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5-Carboxamide tryptamine, a compound with high affinity for 5-hydroxytryptamine$_1$ binding sites, dilates arterioles and constricts arteriovenous anastomoses

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1 The effects of 5-carboxamide tryptamine, which activates non-5-hydroxytryptamine$_2$-'atypical' receptors for 5-hydroxytryptamine (5-HT) in the dog saphenous vein, was studied on the complete distribution of cardiac output and common carotid blood flow in anaesthetized pigs. The drug was infused for 10 min at the rate of 0.025, 0.1 and 0.4 $\mu g\,kg^{-1}\,min^{-1}$ either intravenously (cardiac output distribution) or intra-arterially (carotid distribution).

2 5-Carboxamide tryptamine decreased arterial blood pressure due to a reduction of cardiac output. This reduction was confined to its arteriovenous anastomotic component; the component used for the tissue perfusion (nutrient part) in fact increased. Similar changes were observed in the carotid blood flow distribution.

3 Vasodilatation was observed in several tissues, but the skin, ears and stomach responded most prominently.

4 The effects of 5-carboxamide tryptamine on the carotid distribution were not significantly modified by cyproheptadine (1 $mg\,kg^{-1}$).

5 It is concluded that, like 5-HT, 5-carboxamide tryptamine constricts arteriovenous anastomoses and dilates arterioles by activating non-5-HT$_2$-'atypical' receptors.

6 These 'atypical' 5-HT receptors appear to be of the 5-HT$_1$ type since both 5-carboxamide tryptamine and BEA 1654, a new piperazine derivative, produced similar vascular effects in the carotid bed of the pig and also showed a high and selective affinity for the 5-HT$_1$ binding sites.

Introduction

It has been repeatedly observed that drugs which normally block the effects of 5-hydroxytryptamine (5-HT) on a variety of tissues are not particularly effective at antagonizing the reduction in the carotid blood flow caused by this amine (Saxena *et al.*, 1971; Saxena, 1972; Saxena & de Vlaam-Schluter, 1974; Spira *et al.*, 1976; Mylecharane *et al.*, 1978). More recently, we have found that 5-HT has heterogeneous effects in the different vascular segments within the carotid arterial bed (Saxena & Verdouw, 1982). Although total carotid blood flow may or may not decrease, 5-HT causes a complete redistribution of carotid arterial blood flow because large conducting arteries (Heistad *et al.*, 1976) and cranial extracerebral arteriovenous anastomoses constrict but nutrient vessels (arterioles), particularly those of the skin and ear, dilate (Saxena & Verdouw, 1982). The 5-HT$_2$-antagonists, cyproheptadine (Saxena & Verdouw, 1982), methysergide (Saxena & Verdouw, 1984b), ketanserin and WAL 1307 (Verdouw *et al.*, 1984a), completely reverse the effect of 5-HT on large arteries (as indicated by an increase in total carotid blood flow), but they only partially reduce the vasoconstrictor effect on arteriovenous anastomoses, and even enhance arteriolar vasodilatation. Therefore, it appears that, while the large conducting arteries have 5-HT$_2$-(Cohen *et al.*, 1981; Müller-Schweinitzer & Engel, 1983) or, in older terminology, D-(Gaddum & Picarelli, 1957) receptors, mainly 'atypical' receptors for 5-HT are present in the arteriovenous anastomoses and arterioles (Saxena & Verdouw, 1982; 1984b).

Atypical receptors, for which no specific antagonists are as yet available, are also present on both pre- and post-synaptic sites in the dog isolated saphenous vein (Apperley *et al.*, 1980). Subsequently, the same group of investigators (Feniuk *et al.*, 1981) compared

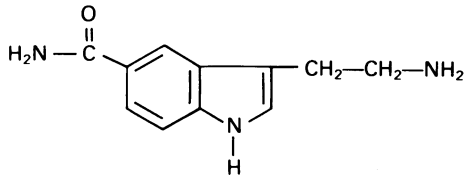

Figure 1 Chemical structure of 5-carboxamide tryptamine.

the activity of some chemical analogues of 5-HT on the dog saphenous vein and on the rabbit aorta; the latter contains the usual 5-HT_2-receptors (Apperley *et al.*, 1976). One of the compounds, 5-carboxamide tryptamine (Figure 1) was not only less effective (maximal effect being less than 60% of that of 5-HT) but also 26 times less potent than 5-HT on the rabbit aorta. On the other hand, 5-carboxamide tryptamine was three times as potent as 5-HT on both the pre- and post-synaptic 5-HT receptors on the dog saphenous vein. In this paper, we describe the cardiovascular effects of 5-carboxamide tryptamine, particularly on the distribution of arterial blood flow into nutritional (capillary) and non-nutritional (arteriovenous anastomotic) circuits in the pig.

Methods

General

Three series of experiments were performed. In the first series the effects of i.v. infusions of 5-carboxamide tryptamine on the distribution of cardiac output, determined by injecting radioactive microspheres into the left atrium, were assessed. In a second group of animals local infusions were used to evaluate the effects of 5-carboxamide tryptamine on the distribution of flow in the common carotid artery. The same procedure was repeated in a third group after blockade of 5-HT_2-receptors with cyproheptadine (1 mg kg^{-1}). In these two series of experiments the microspheres were injected into the same artery into which the drug was infused.

Experimental set-up

After an overnight fast young Yorkshire pigs (26 ± 2 kg) were initially sedated with 120 mg azaperone (Stresnil) i.m., and 120–150 mg metomidate (Hypnodil) i.v., intubated and connected to a respirator for intermittent positive pressure ventilation with a mixture (1:2) of oxygen and nitrous oxide. A continuous i.v. infusion of pentobarbitone sodium (12 mg kg^{-1} h^{-1}, was made during the course of the experiment to maintain anaesthesia. Respiratory rate and tidal volume were adjusted or sodium bicarbonate (8.4%) infused to keep arterial blood gases within normal limits. The body temperature of the animals was kept around 37°C with an electric blanket.

In the first series of experiments a thoracotomy was performed and a cannula was inserted into the left atrial appendage for the injection of microspheres, while a 7F catheter was placed in the mammary artery for the recording of aortic blood pressure and the withdrawal of reference blood samples during microsphere injection. Cardiac output measurements were made in duplicate using a thermodilution catheter inserted via a femoral vein. In addition, one external jugular vein was cannulated without obstructing the flow of blood. During microsphere injections jugular venous blood was withdrawn for the determination of microsphere shunting (Johnson & Saxena, 1978).

In the animals which received the intracarotid infusions of 5-carboxamide tryptamine both common carotid arteries were dissected free and vagosympathectomy was performed bilaterally to avoid reflex influences on the carotid circulation. After removing hubs, two 0.5 mm (external diameter) needles, connected to suitable polythene tubing, were inserted into one of the carotid arteries for the administration of microspheres and 5-carboxamide tryptamine. Blood flow in this artery was measured with a precalibrated flow probe connected to a sine-wave electromagnetic blood flow meter (Skalar, Delft). Arterial blood pressure was recorded with a Statham pressure transducer via a catheter inserted into the left femoral artery.

Distribution of cardiac output and common carotid blood flow

Injection of radioactive microspheres The distribution of cardiac output was determined by injecting a batch ($1-2 \times 10^6$) of microspheres (15 ± 1 (s.d.) μm) labelled with ^{141}Ce, ^{113}Sn, ^{103}Ru, ^{95}Nb or ^{46}Sc (NEN Chemicals GmbH, Dreieich, West Germany) into the left atrium. Aggregation of the microspheres was prevented by adding a drop of Tween 80 and by mechanical agitation before injection. Arterial (12 ml min^{-1} for 90 s) and jugular venous (5 ml min^{-1} for 2 min) blood samples were withdrawn to calibrate flow measurements and to determine jugular venous shunting (see Johnston & Saxena, 1978), respectively. An equivalent volume of haemaccel was administered to replace blood loss. The distribution of carotid blood flow into nutrient and non-nutrient fractions was determined by directly injecting the microspheres ($1-2 \times 10^5$), in 0.5 ml saline over a 15–20 s period against the direction of flow, into the common carotid artery.

Counting of radioactivity At the end of each experiment the animal was killed with an overdose of pentobarbitone sodium. The various tissues were dissected out, weighed and placed in vials. The radioactivity in these vials and in the blood samples was counted for 5–10 min in a γ-scintillation counter (Packard, model 5986) equipped with a multichannel analyser (Contrac) using suitable windows for discriminating the different isotopes (Saxena *et al.*, 1980).

Calculations The microsphere and other data were processed by a PDP-11/70 computer using a set of especially developed programmes (Saxena *et al.*, 1980). The fraction of cardiac output distributed to the various organs ($\dot{Q}_{tis}$) was calculated as:

$$\dot{Q}_{tis}\ (ml\ min^{-1}) = (I_{tis}/I_{art}) \times \dot{Q}_{art} \text{ and}$$
$$\dot{Q}_{tis}\ (\%) = (\dot{Q}_{tis}/CO) \times 100,$$

where I_{tis} and I_{art} are, respectively, the radioactivity (c.p.m.) in that organ and that of the arterial blood sample, while $\dot{Q}_{art}$ is the rate of withdrawal of blood samples and CO is cardiac output in ml min^{-1}. The shunting of microspheres into the external jugular venous blood ($\dot{Q}_{ava}$) was calculated by corresponding formulae:

$$\dot{Q}_{ava}\ (ml\ min^{-1}) = (I_{ven}/I_{art}) \times \dot{Q}_{art} \text{ and}$$
$$\dot{Q}_{ava}\ (\%) = (I_{ven}/I_{art}) \times (\dot{Q}_{art}/\dot{Q}_{ven}) \times 100,$$

where I_{ven} and $\dot{Q}_{ven}$ are the radioactivity (c.p.m.) and the withdrawal rate (ml min^{-1}), respectively, of the jugular venous blood.

The amount of carotid blood distributed to the individual tissues ($\dot{Q}_{tis[car]}$) was calculated by:

$$\dot{Q}_{tis[car]}\ (ml\ min^{-1}) = (I_{tis}/I_{tot}) \times \dot{Q}_{car} \text{ and}$$
$$\dot{Q}_{tis[car]}\ (\%) = (I_{tis}/I_{tot}) \times 100,$$

where I_{tis} and I_{tot} are, respectively, the radioactivity (c.p.m.) in a particular tissue and that detected in all tissues collectively and $\dot{Q}_{car}$ is carotid blood flow (ml min^{-1}) (see Saxena & Verdouw, 1982). Tissue vascular conduction was calculated by dividing respective blood flow values by mean arterial blood pressure.

The values determined for lungs, when microspheres were injected into the carotid artery, represent the arteriovenous anastomotic part of the carotid circulation. Although, in the case of left atrial injection the lungs receive microspheres via both peripheral arteriovenous anastomoses and bronchial arteries, the contribution via the latter route appears to be only about 1% (Baile *et al.*, 1982). Thus, even in this case, the values for 'lung blood flow' can be used as an index of peripheral arteriovenous anastomotic flow (i.e. non-nutrient part of cardiac output). The nutrient part of cardiac output was calculated by subtracting 'lung flow' from cardiac output.

Experimental protocol

In all experiments the baseline values were obtained after the preparation had been in a stable haemodynamic condition for at least 45 min after completion of the surgical procedures. The measurements consisted of recording the heart rate, mean arterial blood pressure and cardiac output or carotid blood flow, while a batch of microspheres was injected into the left atrium (first series) or into the carotid artery (second and third series). Subsequently, all measurements were

Table 1 Heart rate and mean arterial blood pressure changes produced by 5-carboxamide tryptamine in three series of experiments.

	Series	*5-Carboxamide tryptamine* (μg kg^{-1} min^{-1})				*Recovery*
		0	0.025	0.1	0.4	
HR	1	91±3	87±5	85±5	85±3	81±4*
	2	119±8	111±6	101±4*	97±4*	
	3	104±7	95±3	87±3*	83±3*	
MAP	1	10.4±0.4	9.7±0.3	7.5±0.2*	6.6±0.3*	8.2±0.6*
	2	10.9±0.8	9.9±0.3	8.2±0.5*	6.9±0.3*	
	3	12.0±0.7	11.2±0.7	8.4±0.4*	6.2±0.3*	

5-Carboxamide tryptamine was given intravenously to open chested pigs (series 1), whereas the drug was infused into the common carotid artery in untreated (series 2) and cyproheptadine (1 mg kg^{-1}) pretreated (series 3) animals. HR, Heart rate (beats min^{-1}), MAP, mean arterial blood pressure (kPa); *significantly different ($P<0.05$) from the value before the administration of 5-carboxamide tryptamine. Values for HR and MAP before the administration of cyproheptadine were 118 ± 7 beats min^{-1} and 12.6 ± 0.3 kPa, respectively.

repeated after (i) consecutive 10 min i.v. infusions of 5-carboxamide tryptamine, 0.025, 0.1 and 0.4 $\mu g\ kg^{-1}\ min^{-1}$ and after a recovery period of 60 min (series 1, $n=7$); (ii) consecutive 10 min intracarotid infusions of 5-carboxamide tryptamine, 0.025, 0.1 and 0.4 $\mu g\ kg^{-1}\ min^{-1}$ (series 2, $n=7$); or (iii) cyproheptadine (1 $mg\ kg^{-1}$) and, then 30 min later, consecutive 10 min intracarotid infusions of 5-carboxamide tryptamine, 0.025, 0.1 and 0.4 $\mu g\ kg^{-1}\ min^{-1}$ (series 3, $n=7$).

Data presentation and statistical evaluation

Except where otherwise stated, all data in the text and illustrations are presented as mean ± s.e.mean. The significance of the differences between the variables was evaluated by Duncan's new multiple-range test once an analysis of variance (randomized block design) had revealed that the samples represented different populations (Steel & Torrie, 1980). Furthermore, in the cyproheptadine pretreated animals the changes obtained after each dose of 5-carboxamide tryptamine were compared with those in the untreated animals using Student's t test. A P value of 0.05 or less (two-tailed) was considered to be statistically significant.

Drugs

Apart for the anaesthetics, the drugs used in this study were 5-carboxamide tryptamine hydrogen maleate and cyproheptadine hydrochloride. The dose of 5-carboxamide tryptamine is mentioned in terms of the base and that of cyproheptadine in terms of the salt.

Results

Arterial blood gases

The baseline values for arterial blood gases in the experiments of series 1, 2 and 3 were, respectively: pH,

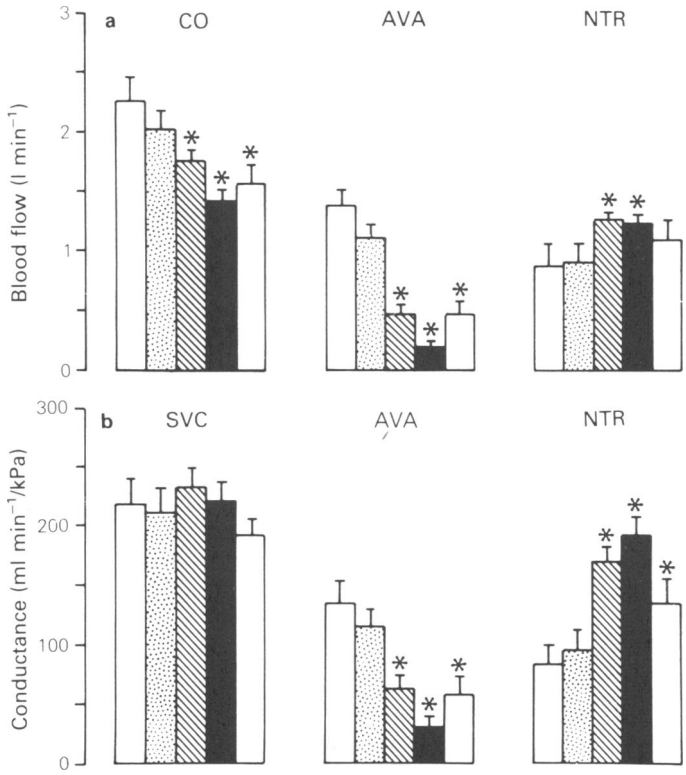

Figure 2 Effect of i.v. infusions of 5-carboxamide tryptamine, 0.025 (▨), 0.1 (▧), and 0.4 (■) $\mu g\ kg^{-1}\ min^{-1}$, on the fractionation of (a) cardiac output (CO) and (b) systemic vascular conductance (SVC) into non-nutrient (arteriovenous anastomotic) and nutrient (NTR) parts. The open columns (□) before and after the drug columns represent baseline values and those obtained 60 min after stopping the last infusion of 5-carboxamide tryptamine, respectively. * $P<0.05$ vs. baseline values.

7.37 ± 0.01, 7.43 ± 0.03 and 7.35 ± 0.01; P_{CO_2}, 38 ± 2, 37 ± 2 and 40 ± 2 mmHg; P_{O_2}, 159 ± 7, 165 ± 14 and 161 ± 5 mmHg; and oxygen saturation, 97.4 ± 0.3, 97.3 ± 0.3 and 99.1 ± 0.1%. These values were not appreciably changed by either cyproheptadine (1 mg kg^{-1}; series 3) or by any of the three doses of 5-carboxamide tryptamine.

Heart rate and mean arterial blood pressure

The values for heart rate and mean arterial blood pressure in the three series of pigs, before and after infusions of 5-carboxamide tryptamine, are shown in Table 1. Intravenous administration of 5-carboxamide tryptamine did not affect heart rate, but after intracarotid infusions of the two highest doses (0.1 and 0.4 μg kg^{-1} min^{-1}) heart rate decreased in both untreated and cyproheptadine-pretreated animals. The same two doses also decreased mean arterial blood pressure significantly in all three series of experiments. Cyproheptadine (1 mg kg^{-1}) slightly decreased heart rate, but did not change the blood pressure.

Cardiac output and systemic vascular conductance

Figure 2 shows the effects of 5-carboxamide tryptamine on cardiac output and systemic vascular conductance and their fractionation into nutrient (tissue) and non-nutrient (arteriovenous anastomotic) parts. It was noted that, during the period when baseline values were obtained, a major part (1.38 ± 0.14 l min^{-1}) of the total cardiac output (2.26 ± 0.21 l min^{-1}) bypassed the tissues via arteriovenous anastomoses. Consequently, only 0.89 ± 0.19 l min^{-1} of the total cardiac output was used for the nutrition of the tissues. 5-Carboxamide tryptamine reduced cardiac output in a dose-dependent manner. This reduction was parallel to that seen in arterial blood pressure (see Table 1) and, hence, systemic vascular conductance remained unchanged. Figure 2 further demon-

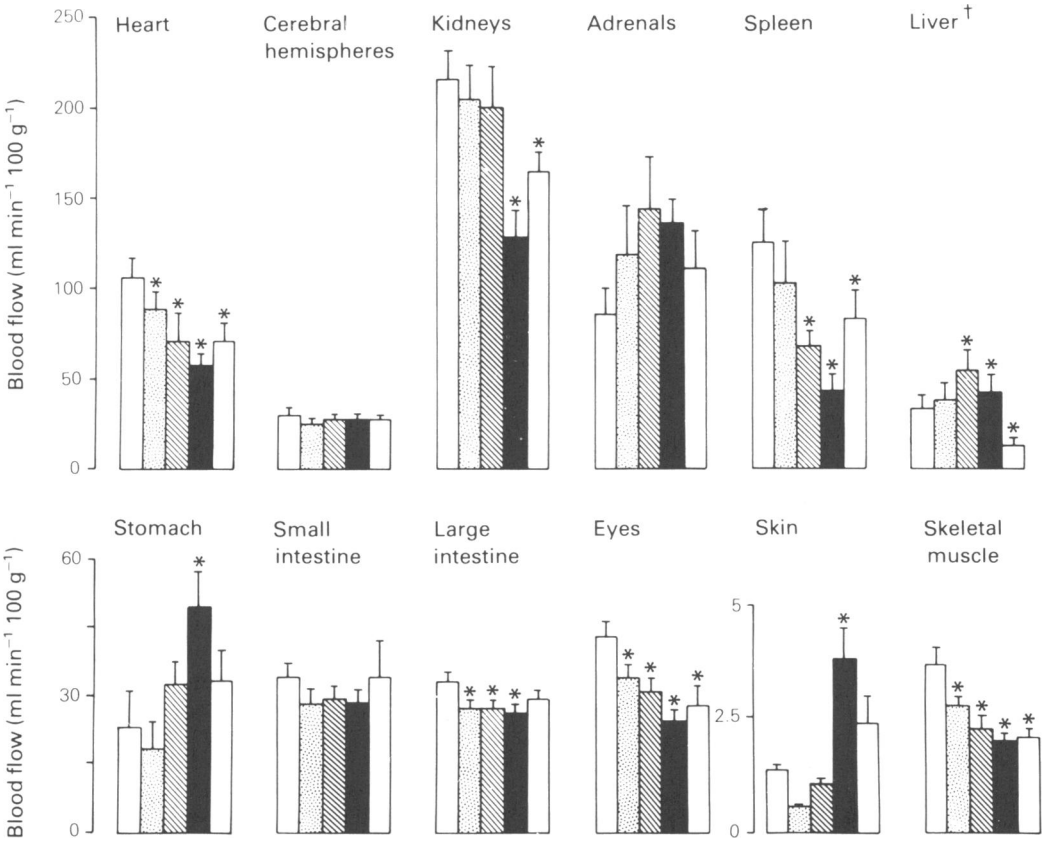

Figure 3 Effect of i.v. infusions of 5-carboxamide tryptamine, 0.025 (▨), 0.1 (▧), and 0.4 (■) μg kg^{-1} min^{-1}, on regional blood flows. The open columns (□) before and after the drug columns represent baseline values and those obtained 60 min after stopping the last infusion of 5-carboxamide tryptamine, respectively. † Hepatic artery. * $P<0.05$ vs. baseline values.

strates that the reduction in cardiac output was entirely at the expense of the arteriovenous anastomotic fraction and that the nutrient fraction of cardiac output in fact increased. The calculated vascular conductance of the non-nutrient (arteriovenous anastomotic) bed decreased substantially while that of the nutrient bed, particularly after the two highest doses of 5-carboxamide tryptamine, increased. Only partial recovery was noticed 60 min after stopping the drug infusion.

Regional blood flow and conductances

The effect of 5-carboxamide tryptamine on regional blood flow is shown in Figure 3. Perfusion of some tissues – heart, kidneys (highest dose), spleen (two highest doses), large intestine, eyes and skeletal muscle – decreased, but that of others either increased (liver, stomach and skin) or remained unchanged (Cerebral hemispheres, adrenals and small intestine). With the highest dose of the drug, skin all over the body became bright red in colour. Although blood flow measurements 60 min after stopping the infusion tended to return towards the respective baseline values, the recovery was not complete in many tissues (Figure 3).

As shown in Figure 4 regional vascular conductances were not significantly changed by the lowest dose (0.025 $\mu g\,kg^{-1}\,min^{-1}$, i.v.) of 5-carboxamide tryptamine. In the heart, eyes and skeletal muscle the higher doses (0.1 and 0.4 $\mu g\,kg^{-1}\,min^{-1}$, i.v.) were also ineffective. The drug, however, decreased vascular conductance in kidneys (only the middle dose), cerebral hemispheres, adrenals, liver, stomach, intestines and the skin. The vasodilator responses, calculated as % increase from the baseline values, were most marked in the skin (396 ± 109%) and stomach (394 ± 116%), which was followed by adrenals (194 ± 54%), liver (161 ± 38%), cerebral hemispheres (45 ± 12%), kidneys (35 ± 14%), and small (32 ± 12%)

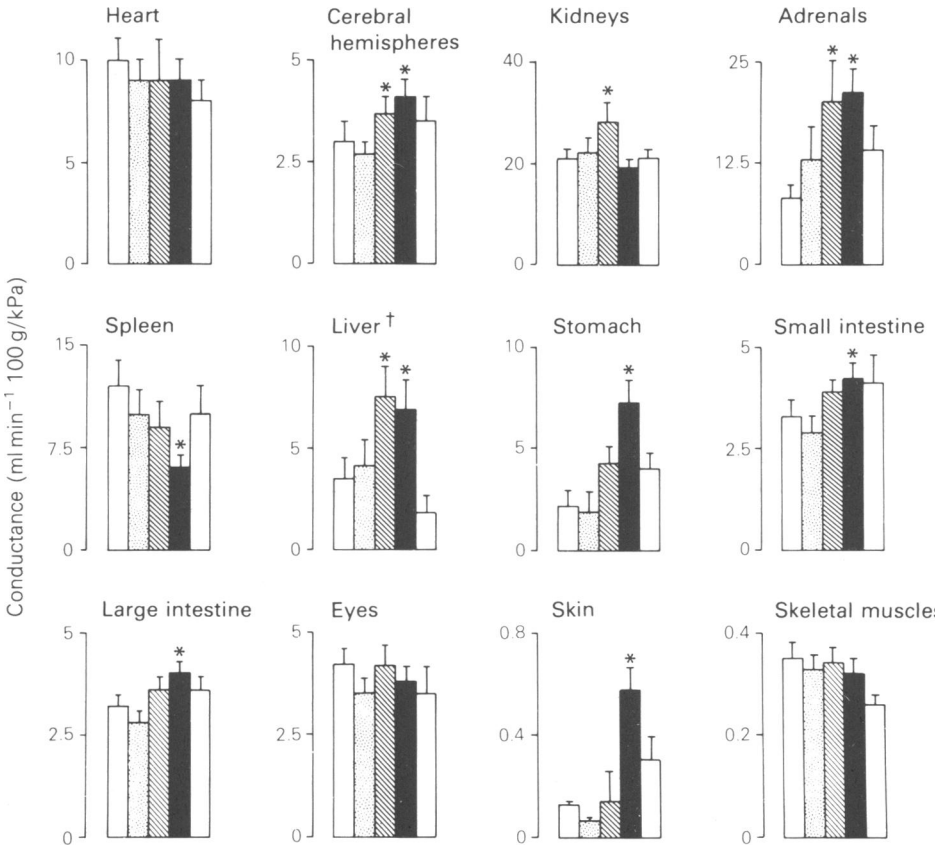

Figure 4 Effect of i.v. infusions of 5-carboxamide tryptamine, 0.025 (▨), 0.1 (▧), and 0.4 (■) $\mu g\,kg^{-1}\,min^{-1}$ on regional vascular conductances. The open columns (□) before and after the drug columns represent baseline values and those obtained 60 min after stopping the last infusion of 5-carboxamide tryptamine, respectively. † Hepatic artery. * $P<0.05$ vs. baseline values.

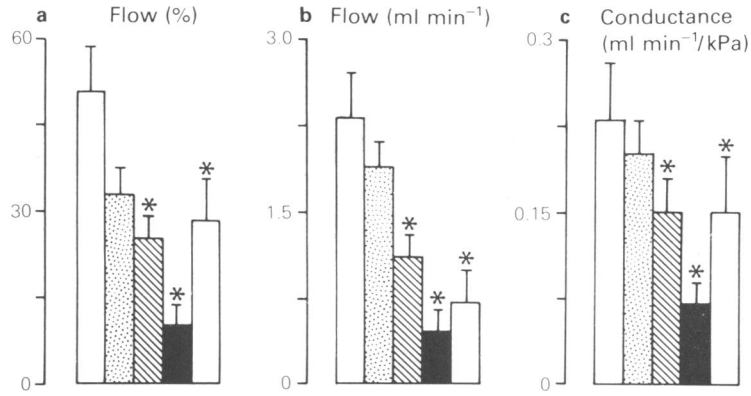

Figure 5 Effect of i.v. infusions of 5-carboxamide tryptamine, 0.025 (▨), 0.1 (▧), and 0.4 (■) $\mu g\,kg^{-1}\,min^{-1}$ on the shunting of blood via the arteriovenous anastomoses into the jugular vein. The open columns (□) before and after the drug columns represent baseline values and those obtained 60 min after stopping the last infusion of 5-carboxamide tryptamine, respectively. * $P<0.05$ vs. baseline values.

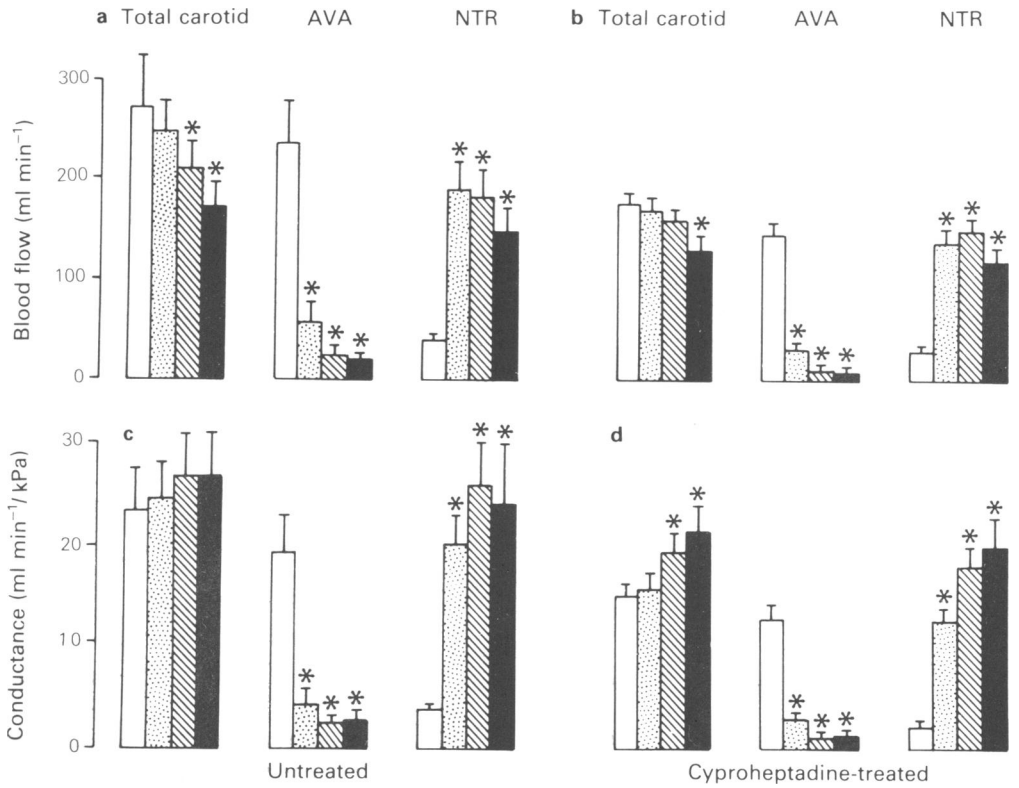

Figure 6 Effect of intracarotid infusions of 5-carboxamide tryptamine on the fractionation of total common carotid blood flow (a and b) and vascular conductance (c and d) into non-nutrient (arteriovenous anastomotic) and nutrient (NTR) parts in untreated (a and c) and cyproheptadine-treated (b and d) pigs. (□) Baseline values; 5-carboxamide tryptamine ($\mu g\,kg^{-1}\,min^{-1}$): (▨) 0.025, (▧) 0.1, and (■) 0.4. * $P<0.05$ vs. baseline values. The % change by 5-carboxamide tryptamine in the two groups of animals was not significantly different.

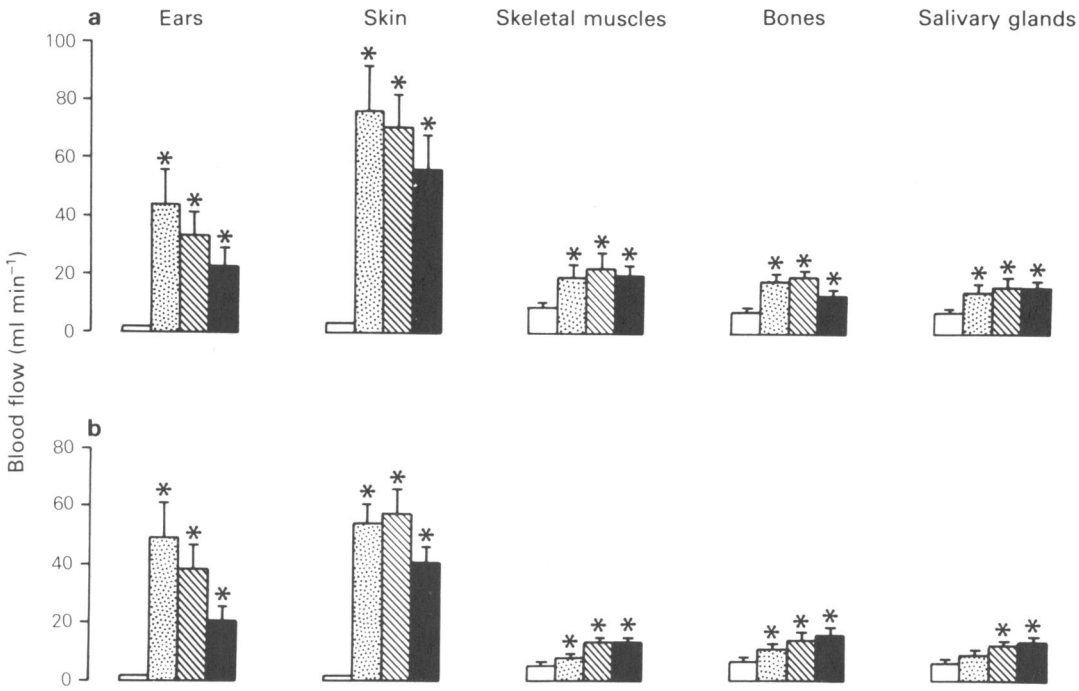

Figure 7 Effect of intracarotid infusions of 5-carboxamide tryptamine on the regional distribution of total common carotid blood flow to some extracerebral structures in untreated (a) and cyproheptadine-treated (b) pigs. (□) Baseline values: 5-carboxamide tryptamine ($\mu g\,kg^{-1}\,min^{-1}$): (▨) 0.025, (▧) 0.1, and (■) 0.4. * $P<0.05$ vs. baseline values. The % change by 5-carboxamide tryptamine in the two groups of animals was not significantly different.

and large (27 ± 9%) intestines. The spleen was the only organ where the vascular conductance decreased after the highest dose of 5-carboxamide tryptamine. Measurements made after 60 min did not significantly differ from those obtained during the baseline period.

Jugular venous shunting

About 50% of the jugular venous blood represented that part which had passed through arteriovenous anastomoses (Figure 5). Administration of 5-carboxamide tryptamine (0.1 and $0.4\,\mu g\,kg^{-1}\,min^{-1}$, i.v.) decreased the microsphere shunting and the calculated vascular conductance of the arteriovenous anastomoses draining into the jugular vein.

Carotid blood flow distribution

As described earlier in pigs (Saxena & Verdouw, 1982; 1984; Verdouw *et al.*, 1984a) a large fraction (83 ± 2%) of the common carotid artery blood flow (232 ± $27\,ml\,min^{-1}$) was shunted through the cranial arteriovenous anastomoses during the control period (baseline measurements; $n=14$). The extracerebral tissues of the head received 15.4 ± 1.4% of the carotid blood flow and only 1.5 ± 0.5% was used for perfusion of the brain. Less than 0.01% of the microspheres injected into the common carotid artery were detected in the systemic tissues (heart or kidneys).

The effects of intracarotid infusions of 5-carboxamide tryptamine (0.025, 0.1 and $0.4\,\mu g\,kg^{-1}\,min^{-1}$) on the fractionation of total carotid blood flow and conductance into arteriovenous anastomotic (non-nutrient) and capillary (tissue; nutrient) parts is shown in Figure 6. In both untreated and cyproheptadine-treated animals the responses to 5-carboxamide tryptamine were rather similar. Total carotid blood flow decreased significantly after the two highest doses in the untreated animals and after the highest dose in the cyproheptadine-treated animals, but arteriovenous anastomotic flow decreased and nutrient flow increased right from the first infusion in both groups.

Regional carotid flow distribution showed that a number of tissues (ears, skin, skeletal muscles, bones and salivary glands) received more blood after 5-carboxamide tryptamine (Figure 7). The responses in the ear and skin, where the maximum effect was already achieved with the first dose, were most marked and their colour changed and became bright red. With the highest infusion rate, skin of the other regions of the

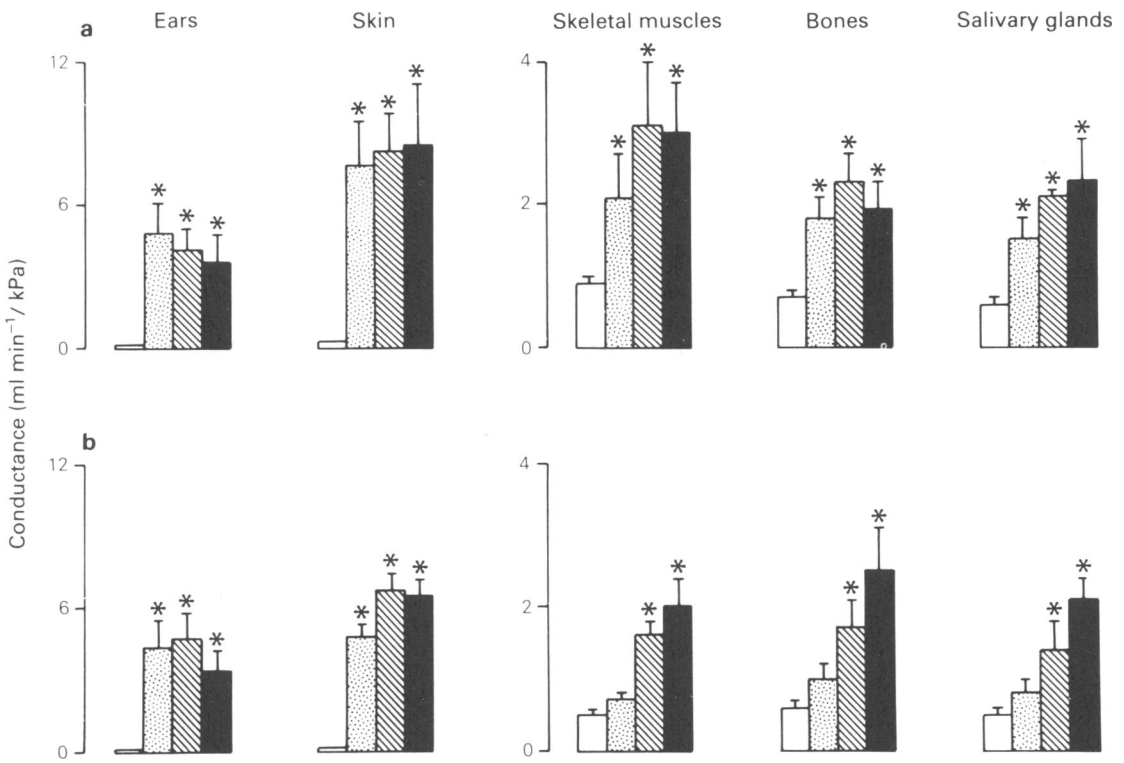

Figure 8 Effect of intracarotid infusions of 5-carboxamide tryptamine on the regional conductance in some extracerebral tissues perfused by the common carotid artery in untreated (a) and cyproheptadine-treated (b) pigs. (□) Baseline values: 5-carboxamide tryptamine (μg kg^{-1} min^{-1}): (▨) 0.025, (▧) 0.1, and (■) 0.4. * $P<0.05$ vs. baseline values. The % change by 5-carboxamide tryptamine in the two groups of animals was not significantly different.

body also showed colour changes. The cerebral fraction of carotid blood flow remained unchanged after 5-carboxamide tryptamine. Neither the distribution itself, as found earlier (Saxena & Verdouw, 1982), nor the responses to 5-carboxamide tryptamine were modified by treatment with 1 mg kg^{-1} cyproheptadine.

Regional carotid conductance was increased in all tissues (Figure 8) except in the brain. The effects of the drug were similar in the untreated and cyproheptadine-treated animals.

Discussion

Shunting of microspheres

The present investigation once again (see Schamhardt *et al.*, 1979; Saxena & Verdouw, 1982; 1984b; Verdouw *et al.*, 1984a) revealed that after both intra-atrial and intracarotid injections, a substantial proportion of the spheres were shunted to the venous side. Though after intra-atrial injection some spheres (about 1%) reach the lungs via bronchial arteries (Baile *et al.*, 1982), as discussed in detail elsewhere (Johnston & Saxena., 1978; Saxena & Verdouw, 1982; Saxena, 1984a) the appearance of 15 μm microspheres in the venous effluent (and subsequent entrapment in the microvasculature of lungs) can be used as an index of arteriovenous anastomotic blood flow. Briefly, this assumption is based on the relative diameters of capillaries (<10 μm), preferential thoroughfare channels (8–18 μm) and arteriovenous anastomoses (generally >25 μm) (Clark & Clark, 1934; Sherman, 1963; Wiedeman, 1963; Baez, 1977; Kayer *et al.*, 1982; Potter & Groom, 1983), and of the vessels (28 μm) where 15 μm spheres are trapped (Dickhoner *et al.*, 1978). A comparison of the blood flows measured with microspheres of four different sizes (10, 15, 25 and 35 μm diameter) has revealed that large arteriovenous anastomoses, where microspheres of 35 μm are trapped but others pass through, are mainly located in the skin and ears of the pig (Saxena & Verdouw, 1984a; 1985). Such arteriovenous anastomoses may also be found in the

dura mater (Rowbotham & Little, 1965), nasal mucosa (Änggård, 1974) and rete mirabile (Gillilan & Markesberry, 1963).

Effects of 5-carboxamide tryptamine

The two highest doses of 5-carboxamide tryptamine caused hypotension which was accompanied by bradycardia in pigs, when the drug was infused into the common carotid artery. The hypotension was entirely due to a fall in the cardiac output since the total peripheral conductance did not change. However, the interesting point is that the reduction in the cardiac output was only noticed in its non-nutrient (arteriovenous anastomotic) fraction; the nutrient fraction increased. Therefore, the calculated vascular conductance of the non-nutrient fraction was lowered but that of the nutrient fraction was enhanced. The shunting of the microspheres in the jugular vein was also reduced. When the drug was infused directly into the carotid artery, right from the lowest dose there was a complete redistribution of carotid blood flow; the arteriovenous anastomotic fraction decreased but the nutrient fraction increased. These results show that 5-carboxamide tryptamine constricts arteriovenous anastomoses but dilates arterioles. Vasodilatation by the drug was observed in several tissues, the most prominent being the stomach, skin and ears. Since the carotid vascular effects of 5-carboxamide tryptamine were the same in the untreated and cyproheptadine-treated pigs, the involvement of 5-HT_2-receptors is precluded. In the case of 5-HT, however, cyproheptadine (Saxena & Verdouw, 1982), methysergide (Saxena & Verdouw, 1984b), ketanserin and WAL 1307 (Verdouw *et al.*, 1984a) – all of which antagonize 5-HT_2-receptors – slightly reduce the arteriovenous anastomotic-constriction but greatly enhance the vasodilatation response. It appears that, unlike 5-HT which constricts arteries and, to some extent, arteriovenous anastomoses by activating 5-HT_2-receptors (Saxena & Verdouw, 1982; 1984b), 5-carboxamide tryptamine does not possess such an activity. This is also indicated by the lack of a pressor effect with this compound in rats pretreated with hexamethonium (Saxena, unpublished). However, like 5-HT (Saxena *et al.*, 1978; Forsyth & Saxena, 1978; Saxena & Verdouw, 1982), this carboxamide derivative can potently constrict arteriovenous anastomoses and dilate arterioles, particularly in the stomach, skin and ears, by stimulating 'atypical' 5-HT receptors. The effect of this compound on the arteriovenous anastomoses was not mediated by a baroreceptor reflex since (i) the responses were also obtained upon local intracarotid infusions, in a dose ($0.025\ \mu g\ kg^{-1}\ min^{-1}$) which did not cause hypotension, (ii) the experiments were performed in animals with bilateral vagosympathectomy and (iii) the arteriovenous anastomoses in the carotid vascular bed of the young pigs used by us were not sensitive to noradrenaline or cervical sympathetic nerve stimulation (Verdouw *et al.*, 1984b).

Nature of 'atypical' 5-HT receptors

There are three main observations which suggest that the 'atypical' 5-HT receptors mediating the constriction of arteriovenous anastomoses and the dilatation of arterioles in the pig are of the 5-HT_1-type. Firstly, amongst a series of seventeen tryptamine derivatives including 5-HT, 5-carboxamide tryptamine has the highest affinity ($K_i = 8.64$ nM) for the 5-HT_1 binding sites (Engel *et al.*, 1983). Secondly, we have recently shown that a piperazine derivative, N-3-acetylaminophenyl piperazine (BEA 1654) – which shows a high affinity for the 5-HT_1 binding sites (K_i values: 32 nM, 5-HT_1; >10000 nM, 5-HT_2; 7939 nM, α_1-adrenoceptors; and 643 nM, α_2-adrenoceptors) – also causes a redistribution of carotid blood flow similar to that induce by 5-HT and 5-carboxamide tryptamine (Jennewein *et al.*, 1984; Verdouw *et al.*, 1985). Lastly, methysergide reduced arteriovenous anastomotic blood flow (Saxena & Verdouw, 1984b) and has some affinity (K_i = 100 nM compared to 1 nM for 5-HT_2 sites) for 5-HT_1 binding sites as well (Leysen & Gommeren, 1984). These 5-HT_1-receptors may also mediate the hypotensive response in the rat (Kalkman *et al.*, 1983) and the presynaptic inhibition of sympathetic neurones present in the dog saphenous vein (Engel *et al.*, 1983) as there is a good correlation between the above effects and the affinity for the 5-HT_1-binding sites of a number of tryptamine derivatives.

In conclusion, our results are consistent with the theory that there are two types of vascular receptors for 5-HT. The usual 5-HT_2-receptors – susceptible to blockade by ketanserin, cyproheptadine and low concentrations of methysergide – mediate vasoconstriction, and are located primarily in the large conducting arteries. The 'atypical' (5-HT_1)-receptors – insensitive to antagonism by ketanserin, cyproheptadine and low concentrations of methysergide – mediate arteriovenous anastomotic constriction and arteriolar dilatation, and are excited by 5-carboxamide tryptamine, BEA 1654 and methysergide. In high concentrations (>1 $mg\ kg^{-1}$) methysergide can probably block 5-HT_1 receptors as indicated by an antagonism of hypotensive responses to 5-HT and 5-carboxamide tryptamine in the rats (Saxena, unpublished).

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