Inhibitory 5-hydroxytryptamine receptors involved in pressor effects obtained by stimulation of sympathetic outflow from spinal cord in pithed rats

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1 A study was made of the effects of 5-hydroxytryptamine (5-HT) on pressor response induced *in vivo* by electrical stimulation of the sympathetic outflow from the spinal cord of pithed rats. All animals had been pretreated with atropine. Intravenous infusion of 5-hydroxytryptamine at doses of 10 and 20 $\mu\text{g kg}^{-1} \text{min}^{-1}$ reduced the pressor effects obtained by electrical stimulation at intervals of 10 min over the 1 h of infusion.

2 This inhibitory action of 5-HT was depressed by cyproheptadine and methiothepin but was not modified by ketanserin or MDL-72222. By contrast, the inhibitory action of 5-HT was lost in pithed rats that had been pretreated with exogenous noradrenaline.

3 The 5-HT₁ receptor agonist 5-carboxamidotryptamine (5-CT) caused an inhibition of the pressor response, whereas the 5-HT₃ receptor agonist, 1-phenylbiguanide, produced a variable but significant increase in the pressor response. The 5-HT₂ receptor agonist, *m*-CPP, did not modify the pressor sympathetic response.

4 Our results suggest that 5-hydroxytryptamine interferes with sympathetic neurotransmission by inhibiting pressor effects as a result of stimulation of the complete sympathetic outflow, and that this inhibition is mainly through a presynaptic 5-HT₁ mechanism.

Keywords: 5-Hydroxytryptamine; 5-hydroxytryptamine receptor agonists; blood pressure; sympathetic; pithed rats; 5-HT₁ mechanisms

Introduction

Many studies conducted under different experimental conditions have shown that 5-hydroxytryptamine (5-HT) has a direct vasoconstrictor action and can also enhance the vasoconstrictor effects of other vasoactive agents. These actions are believed to be mediated via the 5-HT₂ receptor subtype (Fozard, 1984a; Medgett *et al.*, 1984; Vanhoutte, 1985; Saxena *et al.*, 1987; Bagdy *et al.*, 1988; 1989; Leysen *et al.*, 1988; Saxena & Villalon, 1991). 5-HT also has vasodilatory/inhibitory actions, thought to be mediated through the preferential involvement of the 5-HT₁ receptor subtype, although the participation of other mechanisms in these actions is evident (Feniuk *et al.*, 1981; Vanhoutte, 1985; 1987).

5-HT has been reported to have stimulatory actions on the heart, although the mechanisms involved remain to be elucidated fully (Martinez & Lokhandwala, 1980; Göther *et al.*, 1986; Bom *et al.*, 1989). The participation of 5-HT in the control of blood pressure (Cohen, 1984; Grading *et al.*, 1985; Saxena *et al.*, 1987; Dabiré, 1990) and the modulation of cardiac and vascular sympathetic transmission has also been demonstrated. For this modulation, potentiating and inhibitory actions have been proposed, however in both cases there is a disparity between mechanisms postulated to account for such actions (Fozard & Mwaluko, 1976; Fozard, 1984b; Coote *et al.*, 1987; Docherty, 1988; Bom *et al.*, 1989; Shephard *et al.*, 1991; Done & Sharp, 1992).

Our aim was to study both the effects of 5-HT on vascular sympathetic neurotransmission and the influence of peripherally administered antagonists on such effects. Using pithed rats pretreated with atropine, we studied the effects of i.v.-infused 5-HT on the pressor effects obtained by either electrical stimulation of the sympathetic outflow at the spinal cord, or by exogenously applied (i.v.) noradrenaline.

Intravenous administrations of 5-CT, 1-phenylbiguanide and *m*-CPP allowed for a qualitative investigation of the 5-HT receptor mechanisms involved in the pressor effects of electrical sympathetic stimulation in the pithed rat.

Methods

Experimental protocol

Male Wistar rats weighing 270–300 g were used. The animals were kept and supplied by the Animalarium of the Faculty of Pharmacy of the University of Salamanca.

The animals were anaesthetized with sodium pentobarbital (60 mg kg⁻¹, i.p.). A tracheal cannulation was performed and the animals were then ventilated using a Harvard respiratory pump (1 ml air 100 g⁻¹, 45 strokes min⁻¹). Pithing was performed as described by Gillespie & Muir (1967). A steel rod (1.5 mm diameter) was inserted through the orbit and foramen magnum, and down the vertebral foramen. The rod was advanced until the tip had reached the level of S1, which corresponded to a total distance of approximately 15 cm.

The right jugular vein and the left carotid artery were cannulated. These allowed for the intravenous administration of drugs and the measurement and recording of blood pressure respectively. Blood pressure was monitored using a Letic pressure transducer connected to a PRS 205 amplifier, and displayed on one channel of a Letic Polygraph 4000. Heart rate was measured by analysis of the blood pressure data, by a CAR 1000 tachograph connected to the same PRS 205 amplifier.

The entire sympathetic outflow from the spinal cord was stimulated by the use of a Cibertec Stimulator CS-9. Two electrodes were employed: one was connected to the pithing rod (the stimulating electrode), while the other electrode (the

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indifferent electrode) was inserted subcutaneously into a leg.

Prior to electrical stimulation, the animals were pretreated with *d*-tubocurarine (2 mg kg^{-1} i.v.) and atropine (1 mg kg^{-1} i.v.) and left for 10 min until the blood pressure and heart rate levels had completely stabilized.

Two initial stimulations, 10 min apart, were made ($15 \pm 3 \text{ V}$, 5 Hz , 0.1 ms , 25 s). The mean increase in mean blood pressure obtained after these two stimulations was used as the control value (E_0). After the second stimulation intravenous infusion of saline (1 ml h^{-1}), 5-HT ($10, 20, 30$ and $40 \mu\text{g kg}^{-1} \text{ min}^{-1}$, 1 ml h^{-1}), 5-CT, 1-phenylbiguanide or *m*-CPP ($10 \mu\text{g kg}^{-1} \text{ min}^{-1}$, 1 ml h^{-1}) was performed. Each infusion was continuous over 1 h. Stimulations were performed under the above conditions every 10 min during the infusion. These stimulations were designated E_1 , E_2 , E_3 , E_4 , E_5 and E_6 .

In order to analyse the mechanism of action of 5-HT, different antagonists were administered intravenously. These antagonists – ketanserin (0.5 mg kg^{-1}), cyproheptadine (1 mg kg^{-1}), methiothepin (0.1 mg kg^{-1}), and MDL-72222 (2 mg kg^{-1}) – were administered 5 min before the infusion of $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$ 5-HT. Two of the antagonists, methiothepin and MDL-72222, were also administered i.v. 5 min before the infusion of $10 \mu\text{g kg}^{-1} \text{ min}^{-1}$ 5-CT or 1-phenylbiguanide respectively.

In another set of experiments, the pressor effects were obtained by the intravenous administration of noradrenaline ($0.5 \mu\text{g kg}^{-1}$ every 15 min). A control group received i.v. noradrenaline and saline (1 ml h^{-1}), and a second group received both noradrenaline and $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$ 5-HT.

Drugs employed

The following drugs were used in our experiments: pentobarbital sodium (Claudio Barcia), heparin sodium (Roche), *d*-tubocurarine hydrochloride (Sigma), 5-HT-creatinine sulphate (Sigma), atropine sulphate (Scharlau), ketanserin (Janssen), cyproheptadine hydrochloride (Fides), methiothepin mesylate (RBI), 3-tropanyl-3,5-dichlorobenzoate (MDL-72222, RBI), 1-phenylbiguanide (RBI), carboxamidotryptamine maleate, 5-CT (RBI), 1-(3-chlorophenyl)piperazine dihydrochloride, *m*-CPP dihydrochloride (RBI), noradrenaline bitartrate (Sigma).

All drugs used were dissolved in distilled water at the time of the experiments, with the exception of ketanserin, which was dissolved in 0.04 mol l^{-1} lactic acid, and MDL-72222 and *m*-CPP, which were both dissolved in 0.01 N HCl .

Expression and analysis of results

Modifications in blood pressure were expressed as mmHg above the mean control blood pressure, measured both before electrical stimulation and as the stabilized maximum post stimulation.

All data were expressed as the mean value $\pm$ s.e.mean of at least five experiments. The statistical significance was determined using Student's *t*-test for grouped data ($*P < 0.05$; $**P < 0.01$ and $***P < 0.001$). The figures show the values that proved to be statistically significant when compared with the corresponding ones in the control group with the exception of Figure 2, in which they are compared with the corresponding values in the 5-HT perfused group.

Results

The mean resting blood pressure in these studies was $41.6 \pm 0.7 \text{ mmHg}$ ($n = 156$). Electrical stimulation of the entire sympathetic outflow from the spinal cord of pithed rats elicited increases in the mean blood pressure ($46 \pm 3.4 \text{ mmHg}$, $n = 40$) with no appreciable changes in heart rate. This observation is consistent with results reported by other

authors (Gillespie & Muir, 1967; Borkowski & Quinn, 1983; Zukowska-Grojec *et al.*, 1983; Roquebert *et al.*, 1990). The rises in blood pressure remained stable in the animals receiving 1 ml kg^{-1} i.v. saline infusion (Figure 1).

With respect to the control group and its own E_0 , intravenous infusion of 5-hydroxytryptamine led to a reduction in the blood pressure increases resulting from stimulations E_1 to E_6 . This reduction was observed at the $10 \mu\text{g kg}^{-1} \text{ min}^{-1}$ dose of 5-HT, although the magnitude of the reduction only became significant with the $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$ dose. Thereafter, smaller and more variable reductions were observed when $40 \mu\text{g kg}^{-1} \text{ min}^{-1}$ 5-HT were perfused (Figure 1).

The selective 5-HT₂ receptor antagonist, ketanserin (Van Nueten *et al.*, 1981; Cohen, 1984; Petterson *et al.*, 1984), at doses that did not modify the pressor response by α -adrenergic blockade, did not alter the inhibitory action of 5-HT (Figure 2). Similarly, the 5-HT₃ receptor antagonist, MDL-72222, was not effective in blocking the inhibitory action of 5-HT (Figure 2). Cyproheptadine, a 5-HT₁ and

Figure 1 Influence of i.v. infusion of 5-HT on blood pressure modifications (ΔMBP) caused by electrical stimulation of the complete sympathetic outflow from the spinal cord of pithed rats. Control: saline solution 1 ml h^{-1} ; 5-HT: $10, 20$ and $40 \mu\text{g kg}^{-1} \text{ min}^{-1}$. $\square$, E_0 ; $\blacksquare$, E_1 ; $\square$ with diagonal lines, E_2 ; $\square$ with horizontal lines, E_3 ; $\square$ with vertical lines, E_4 ; $\square$ with cross-hatch, E_5 ; $\square$ with dots, E_6 .

Figure 2 Effect of saline (1 ml kg^{-1}), cyproheptadine (Cyp, 1 mg kg^{-1}), methiothepin (Met, 0.1 mg kg^{-1}), ketanserin (Ket, 0.5 mg kg^{-1}) and MDL-72222 (MDL, 2 mg kg^{-1}) on 5-hydroxytryptamine-induced inhibition of the mean blood pressure increases (ΔMBP) caused by electrical stimulation of the complete sympathetic outflow. Control: saline (1 ml h^{-1}). $\square$, E_0 ; $\blacksquare$, E_1 ; $\square$ with diagonal lines, E_2 ; $\square$ with horizontal lines, E_3 ; $\square$ with vertical lines, E_4 ; $\square$ with cross-hatch, E_5 ; $\square$ with dots, E_6 .

5-HT₂ antagonist (Stone *et al.*, 1961), did not alter the pressor response achieved by stimulation of the entire sympathetic outflow in the control group perfused with saline, although it did abolish the inhibition exerted by 5-HT (Figure 2). With methiothepin, a preferential 5-HT₂ antagonist which also blocks 5-HT₁ receptors (Saxena & Villalon, 1990), the action of $20 \mu\text{g kg}^{-1} \text{min}^{-1}$ 5-HT was also abolished (Figure 2).

Intravenous infusion of 5-CT ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$) resulted in a significant, higher degree of pressor response inhibition than 5-HT (Figure 3). This inhibitory effect was blocked by pretreatment with methiothepin (Figure 4).

The selective 5-HT₂ receptor agonist, *m*-CPP (Humphrey *et al.*, 1993), was without effect on the pressor responses evoked by sympathetic stimulation (Figure 3). Increases in blood pressure after sympathetic stimulation were significantly potentiated in the 1-phenylbiguanide-perfused group. This enhancement was inhibited by pretreatment with MDL-72222 (Figure 5).

5-HT failed to inhibit any of the measured physiological parameters in those animals in which pressor response was evoked by the i.v. administration of noradrenaline (Figure 6).

Figure 3 Mean blood pressure modifications (ΔMBP) caused by electrical stimulation of the total sympathetic outflow of pithed rats, and influence of i.v. infusion of 5-HT ($20 \mu\text{g kg}^{-1} \text{min}^{-1}$), 5-CT ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$), *m*-CPP ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$) and 1-phenylbiguanide ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$) on these modifications. Control: saline (1 ml h^{-1}). $\square$, E_0 ; $\blacksquare$, E_1 ; ▨ , E_2 ; ▩ , E_3 ; ▧ , E_4 ; ▦ , E_5 ; ⊞ , E_6 .

Figure 4 Abolition of the inhibitory effects of 5-carboxamido-tryptamine ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$) on the mean blood pressure modifications (ΔMBP) caused by electrical stimulation of the total sympathetic outflow of pithed rats, by methiothepin (0.1 mg kg^{-1}). Control: saline (1 ml h^{-1}). $\square$, E_0 ; $\blacksquare$, E_1 ; ▨ , E_2 ; ▩ , E_3 ; ▧ , E_4 ; ▦ , E_5 ; ⊞ , E_6 .

Discussion

As suspected from previous studies carried out in our laboratory (unpublished results) and from studies published by other workers (Martinez & Lokhandwala, 1980; Feniuk *et al.*, 1981; Vanhoutte, 1983; 1985; Grading *et al.*, 1985; Saxena *et al.*, 1987; Hollenberg, 1988; Saxena & Villalon, 1991; Shephard *et al.*, 1991; Done & Sharp, 1992), 5-HT interferes with adrenergic neurotransmission and reduced the increase in mean blood pressure achieved by sympathetic stimulation. However, it did not affect the increases in blood pressure elicited by the exogenous administration of noradrenaline.

This inhibition is only observed at low doses of 5-HT (10 and $20 \mu\text{g kg}^{-1} \text{min}^{-1}$), whereas at a dose of $40 \mu\text{g kg}^{-1}$

Figure 5 Block by MDL-72222 (2 mg kg^{-1}) of the enhancing effect of 1-phenylbiguanide ($10 \mu\text{g kg}^{-1} \text{min}^{-1}$) on the mean blood pressure modifications (ΔMBP) caused by electrical stimulation of the total sympathetic outflow of pithed rats. Control: saline (1 ml h^{-1}). $\square$, E_0 ; $\blacksquare$, E_1 ; ▨ , E_2 ; ▩ , E_3 ; ▧ , E_4 ; ▦ , E_5 ; ⊞ , E_6 .

Figure 6 Influence of i.v. infusion of saline (1 ml h^{-1}) and 5-HT ($20 \mu\text{g kg}^{-1} \text{min}^{-1}$) on blood pressure modifications (ΔMBP) caused by i.v. exogenous administration of noradrenaline ($0.5 \mu\text{g kg}^{-1}$) in pithed rats. $\square$, E_0 ; $\blacksquare$, E_1 ; ▨ , E_2 ; ▩ , E_3 ; ▧ , E_4 .

min⁻¹ there is no clear reduction. These initial results seem to show that, under our experimental conditions, 5-HT only inhibits adrenergic neurotransmission at doses below 40 µg kg⁻¹ min⁻¹.

Possibly, this biogenic amine could exert a double effect on the sympathetic nervous system, which would be inhibitory at low doses and perhaps potentiating at elevated doses (above 40 µg kg⁻¹ min⁻¹). Under different experimental conditions and working with species other than the rat, other authors have obtained results leading them to propose similar effects of 5-HT: inhibiting or potentiating sympathetic actions. The nature, inhibitory or stimulatory, being dependent on the dose of 5-HT or on the level of sympathetic tone (Martinez & Lokhandwala, 1980; Van Nueten *et al.*, 1984).

The inhibitory effect was reproduced by the administration of the selective 5-HT₁ receptor agonist, 5-CT. The possible potentiating effect was obtained by administration of 1-phenylbiguanide, a selective 5-HT₂ receptor agonist.

This evidence, together with the results achieved with a dose of 20 µg kg⁻¹ min⁻¹ 5-HT in the presence of different antagonists, implies that no 5-HT₂ serotonergic mechanisms participate in this inhibitory effect. The reasoning behind this is that 0.5 mg kg⁻¹ ketanserin, a 5-HT₂ receptor antagonist, does not modify the effect of 5-HT. *In vivo* studies by other authors have established that the inhibitory effect of 5-HT on adrenergic neurotransmission is not affected by 5-HT₂ receptor antagonists (McGrath, 1977; Van Nueten *et al.*, 1981).

In the light of the results obtained with cyproheptadine and methiothepin, this inhibitory effect of 5-HT must involve serotonergic mechanisms acting via 5-HT₁ receptors. Cyproheptadine and methiothepin blocked the inhibitory effects

of 5-HT on the responses to sympathetic stimulation, and methiothepin also resulted in a dis-inhibition of 5-CT effects.

The results obtained from utilizing stimulation of the entire sympathetic outflow would, therefore, suggest that low doses of 5-HT inhibit pressor responses by a 5-HT₁-mediated mechanism that is perhaps presynaptic in nature. This inhibition might be due to a decrease in noradrenaline release. With respect to this, in 1990 Dabiré, working with the 5-HT_{1A} agonist 8-OH-DPAT reported that peripheral stimulation of 5-HT₁ receptors could reduce blood pressure by a presynaptic effect able to decrease the release of sympathetic noradrenaline.

Higher doses of 5-HT however, resulted in an enhancement of the effects of sympathetic stimulation. No such enhancement was seen upon exogenous noradrenaline administration, and it is probable that this enhancement is due to presynaptic 5-HT₂ activation. In this way, 5-HT₂ activation could elicit noradrenaline release, thereby causing the observed enhancement.

In summary, the effects of 5-HT and the serotonergic mechanisms involved in cardiovascular sympathetic neurotransmission in the pithed rat are mainly presynaptic in nature. These presynaptic mechanisms act to inhibit or facilitate the release of noradrenaline from sympathetic nerve terminals. The inhibitory mechanisms involve the activation of the 5-HT₁ receptor subtype, whereas those that enhance noradrenaline release involve the 5-HT₂ receptor subtype.

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