5-HT antagonists and at which methysergide is a partial agonist (Apperley *et al.*, 1980; Feniuk *et al.*, 1985). There is evidence to suggest that similar receptors also occur in the basilar artery of various species (Forster & Whalley, 1982; Peroutka *et al.*, 1983; Edvinsson *et al.*, 1984) though ketanserin does have marked 5-HT antagonistic activity in some studies (Van Nueten *et al.*, 1981; Mullier-Schweinitzer & Engel, 1983).

In this study in the rabbit basilar artery 5-CT was twice as potent as 5-HT itself, which is virtually identical to its relative potency in the dog saphenous vein and in contrast to its potency in 5-HT_2 receptor-containing preparations where it is about 25 times weaker than 5-HT (see Humphrey, 1984). Furthermore, as in the dog saphenous vein, methysergide was in the order of 10 times less potent than 5-HT in the rabbit basilar artery and appeared to produce a lower maximum response (see Apperley *et al.*, 1980). The data with agonists therefore suggest that the 5-HT receptors in the rabbit basilar artery and dog saphenous vein are similar.

The data with antagonists confirms that the contractile actions of 5-HT, methysergide and 5-CT are not mediated predominantly by 5-HT_2 receptors or α-adrenoceptors. In the case of 5-HT, experiments with mepyramine and indomethacin indicate that histamine H_1-receptors and prostaglandin release are not involved either (unpublished observations). These findings, together with the high potency of 5-HT suggests that it is acting through a specific 5-HT receptor on the smooth muscle which is not of the 5-HT_2 type. In the absence of a specific receptor blocking drug, this receptor appears to be potently stimulated by 5-CT and moderately so by methysergide, which seems to be a partial agonist. This profile in the rabbit basilar artery is almost identical to the situation in the dog saphenous vein where the 5-HT receptor has been described as '5-HT_1-like' (Feniuk *et al.*, 1985).

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