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# 5-Carboxamidotryptamine is a selective agonist at 5-hydroxytryptamine receptors mediating vasodilatation and tachycardia in anaesthetized cats

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**1** We have attempted to characterize the 5-hydroxytryptamine (5-HT) receptors mediating bronchoconstriction, vasodilatation, vasodepression and tachycardia in anaesthetized cats following bilateral vagosympathectomy and β-adrenoceptor blockade with propranolol.

**2** 5-HT (1–100 μg kg$^{-1}$ i.v.) caused dose-related bronchoconstriction and tachycardia but variable and complex effects on diastolic blood pressure and carotid arterial vascular resistance.

**3** In contrast, 5-carboxamidotryptamine (5-CT; 0.01–1 μg kg$^{-1}$ i.v.) caused consistent, dose-related decreases in diastolic blood pressure and carotid arterial vascular resistance and increases in heart rate. 5-CT did not cause bronchoconstriction.

**4** The 5-HT-induced bronchoconstriction was dose-dependently antagonized by methiothepin, methysergide and ketanserin (10–100 μg kg$^{-1}$ i.v.). The highest doses used of these antagonists did not antagonize bronchoconstriction induced by prostaglandin $F_{2\alpha}$. The high potency of all three antagonists indicate a 5-$HT_2$-receptor mediated effect.

**5** The 5-HT- and 5-CT-induced tachycardia as well as the 5-CT-induced vasodepressor and carotid arterial vasodilator responses were dose-dependently antagonized by low doses of methiothepin (10–100 μg kg$^{-1}$ i.v.) and by high doses of methysergide (100–1000 μg kg$^{-1}$ i.v.) but were little affected by ketanserin in doses up to 1000 μg kg$^{-1}$ i.v. These selective effects of 5-CT appear to be mediated by '5-$HT_1$-like' receptors.

## Introduction

The effects of 5-hydroxytryptamine (5-HT) on the cardiovascular system are variable and complex (Erspamer, 1966) and undoubtedly result from a number of different mechanisms involving more than one type of 5-HT receptor (see Humphrey, 1983). We have therefore examined the cardiovascular effects of 5-carboxamidotryptamine (5-CT) which has been shown to be a selective agonist at some 5-HT receptors *in vitro*, being particularly potent at those mediating relaxation of vascular smooth muscle (Feniuk *et al.*, 1981; 1984).

In these experiments, in anaesthetized cats, we have not only compared the cardiovascular actions of 5-HT with those produced by 5-CT but also examined the effect of these drugs on tracheal inflation pressure. The effects of a variety of 5-HT receptor blocking drugs on these responses have been investigated.

A preliminary account of these results has been presented to the British Pharmacological Society (Connor *et al.*, 1985). At the same meeting, a report describing the mechanism of the tachycardia elicited by 5-HT in spinal cats was also presented (Heiligers *et al.*, 1985).

## Methods

Cats of either sex (1.5–3.5 kg) were anaesthetized with pentobarbitone (35–42 mg kg$^{-1}$ i.p.). A cannula was inserted into the trachea and the cat artifically respired (Palmer ventilation pump) with room air at a rate of 20 strokes per min. A stroke volume of approximately 14 ml kg$^{-1}$ provided a positive inspiratory pressure of 4–8 mmHg which was measured with a pressure transducer (Pye Ether Ltd, type UP1) connected to a side branch of the tracheal cannula. Bronchoconstriction was recorded as an increase in tracheal pressure over the basal inflation pressure produced by the pump (Dixon & Brodie, 1903). Stroke volume was adjusted so that arterial pH, $P_{CO_2}$ and $P_{O_2}$, measured on an ABL-I blood gas analyser, could be maintained within normal physiological limits (pH 7.30–7.45;

$P_{CO_2}$, 20–35 mmHg; $P_{O_2}$, 80–125 mmHg; body temperature 37°C). A femoral artery was cannulated for measurement of arterial blood pressure with a Bell & Howell pressure transducer (type 4-442-001) and the heart rate derived from the blood pressure signal with a Devices instantaneous rate meter. Mean blood flow in the right common carotid artery was recorded by a cuffed electromagnetic flow probe connected to a Statham (SP2202) flow meter. Arterial blood pressure, heart rate, mean carotid flow, carotid vascular resistance and respiratory inflation pressure were continually displayed on a Devices M19 chart recorder. A femoral vein was cannulated for the administration of drugs. In all experiments the right and left vagus and cervical sympathetic nerves were sectioned. In order to prevent any possible action of higher doses of 5-HT or 5-CT on β-adrenoceptors either directly (see Edvisson *et al.*, 1978) or indirectly (see Fozard & Mobarok Ali, 1978), all cats, except those in which isoprenaline was used as an agonist, were pretreated with propranolol, 1 mg $kg^{-1}$ i.v., 15 min prior to administration of drugs; a dose known to produce marked blockade of β-adrenoceptors throughout the time course of the experiments (Apperley *et al.*, 1976). Preliminary experiments in 2 cats showed that propranolol did not modify the cardiovascular actions of 5-CT qualitatively or quantitatively.

*Dosing schedule*

Dose-effect curves to the agonists were obtained by administering increasing doses 10–15 min apart. At least four doses of agonist were used to construct each dose-effect curve which was then repeated three times with a 30 min interval between each. Increasing doses of antagonist were administered 15 min before the second, third and fourth dose-effect curves. The doses of antagonist referred to in the text are the amounts administered in between each dose-effect curve. Only one agonist-antagonist interaction was studied in a single cat and preliminary experiments showed that the agonist dose effect curves were reproducible over the time course of the experiment. The effects of the antagonist were measured 15 min after dosing when haemodynamic variables had stabilized.

*Statistics and calculations*

Although carotid arterial vascular resistance was displayed electronically in each experiment, peak changes were calculated by dividing mean arterial pressure (⅓ pulse pressure + diastolic pressure) by the mean carotid arterial blood flow.

Responses to a given dose of agonist were plotted as the arithmetic mean ± s.e.mean. Antagonist potency was determined by calculating the dose-ratio i.e. dose of agonist to produce a given response in the presence of antagonist divided by the dose of agonist to produce the same response in the absence of antagonist. The dose-ratios were measured on the linear portion of the dose-effect curve and the data combined by determining the geometric mean (95% confidence limits).

## Results

The basal haemodynamic variables before administration of 5-HT, 5-CT or isoprenaline to the cats used in these experiments are shown in Table 1. There was no difference in any of the parameters between untreated cats and those treated with propranolol.

*Effects of 5-hydroxytryptamine*

5-Hydroxytryptamine (1–100 μg $kg^{-1}$ i.v.) produced complex and inconsistent effects on arterial blood pressure and carotid vascular resistance. The responses were variable and consisted of both increases and subsequent decreases in diastolic blood pressure and carotid vascular resistance. For this reason quantification of these responses was not possible. 5-HT also caused a dose-related tachycardia and an increase in respiratory inflation pressure.

*Effects of 5-carboxamidotryptamine*

In contrast to the complex effects of 5-HT, 5-CT (0.01–1 μg $kg^{-1}$ i.v.) produced dose-related decreases in diastolic blood pressure and carotid arterial vascular resistance. Like 5-HT, 5-CT produced a dose-related tachycardia and was approximately fifty times more potent than 5-HT in this respect. 5-Carboxamidotryptamine, unlike 5-HT, produced no increase in respiratory inflation pressure. An experimental recording illustrating the effects of 5-HT and 5-CT is shown in Figure 1.

*Effect of antagonists on 5-HT-induced bronchoconstriction*

The 5-HT-induced bronchoconstrictor responses were potently antagonized by all three 5-HT antagonists examined. Methiothepin (10–100 μg $kg^{-1}$ i.v.) methysergide (10–100 μg $kg^{-1}$ i.v.) and ketanserin (10–100 μg $kg^{-1}$ i.v.) all caused a dose-dependent antagonism of the 5-HT-induced bronchoconstriction (Figure 2). Although methiothepin and methysergide appeared to be slightly more potent than ketanserin at blocking the 5-HT bronchoconstrictor effects, precise measurements of their relative antagonistic potencies were not made because methiothepin and methysergide caused flattening of the dose-response curves to 5-HT. None of the antagonists produced any change in respiratory inflation pressure at any dose examined.

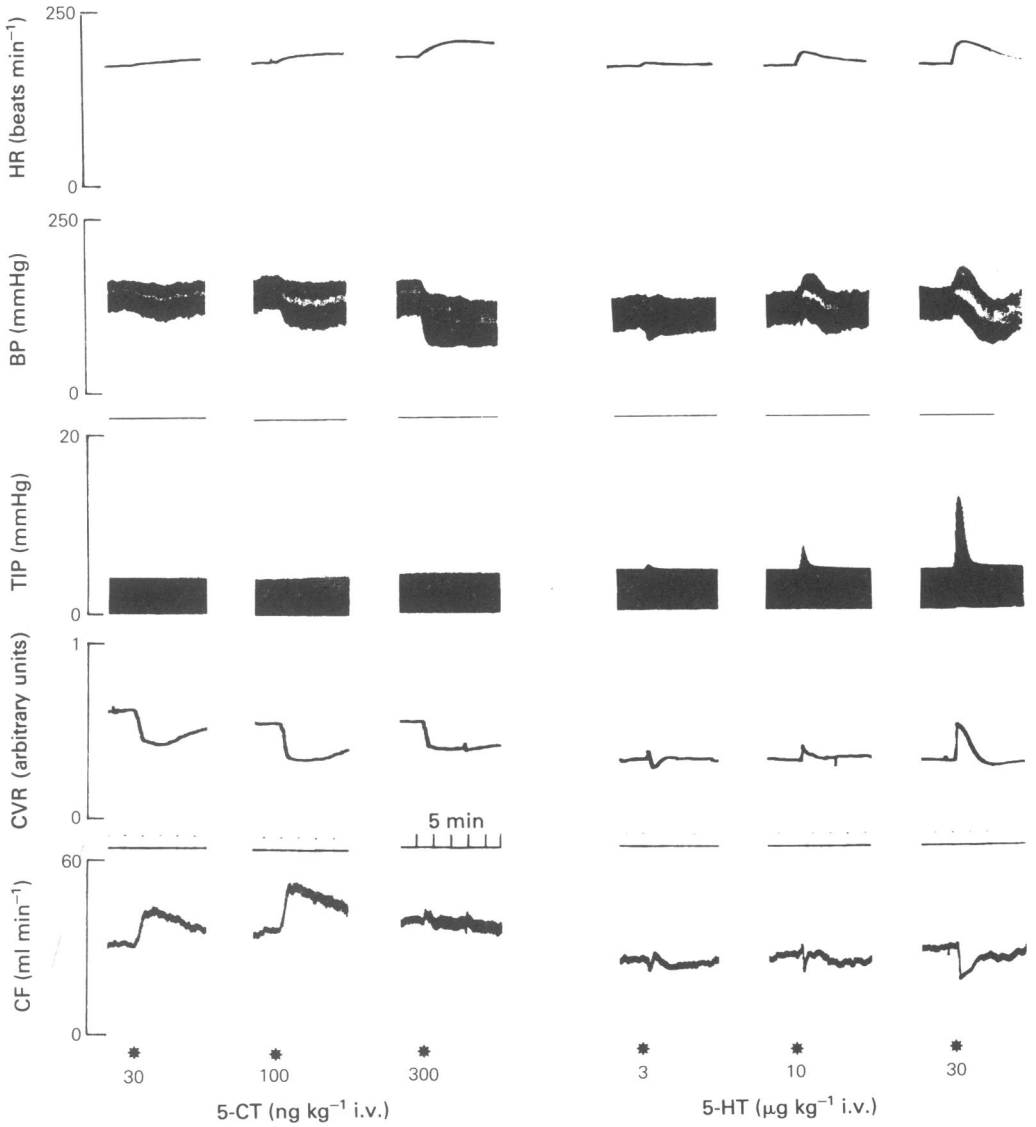


**Figure 1** Experimental recordings illustrating the effects of intravenous 5-carboxamidotryptamine (5-CT) and 5-hydroxytryptamine (5-HT) in anaesthetized cats. Cats were bilaterally vagosympathectomized and pretreated with propranolol (1 mg $kg^{-1}$ i.v.). The effects on heart rate (HR), arterial blood pressure (BP), tracheal inflation pressure (TIP), carotid vascular resistance (CVR, displayed electronically) and carotid blood flow (CF) are shown.

Neither methiothepin, methysergide nor ketanserin at a dose of 100 μg $kg^{-1}$ i.v. produced any antagonism of the bronchoconstriction induced by prostaglandin $F_{2\alpha}$ (0.3–3 μg $kg^{-1}$ i.v.), the geometric mean (95% confidence limits) dose-ratios being 1.1 (0.5–2.5), 0.9 (0.7–1.3) and 1.0 (0.7–1.5), respectively. These values are each derived from 4 experiments.

*Effect of antagonists on 5-HT and 5-CT-induced tachycardia*

Both 5-HT and 5-CT produced dose-related increases in heart rate and 5-HT was about fifty times weaker than 5-CT in this respect. Methiothepin

**Table 1** Basal haemodynamic variables in propranolol-treated and untreated cats

| | *Systolic pressure* (mmHg) | *Diastolic pressure* (mmHg) | *Heart rate* (beats $min^{-1}$) | *Carotid flow* (ml $min^{-1}$) | *Carotid vascular resistance* (mmHg min $ml^{-1}$) |
|---|---|---|---|---|---|
| Propranolol-trated cats ($n = 33$) | 113 ± 3 | 79 ± 3 | 177 ± 5 | 26 ± 1 | 3.8 ± 0.2 |
| Untreated cats ($n = 8$) | 119 ± 7 | 80 ± 7 | 184 ± 10 | 25 ± 3 | 4.1 ± 0.7 |

All values are means ± s.e.mean from $n$ cats.

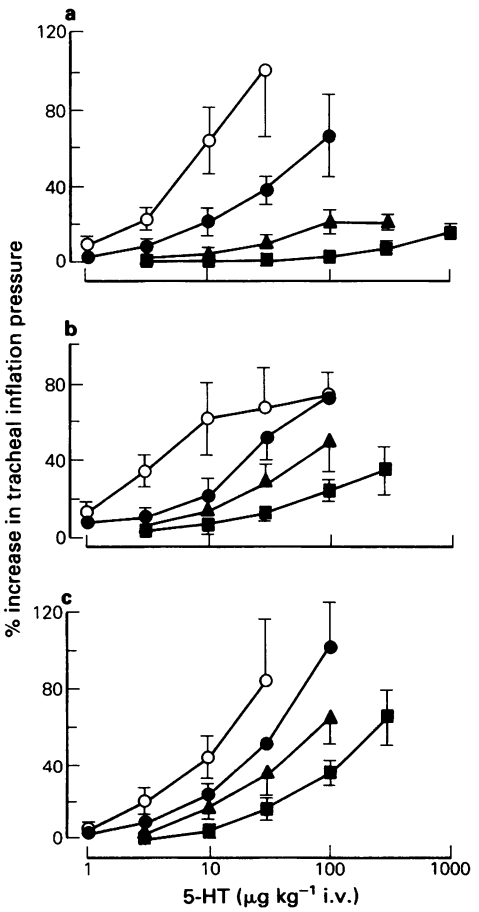


**Figure 2** Effects of (a) methiothepin, (b) methysergide and (c) ketanserin on bronchoconstrictor responses to intravenously administered 5-hydroxytryptamine (5-HT) in anaesthetized cats. Control dose-effect curves to 5-HT shown by (○) and in the presence of increasing doses of antagonist, (●) 10, (▲) 30 and (■) 100 μg $kg^{-1}$. Values are means, with vertical lines showing s.e.mean, from 4 experiments.

(10–100 μg $kg^{-1}$ i.v.) caused a dose-dependent inhibition of the tachycardia induced by 5-HT and 5-CT and was equally effective against both agonists (Figures 3 and 4). Higher doses of methysergide (100–1000 μg $kg^{-1}$ i.v.) than those required to antagonize the 5-HT-induced bronchoconstriction were needed to antagonize the 5-HT- and 5-CT-induced tachycardia. The antagonism was again dose-dependent and similar, regardless of whether 5-HT or 5-CT was used as the agonist (Figures 3 and 4). In marked contrast to its potent antagonistic effects against 5-HT-induced bronchoconstriction, ketanserin in doses up to 1000 μg $kg^{-1}$ i.v. had no effect on either the 5-HT- or 5-CT-induced tachycardia.

The highest doses of the antagonists used, methiothepin (100 μg $kg^{-1}$ i.v.), methysergide (1000 μg $kg^{-1}$ i.v.) and ketanserin (1000 μg $kg^{-1}$ i.v.), decreased heart rate from 195 ± 2, 171 ± 6 and 177 ± 8 beats $min^{-1}$ to 183 ± 11, 166 ± 6 and 166 ± 8 beats $min^{-1}$, respectively.

Despite the fact that these antagonists caused small decreases in heart rate, neither methiothepin (in doses up to 300 μg $kg^{-1}$ i.v.) nor methysergide (in doses up to 1000 μg $kg^{-1}$ i.v.) modified the tachycardia produced by isoprenaline (1–100 ng $kg^{-1}$ i.v.) (see Table 2).

### *Effect of antagonists on 5-CT-induced decreases in carotid arterial vascular resistance and vasodepressor responses*

The 5-CT-induced decrease in carotid vascular resistance and decrease in diastolic blood pressure were both dose-dependently antagonized by methiothepin (10–100 μg $kg^{-1}$ i.v.) and higher doses of methysergide (100–1000 μg $kg^{-1}$ i.v.). Ketanserin in doses up to 1000 μg $kg^{-1}$ i.v. did not affect the 5-CT-induced decrease in diastolic blood pressure and caused only a small (less than two fold) rightward displacement of the 5-CT dose-effect curve for decreases in carotid vascular resistance. These results are summarized in Figures 5 and 6.

The highest doses of methiothepin, methysergide

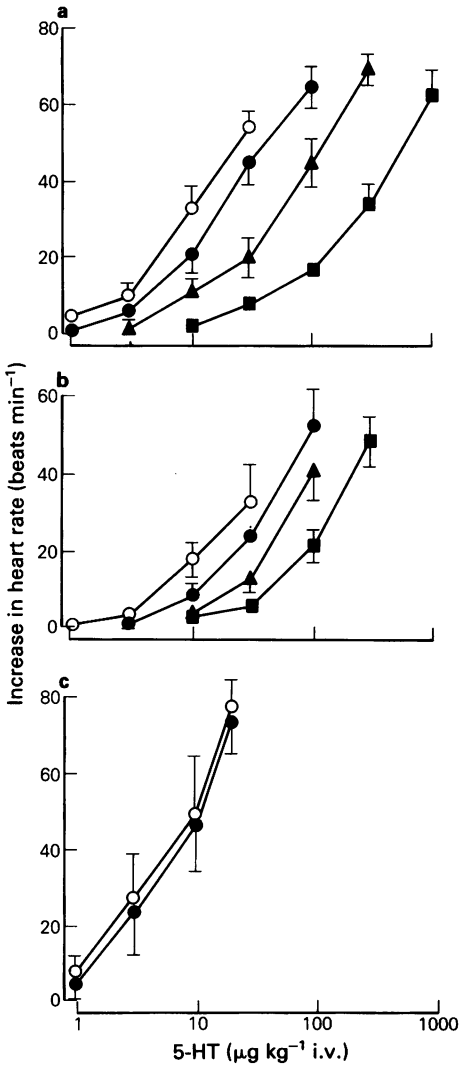


**Figure 3** Effect of (a) methiothepin, (b) methysergide and (c) ketanserin on increases in heart rate produced by intravenously administered 5-hydroxytryptamine (5-HT) in anaesthetized cats. Control dose-effect curves to 5-HT shown by (○) and dose-effect curves in presence of increasing doses of antagonists are shown: (a) (●), 30 (▲) and 100 (■) $\mu g\,kg^{-1}$; (b) 100 (●), 300 (▲) and 1000 (■) $\mu g\,kg^{-1}$; (c) 1000 $\mu g\,kg^{-1}$ (●). Values are means, with vertical lines showing s.e.mean, from 4 experiments.

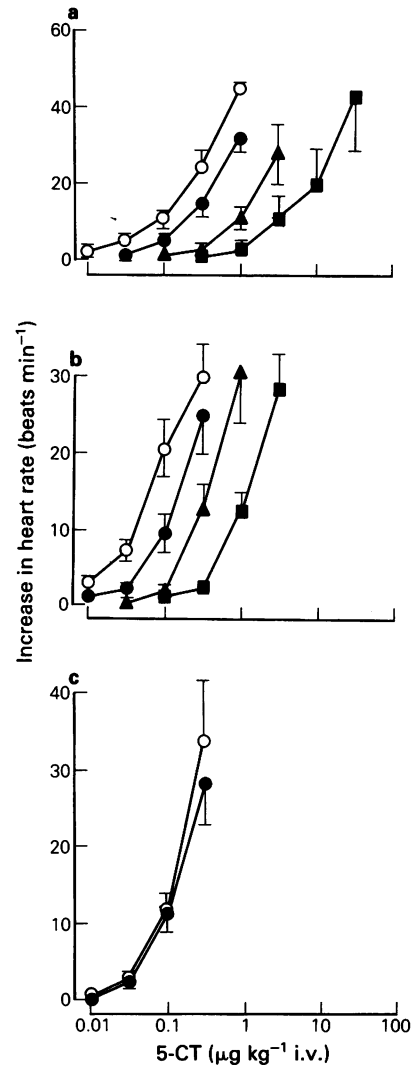


**Figure 4** Effect of (a) methiothepin, (b) methysergide and (c) ketanserin on increases in heart rate produced by intravenously administered 5-carboxamidotryptamine (5-CT) in anaesthetized cats. Control dose-effect curves to 5-CT shown by (○) and dose-effect curves to 5-CT in presence of increasing doses of antagonist are shown: (a) 10 (●), 30 (▲) and 100 (■) $\mu g\,kg^{-1}$; (b) 100 (●), 300 (▲) and 1000 (■) $\mu g\,kg^{-1}$; (c) 1000 $\mu g\,kg^{-1}$ (●). Values are means, with vertical lines showing s.e.mean, from 4–6 experiments.

and ketanserin studied decreased diastolic blood pressure from 76 ± 5, 81 ± 5 and 72 ± 3 mmHg to 57 ± 4, 65 ± 4 and 52 ± 1 mmHg, respectively. Carotid vascular resistance was not altered by either the highest dose of methiothepin or that of ketanserin, whilst methysergide increased carotid vascular resistance from 3.9 ± 0.5 mmHg $min\,ml^{-1}$ to 5.0 ± 0.6 mmHg $min\,ml^{-1}$.

Despite the fact that these antagonists caused some decrease in diastolic blood pressure even the higher doses of methiothepin (300 $\mu g\,kg^{-1}$ i.v.) did not modify the decrease in carotid arterial vascular resis-

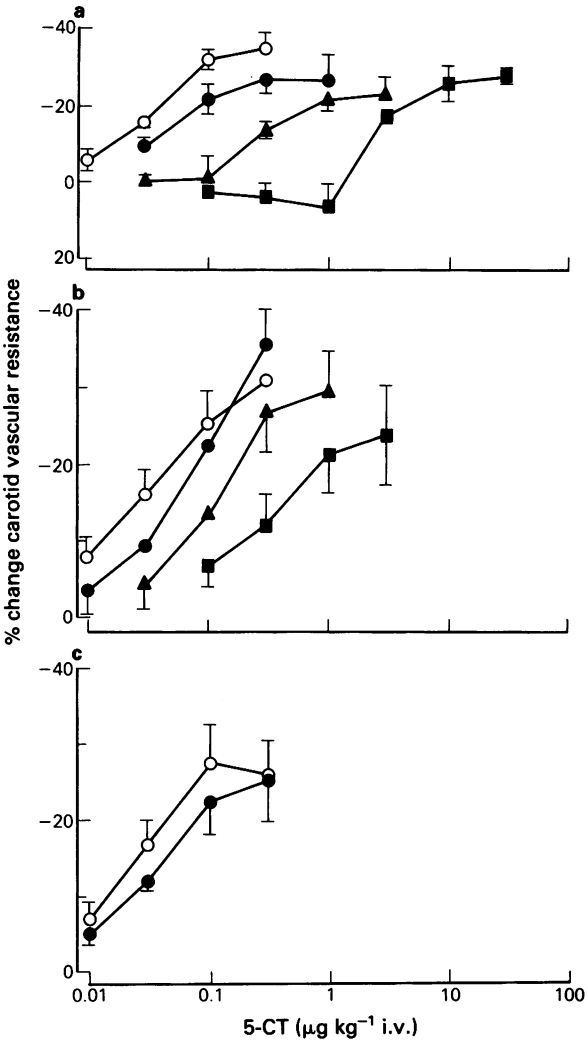


**Figure 5** Effect of (a) methiothepin, (b) methysergide and (c) ketanserin on vasodilator responses to intravenously administered 5-carboxamidotryptamine (5-CT) in anaesthetized cats. Control dose-effect curves to 5-CT shown by (○) and dose-effect curves to 5-CT in presence of increasing doses of antagonist are shown: (a) 10 (●), 30 (▲) and 100 (■) $\mu g\,kg^{-1}$; (b) 100 (●), 300 (▲) and 1000 (■) $\mu g\,kg^{-1}$; (c) $1000\,\mu g\,kg^{-1}$ (●). Values are means, with vertical lines showing s.e.mean, from 4–6 experiments.

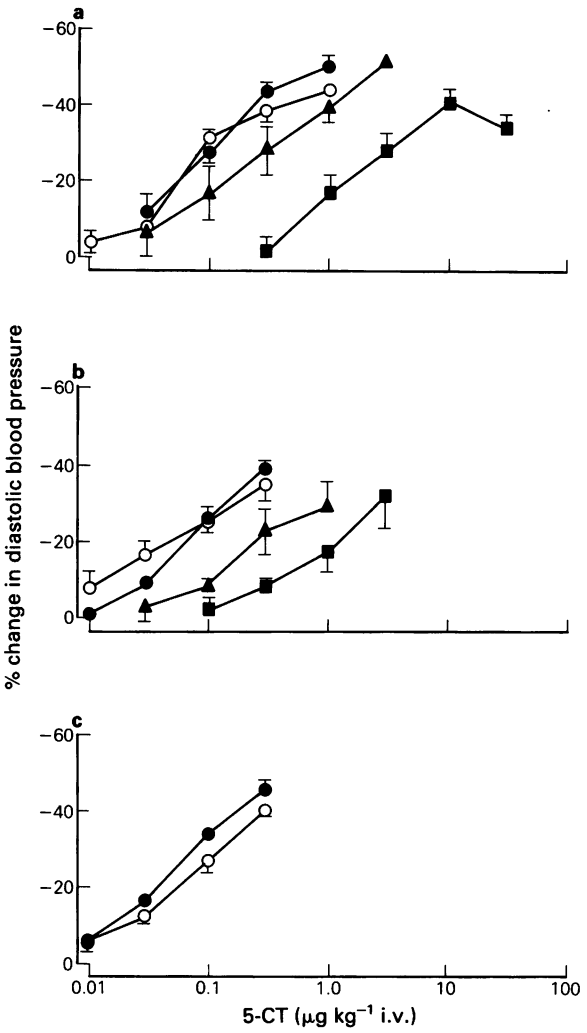


**Figure 6** Effect of (a) methiothepin, (b) methysergide and (c) ketanserin on vasodepressor responses to intravenously administered 5-carboxamidotryptamine (5-CT) in anaesthetized cats. Control dose-effect curves to 5-CT shown by (○) and dose-effect curves to 5-CT in presence of increasing doses of antagonist are shown: (a) 10 (●), 30 (▲) and 100 (■) $\mu g\,kg^{-1}$; (b) 100 (●), 300 (▲) and 1000 (■) $\mu g\,kg^{-1}$; (c) $1000\,\mu g\,kg^{-1}$ (●). Values are means, with vertical lines showing s.e.mean, from 4–6 experiments.

tance or decreases in diastolic blood pressure produced by isoprenaline (see Table 2). Similarly, methysergide ($1000\,\mu g\,kg^{-1}$ i.v.) did not affect the vasodepressor action of isoprenaline and in three out of four experiments it had little effect on the isoprenaline-induced decrease in carotid vascular resistance. In a fourth experiment methysergide produced a seven fold rightward displacement of the isoprenaline dose-response curve for carotid vasodilatation. The mean data are shown in Table 2.

**Table 2** Antagonistic activity of methiothepin and methysergide on the cardiovascular actions of 5-hydroxytryptamine (5-HT), 5-carboxamidotryptamine (5-CT) and isoprenaline in anaesthetized cats

| *Antagonist (dose $\mu g\,kg^{-1}$ i.v.)* | *Agonist* | *Agonist dose-ratios Increase in heart rate* | *Decrease in carotid vascular resistance* | *Decrease in diastolic blood pressure* |
|---|---|---|---|---|
| Methiothepin (100) | 5-HT | 31 (18–54) | | — |
| Methiothepin (100) | 5-CT | 65 (22–186) | 130 (78–215) | 34 (10–111) |
| Methiothepin (300) | Isoprenaline | 0.8 (0.5–1.1) | 1.5 (0.6–3.0) | 1.2 (0.3–4.2) |
| Methysergide (1000) | 5-HT | 8 (4–15) | — | — |
| Methysergide (1000) | 5-CT | 19 (13–26) | 21 (9–48) | 25 (5–129) |
| Methysergide (1000) | Isoprenaline | 0.8 (0.5–1.5) | 2.1 (0.3–18.1) | 0.7 (0.2–2.3) |

Values are geometric means (95% confidence limits) from 4–6 experiments with each agonist.

## Discussion

The aim of this study was to characterize the 5-HT receptors mediating bronchoconstriction, tachycardia, vasodepression and vasodilatation in anaesthetized cats. Since the effects of 5-HT on the cardiovascular system of the cat are complex (see Erspamer, 1966) and result from activation of a number of 5-HT receptor types (see Humphrey, 1983), we have examined not only the profile of some 5-HT antagonists, but also the pharmacological activity of 5-CT which has been shown to be a selective agonist at 5-HT receptors mediating relaxation of smooth muscle *in vitro* (Feniuk *et al.*, 1984).

The ability of 5-HT to produce bronchoconstriction in a variety of species including the cat has long been known (Reid & Rand, 1952; Herxheimer, 1953; Konzett, 1956; Reiche & Frey, 1983), but few quantitative studies characterizing the 5-HT receptor mediating this effect have been carried out. In this study, 5-HT produced dose-related bronchoconstriction and this effect was potently and selectively antagonized by methiothepin, methysergide and ketanserin. A direct comparison of the potency of these antagonists was not possible since methiothepin clearly produced an unsurmountable antagonism of the 5-HT-induced bronchoconstriction whilst the antagonism produced by ketanserin appeared surmountable. Nevertheless, all three antagonists were effective in doses as low as $10\,\mu g\,kg^{-1}$ i.v. The results suggest that the 5-HT receptor mediating bronchoconstriction in the cat can be characterized as a 5-$HT_2$-receptor on the basis that all three antagonists show a high affinity for 5-$HT_2$ recognition sites identified from ligand binding studies (Leysen *et al.*, 1981). Further, more circumstantial evidence for the involvement of 5-$HT_2$-receptors comes from the lack of bronchoconstrictor action of 5-CT. Thus, we have previously demonstrated that 5-CT is a much weaker agonist than 5-HT at 5-$HT_2$ receptors which mediate contraction of the rabbit isolated aorta (Feniuk *et al.*, 1981; Humphrey *et al.*, 1982). In the present study, 5-CT in doses up to $1\,\mu g\,kg^{-1}$ was devoid of bronchoconstrictor action though higher doses were not used because of its marked cardiovascular actions (see below). The conclusion that 5-$HT_2$-receptors mediate the bronchoconstrictor action of 5-HT has been reached by others in experiments *in vitro* (Van Nueten *et al.*, 1983).

The most interesting findings obtained from the present study result from our attempts to characterize the 5-HT receptor mediating the increase in heart rate, as well as vasodepression and carotid vasodilatation, by using the selective 5-HT receptor agonist, 5-CT. Although the effect of 5-HT on the heart rate of the intact animal is complex involving activation of vagal fibres (Paintal, 1973; Fozard, 1984) as well as the release of catecholamines (Trendelenburg, 1960; Fozard & Moborak Ali, 1978), our study was not complicated by such mechanisms, since the cats were both bilaterally vagosympathectomised and pretreated with a high dose of the β-adrenoceptor blocking agent, propranolol. Under these conditions, both 5-HT and 5-CT produced dose-related increases in heart rate. Interestingly, 5-CT was about fifty times more active than 5-HT at causing tachycardia which is remarkably similar to the relative potency of these two compounds at causing relaxation of some isolated

smooth muscle preparations (Feniuk *et al.*, 1984). That this tachycardia occurred in vagotomised cats and in the presence of β-adrenoceptor blockade suggests that the effect of 5-HT and 5-CT was mediated directly on the myocardium and not as a consequence of neuronal depolarization or reflex activity. Furthermore, the specific antagonistic action of some 5-HT receptor blocking agents suggests that the tachycardia was mediated through specific 5-HT receptors. A similar conclusion was reached by Trendelenburg (1960) using cat isolated atria, but a detailed analysis of the receptor mechanism involved was undoubtedly hindered by the lack of specific and selective 5-HT antagonists at his disposal. Nevertheless, Trendelenburg (1960) suggested that the 5-HT receptor mediating tachycardia was a D-receptor since the tachycardia could be antagonized by (+)-lysergic acid diethylamide (LSD). It is, however, clear that D-receptors for 5-HT are not a homogeneous group (Feniuk, 1984); furthermore, LSD appears capable of binding to at least two types of 5-HT recognition site (Peroutka & Snyder, 1979; Leysen *et al.*, 1981). In our experiments, both methiothepin ($10-100\,\mu g\,kg^{-1}$ i.v.) and methysergide ($100-1000\,\mu g\,kg^{-1}$ i.v.) produced a dose-dependent and selective antagonism of the tachycardia caused by both 5-HT and 5-CT. Furthermore, although methiothepin was more potent than methysergide in this respect, neither antagonist produced a preferential blockade of either the 5-HT- or 5-CT-induced tachycardia (see Table 2) suggesting that both agonists are acting at a common receptor type. The lack of an antagonistic action of ketanserin in doses up to $1000\,\mu g\,kg^{-1}$ i.v., together with the high agonistic potency of 5-CT, clearly differentiates the 5-HT receptor mediating tachycardia from the 5-$HT_2$-receptor mediating bronchoconstriction.

In marked contrast to the complex nature of the vascular effects of 5-HT, 5-CT produced decreases in diastolic blood pressure and carotid arterial vascular resistance in similar doses to those causing tachycardia. Furthermore, since these effects occurred in animals which had been pretreated with propranolol, it is highly unlikely that they were due to stimulation of β-adrenoceptors. In general, the profile of the antagonistic actions of methiothepin, methysergide and ketanserin was similar to their effects against the 5-HT- and 5-CT-induced tachycardia. Low doses of methiothepin ($30-100\,\mu g\,kg^{-1}$ i.v.) and higher doses of methysergide ($300-1000\,\mu g\,kg^{-1}$ i.v.) dose-dependently and selectively antagonized the vasodepressor and carotid arterial vasodilator action of 5-CT. In addition, a high dose of ketanserin had no antagonistic action against the vasodepressor action of 5-CT although it caused a small (less than two fold) rightward displacement of the dose-response curve for the effect of 5-CT on carotid arterial vascular resistance. The mechanism of this small antagonistic effect of ketanserin is not known. It is unlikely to be due to blockade of 5-$HT_2$-receptors (compare antagonism of 5-HT-induced bronchoconstriction). Nevertheless, it is clear that methiothepin and methysergide were much more potent in antagonizing the vasodilator and vasodepressor actions of 5-CT. Like the 5-HT receptor mediating increases in heart rate, the 5-HT receptor mediating vasodilatation and vasodepression can be clearly differentiated from the 5-$HT_2$-receptor mediating bronchoconstriction by the lack of, or weak, antagonistic action of ketanserin and the high agonistic potency of 5-CT.

What then is the nature of the 5-HT-receptor mediating tachycardia, vasodilatation and vasodepression? We believe that the same 5-HT receptor mediates all three responses. This contention is based upon three pieces of experimental evidence. Firstly, neither methiothepin nor methysergide showed any preferential antagonistic action with regard to the 5-HT- or 5-CT-induced changes in heart rate, blood pressure or carotid vascular resistance (Table 2). Secondly, the rank order of antagonist potency was identical in all three cases i.e. methiothepin > methysergide >> ketanserin (virtually inactive). Finally, 5-CT was about fifty times more potent than 5-HT at producing both tachycardia (this study) and relaxation of isolated vascular smooth muscle (Feniuk *et al.*, 1983; 1984). Interestingly, the relaxant response of isolated vascular smooth muscle to 5-HT and 5-CT, like that produced by β-adrenoceptor stimulation, appears to be associated with an elevation of intracellular cyclic AMP (Trevethick *et al.*, 1984; 1986).

The general profile of action of both the agonists and antagonists at the 5-HT receptor mediating tachycardia, vasodilatation and vasodepression bears many similarities to the characteristics of the 5-$HT_1$ recognition site identified from ligand binding studies. Leysen *et al.* (1981) have described an order of antagonist potency of methiothepin > methysergide >> ketanserin at 5-$HT_1$ binding sites in rat frontal cortex. Furthermore, 5-CT is the most potent 5-HT receptor agonist yet identified which is capable of displacing 5-HT from the 5-$HT_1$ binding site in rat cerebral cortex (Engel *et al.*, 1983). However, it is now clear that the 5-$HT_1$ recognition site is not a homogeneous population of binding sites and reflects the presence of at least two subtypes (Pedigo *et al.*, 1981). Furthermore, although propranolol has some affinity for the 5-$HT_1$ binding site (Nahorski & Willcocks, 1983), it does not antagonize the actions of 5-HT which are mimicked by 5-CT in cardiac or vascular smooth muscle *in vitro* or *in vivo* (this study; Feniuk *et al.*, 1983; 1984; unpublished observations). On the basis of present knowledge it would be unwise to attempt to correlate the results from our functional studies with one of the subtypes identified from the

ligand binding studies. It does, however, seem reasonable to describe the 5-HT receptor mediating tachycardia, vasodilatation and vasodepression as '5-$HT_1$-like'.

In conclusion, our findings indicate that 5-$HT_2$-receptors mediate bronchoconstriction in the anaesthetized cat and that this receptor can be characterized by the high antagonistic potencies of methiothepin, methysergide and ketanserin. The '5-$HT_1$-like' receptor which appears to mediate tachycardia, vasodilatation and vasodepression can be characterized by the high agonistic potency of 5-CT and a rank order of antagonist potency of methiothepin > methysergide >> ketanserin (virtually inactive). Finally, 5-CT is a highly selective 5-HT receptor agonist and will be useful for the characterization of 5-HT receptors both *in vivo* and *in vitro*.

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