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Mesenteric vasoconstrictor response to 5-hydroxytryptamine in the in situ blood autoperfused rat mesentery: involvement of 5-HT_{2B} and/or 5-HT_{2C} receptor activation

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Abstract

Using a number of agonist and antagonist compounds, we attempted to characterize the responses and receptors involved in the effects of 5-hydroxytryptamine (5-HT) in the in situ blood perfused rat mesentery. An intra-arterial (i.a.) bolus injection of 5-HT increased mesenteric perfusion pressure in a dose-dependent way but did not change the systemic blood pressure. The selective 5-HT_2 receptor agonists α-methyl-5-HT, 1-(3-chlorophenyl)piperazine dihydrochloride (*m*-CPP) and (±)-1-(4-iodo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (DOI), caused a local vasoconstrictor effect in the autoperfused vascular mesenteric bed. Intra-arterial injection of 5-carboxamidotryptamine (5-CT) and 1-(*m*-chlorophenyl)-biguanide (*m*-CPBG) did not modify the mesenteric perfusion pressure. The vasoconstrictor effect elicited by 5-HT and α-methyl-5-HT was significantly decreased by ritanserin and by a selective 5-$HT_{2B/2C}$ receptor antagonist, *N*-3-pyridinyl-3,5-dihydro-5-methyl-benzo[1,2-*b*:4,5-*b*′]dipyrrole-1(2*H*)-carboxamide hydrochloride (SB 206553), but was not modified by prazosin, propranolol, indomethacin or enalapril pretreatment. Our data suggest that the vasoconstrictor serotonergic response induced in the in situ autoperfused rat mesenteric vascular bed is mainly mediated by activation of 5-HT_{2B} and/or 5-HT_{2C} receptors.

Keywords: 5-HT (5-hydroxytryptamine, serotonin); α-Methyl-5-hydroxytryptamine; Vasoconstrictor effect; Mesenteric blood flow; 5-$HT_{2B/2C}$ receptor

1. Introduction

5-Hydroxytryptamine (5-HT) is present in gastrointestinal tissues and can elicit contraction or relaxation by activation of a broad variety of mechanisms and receptors, depending on the species, the experimental conditions, the region of the gastrointestinal tract-stimulated, the regional variations in 5-HT receptors, and most importantly, the nature of the 5-HT receptors involved (Mohan Dhasmana et al., 1993).

The 5-HT receptor family is currently divided into seven main types comprising at least 15 different receptors. The 5-HT_2 receptor sub-family comprises the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors, all of which belong to the G protein-coupled receptor superfamily. This receptor family is important in the mediation of many physiological functions, including vascular and non-vascular smooth muscle contraction, platelet aggregation, uterine smooth muscle growth, and gastrointestinal functioning (Roth et al., 1998).

The vasoconstrictor effects of 5-HT have been addressed by several authors in in vitro models and in different species. Thus, this effect has been studied in the isolated mesenteric resistance arteries of rats (Kawasaki et al., 1989; Warner, 1990; Dohi and Lüscher, 1991), of guinea pigs (Meehan and Kreulen, 1990), of dogs (Shimamoto et al., 1993, 1994), and of rabbits (Choppin and Connor, 1995, 1996). Some of these authors concluded that the vasoconstrictor responses of rat mesenteric arteries to 5-HT are mediated by 5-HT_2 receptors (Kawasaki et al., 1989; Dohi and Lüscher, 1991). Serotonergic 5-HT_2 receptors are present on vascular smooth muscle cells and their activation leads to vasoconstriction. However, in the case of the mesenteric arteries of dogs and rabbits, the vasoconstrictor responses are mediated by 5-$HT_{1\text{-like}}$ receptors (Shimamoto et al., 1993, 1994; Choppin and Connor, 1995). Conflicting claims have been made as regards 5-HT

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receptors mediating the effects of 5-HT on the mesenteric vasculature.

The activation of vascular smooth muscle 5-HT_2 receptors by 5-HT causes vasoconstriction through two mechanisms — direct and indirect — by amplifying the vasoconstriction stimuli caused by a variety of agonists through their corresponding receptors (Taylor and Kaumann, 1994). The in vitro perfused mesentery is a useful laboratory model that has been extensively used to study the effects of several different agents. However, 5-HT receptors subtypes in the mesenteric vascular bed have not been defined due to the conflicting results obtained with different species as well as different experimental models. The in vitro rat mesentery, the mesenteric vasculature, is trimmed from intestines during isolation and hence its smaller arterioles are absent. Owing to the absence of smaller arterioles and because perfusion is carried out with an artificial medium, the in vitro data may not reflect qualitatively the responses to the mesenteric vascular bed with regard to in vivo. Jackson and Campbell (1980) proposed that the in situ rat mesentery model was more sensitive than was the in vitro model, apparently due to in the in situ model, the perfusion of the mesentery with blood and the smaller mesenteric arterioles, being left intact.

In the light of the above, the present study was designed to define the 5-HT receptor subtypes of the mesenteric vascular beds of rats in vivo and to study the possible existence of peripheral mechanisms that might be activated by exogenous 5-HT or 5-HT receptor agonists in the mesentery. 5-HT and 5-HT receptor agonists were injected directly into the artery of the mesenteric vascular beds of anaesthetised rats.

2. Materials and methods

2.1. Animal preparation

Male Wistar rats weighing 330–400 g from the Animal House of the University of Salamanca (P.A.E.-SA001) were used in all experiments. The rats were anaesthetised with sodium pentobarbital (60 mg kg^{-1}, i.p.). After the induction of anaesthesia, a tracheotomy was performed and catheters were placed in the right and left carotid arteries. The right carotid artery was cannulated for blood pressure measurements using a Spectramed model P23 XL pressure transducer and a Grass model 7 Physiograph recorder. The left jugular vein was cannulated for drug administration. The animals were kept warm with a heating lamp.

Rats were prepared for in situ perfusion of mesenteric beds. The vascular beds were perfused using an extracorporeal circuit and a constant flow Gilson peristaltic pump. The left carotid artery was cannulated with the inflow end of the extracorporeal flow line. The superior mesenteric artery was exposed by a midline laparotomy and deflection of the intestines to the right side of animal. Ties were placed around the mesenteric artery, one of them near to the abdominal aorta artery. Heparin (5 mg kg^{-1}) was then given intravenously and an intravenous infusion of normal saline (0.9% NaCl) was initiated at a rate of 1 ml h^{-1} and continued throughout the experiment.

After the mesenteric tie near to the aorta had been tightened, blood immediately began to flow from the carotid to the superior mesenteric artery; the circuit was thus established with no interruption of blood flow to the mesenteric bed. Blood was pumped from the right carotid artery to the mesenteric vascular bed from which the superior mesenteric artery was the only outlet.

The distal portion of the external circuit was connected to a Spectramed model P23 XL pressure transducer and a Grass model 7 Physiograph recorder. At the beginning of each experiment, flow was adjusted to render the perfusion pressure equal to the systemic pressure. Flow was kept constant throughout the experiment, changes in the perfusion pressure reflecting the changes in the vascular resistances. The flow rate through the mesenteric vascular bed ranged from 1.5 and 2 ml min^{-1} (Jackson and Campbell, 1980). In all experiments, atropine (1 mg kg^{-1}) was administered intravenously before the saline infusion was started in order to block the cholinergic effect.

2.2. Experimental protocols

After a 15 min period to allow blood pressure and perfusion pressure to stabilise, the next experiments were performed using five animals to evaluate each dose of agonist or antagonist and each animal preparation to evaluate only one agonist or antagonist.

2.2.1

5-HT, 5-carboxamidotryptamine (5-CT), (±)-1-(4-iodo-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (DOI), α-methyl-5-HT, 1-(3-chlorophenyl)piperazine dihydrochloride (*m*-CPP), or 1-(*m*-chlorophenyl)-biguanide (*m*-CPBG), at doses of 1, 6.3, 12.5 and 25 μg kg^{-1} were administered locally via the distal cannula, intra-arterially (i.a.), by bolus injection of a maximum of 10 μl using a microsyringe (Exmire microsyringe), 5 min elapsing between each drug dose. Initially, lower doses (0.0625, 0.125 and 0.5 μg kg^{-1}) of all agonists and a higher dose of *m*-CPP and DOI (33.3 μg kg^{-1}) were also evaluated.

2.2.2

In order to analyse the mechanism of action of 5-HT, several antagonists were administered intravenously. These antagonists (ritanserin 1 mg kg^{-1}, propranolol 2 mg kg^{-1}, prazosin 0.1 mg kg^{-1}, enalapril 5 mg kg^{-1} or indomethacin 2 mg kg^{-1}) were administered 10–15 min before i.a. administration of the corresponding dose–response curve of 5-HT (1, 6.3, 12.5, 25 μg kg^{-1}) or α-methyl-5-HT (1, 6.3, 12.5, 25 μg kg^{-1}).

2.2.3

To confirm the subtype of 5-HT_2 receptors involved in the effects of 5-HT and α-methyl-5-HT, a new selective

5-$HT_{2B/2C}$ receptor antagonist, *N*-3-pyridinyl-3,5-dihydro-5-methyl-benzo[1,2-*b*:4,5-*b*′]dipyrrole-1(2*H*)-carboxamide hydrochloride (SB 206553, 0.5 mg kg^{-1}), was administered 10–15 min before i.a. administration of 5-HT and α-methyl-5-HT.

2.3. Drugs used

The following drugs were used: pentobarbital sodium (Sigma), heparin sodium (Roche), atropine sulphate (Scharlau), 5-hydroxytryptamine-creatinine sulphate (Sigma), 5-CT maleate (Research Biochemicals International), DOI hydrochloride (Research Biochemicals International), α-methyl-5-HT (Research Biochemicals International), *m*-CPP dihydrochloride (Research Biochemicals International), *m*-CPBG hydrochloride (Research Biochemicals International), SB 206553 hydrochloride (Research Biochemicals International), ritanserin (Janssen Pharmaceutica), D-L-propranolol hydrochloride (ICI Pharmaceuticals), enalapril maleate (Merck, Sharp and Dohme), indomethacin trihydrate sodium salt (Merck, Sharp and Dohme), prazosin (Pfizer). All drugs used were dissolved in distilled water at the time of the experiments with the exception of ritanserin and *m*-CPP, which were dissolved in 0.04 mol l^{-1} lactic acid and 0.01 M HCl, respectively.

2.4. Statistics

The results are given as means ± S.E.M. of five experiments. Changes in mesenteric vascular resistance are given as increases, in mm Hg, in perfusion pressure in comparison to control values. Statical significance was calculated by one way analysis of variance (ANOVA) followed by the Newman–Keuls multiple comparison test. The differences were considered significant when $P < 0.05$.

3. Results

3.1. Mesenteric vascular effect of 5-HT receptor agonists: 5-HT, α-methyl-5-HT, DOI, m-CPP, 5-CT and m-CPBG

The mean resting blood pressure and perfusion pressure values in these studies were 90.3 ± 6.9 mm Hg ($n = 90$) and 94.8 ± 3.2 mm Hg ($n = 90$), respectively.

In the first group of experiments, ($n = 30$), local injection of increasing doses of 5-HT (1.0, 6.3, 12.5 and 25.0 μg kg^{-1}) had no effect on systemic blood pressure but increased perfusion pressure in the in situ autoperfused rat vascular beds in a dose-dependent way (Fig. 1). Likewise, at doses from 1.0 to 25.0 μg kg^{-1} the selective 5-HT_2 receptor agonist α-methyl-5-HT increased the perfusion pressure (Fig. 1) without modifying blood pressure. In the same way, the 5-HT_2 receptor agonists DOI, a 5-$HT_{2A/2C}$ receptor agonist, and *m*-CPP, a 5-HT_{2C} receptor agonist, also increased the perfusion pressure at doses from 1.0 to 25.0 μg kg^{-1} to a lesser exent than α-methyl-5-HT (Fig. 1).

By contrast, neither systemic blood pressure or perfusion pressure was modified by local administration of similar doses of 5-CT and *m*-CPBG, 5-HT_1 and 5-HT_3 receptor agonists, respectively (Fig. 1).

3.2. Effect of antagonists on 5-HT or α-methyl-5-HT mesenteric vasoconstrictor-induced effect

Pretreatment with 1 mg kg^{-1} of the 5-HT_2 receptor antagonist ritanserin ($n = 10$) inhibited the vasoconstrictor responses to 5-HT and α-methyl-5-HT (Figs. 2 and 3).

In another series of experiments the effects of 5-HT and α-methyl-5-HT were tested after indomethacin (2 mg kg^{-1}) treatment ($n = 10$). During this pretreatment, no changes

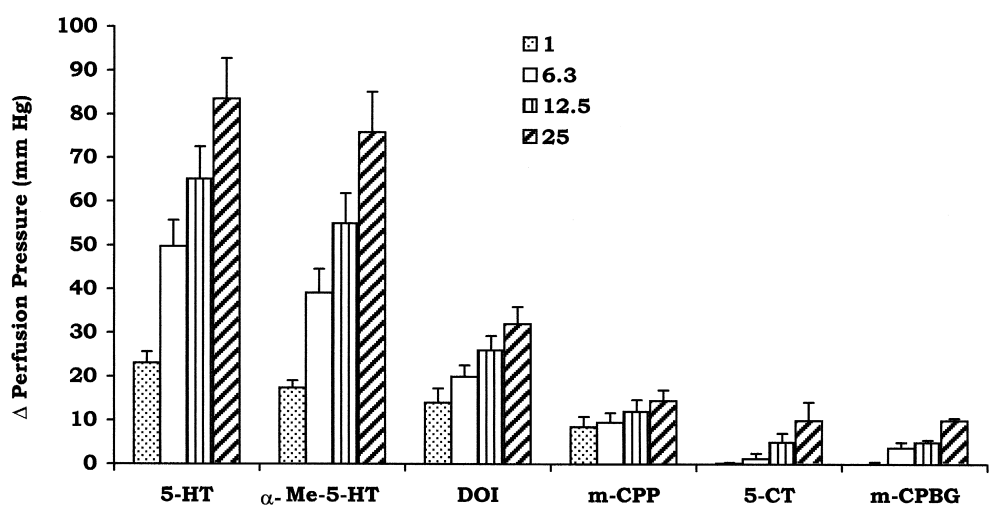

Fig. 1. Effect of mesenteric intra-arterial administration of different doses of 5-HT receptor agonists (1–25 μg kg^{-1}) on perfusion pressure in the in situ autoperfused rat mesentery. 5-HT, α-methyl-5-HT, DOI, *m*-CPP, 5-CT and *m*-CPBG.

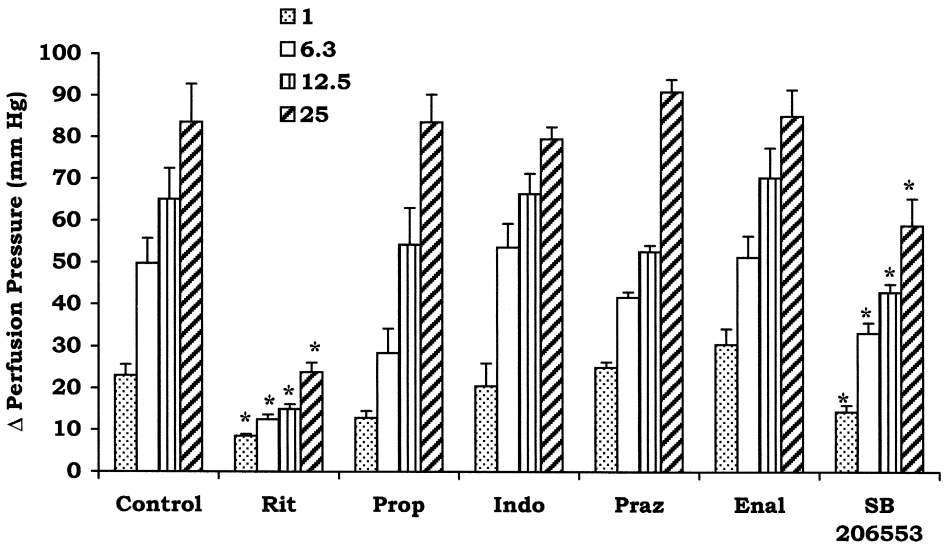

Fig. 2. Effect of 1 mg kg^{-1} of ritanserin (Rit), 2 mg kg^{-1} of propranolol (Prop), 2 mg kg^{-1} of indomethacin (Indo), 0.1 mg kg^{-1} of prazosin (Praz), 5 mg kg^{-1} of enalapril (Enal) and 0.5 mg kg^{-1} of SB 206553 pretreatment on the mesenteric vasoconstrictor effect induced by intra-arterial administration of 5-HT (Control, 1–25 μg kg^{-1}) in the in situ autoperfused rat mesentery. $^{*}P < 0.05$ with respect to saline group, which received the same 5-HT doses without antagonist pretreatment.

were observed in mean blood pressure. Ten minutes after intravenous administration of indomethacin, both 5-HT and α-methyl-5-HT increased the perfusion pressure (Figs. 2 and 3).

The possible role of α and β-adrenoceptors in the responses to 5-HT and α-methyl-5-HT was determined by pretreatment with an α-adrenoceptor antagonist, prazosin (0.1 mg kg^{-1}, a dose that blocks adrenaline vasoconstriction in this experimental model), or D,L-propranolol (2 mg kg^{-1}), a non-selective β-adrenoceptor antagonist ($n = 20$). The vasoconstrictor effects elicited by 5-HT and α-methyl-5-HT were not affected by the α- and β-adrenoceptor-blocking agent either (Figs. 2 and 3). However, as expected, prazosin alone reduced systemic blood pressure by 18.3 ± 4.2 mm Hg without affecting the perfusion pressure.

In another set of experiments, the animals were pretreated with the angiotensin-converting enzyme inhibitor

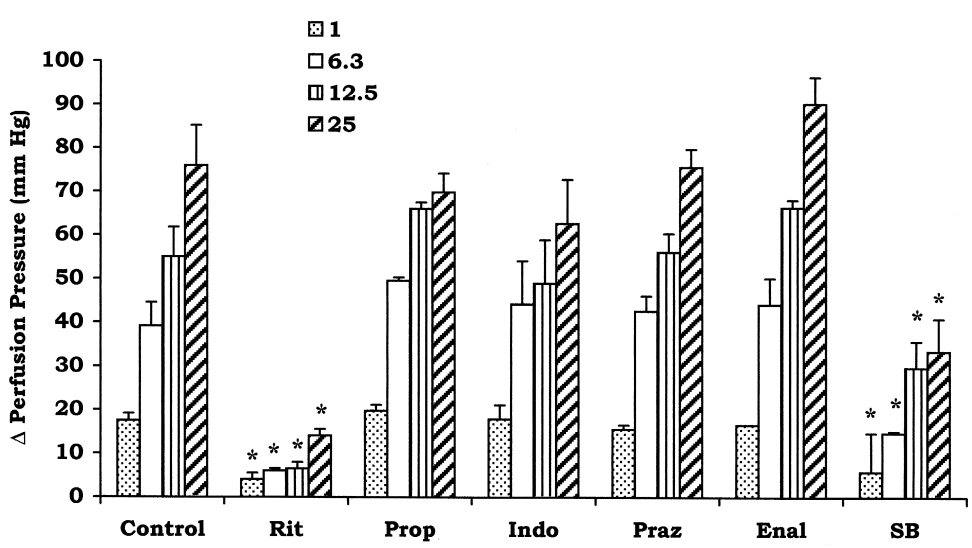

Fig. 3. Effect of 1 mg kg^{-1} of ritanserin (Rit), 2 mg kg^{-1} of propranolol (Prop), 2 mg kg^{-1} of indomethacin (Indo), 0.1 mg kg^{-1} of prazosin (Praz), 5 mg kg^{-1} of enalapril (Enal) and 0.5 mg kg^{-1} of SB 206553 pretreatment on the mesenteric vasoconstrictor effect induced by intra-arterial administration of α-methyl-5-HT (Control, 1–25 μg kg^{-1}) in the in situ autoperfused rat mesentery. $^{*}P < 0.05$ with respect to saline group, which received the same α-methyl-5-HT doses without antagonist pretreatment.

enalapril (5 mg kg^{-1}) (n = 10). The vasoconstrictor effects elicited by 5-HT and α-methyl-5-HT were not affected by this angiotensin-converting enzyme inhibitor (Figs. 2 and 3). In contrast, SB 206553, a new selective 5-$HT_{2B/2C}$ receptor antagonist ($n = 10$) significantly attenuated the 5-HT-induced vasoconstriction in the autoperfused rat mesentery (Fig. 2). A dose of 0.5 mg kg^{-1} of SB 206553 also inhibited the vasoconstrictor effect of α-methyl-5-HT (Fig. 3).

4. Discussion

According to indications of Jackson and Campbell (1980), the technique used in our experiment, which allows continuous measurement of mesenteric blood flow in the rat and the assessment of rapid changes in mesenteric blood flow induced by direct intra-arterial drug administration to the mesentery, enables the evaluation, in anaesthetised rats, of both the direct local mesenteric action of 5-HT and the possible indirect actions induced by the release of vasoconstrictor or vasodilator humoral agents, as has been suggested to occur with this agent in other animal species (Taylor and Kaumann, 1994). This preparation can supply useful information about the behaviour of mesenteric circulation in vivo. We wish to emphasise that the mesenteric vascular bed may be the destination for 10% of cardiac output, and obviously, changes in this area must have important effects on the whole cardiovascular system (Warner, 1990).

Local intra-arterial administration of 5-HT to intact animals significantly increased the perfusion pressure in a dose-dependent way. Our data are consistent with previous findings for isolated perfused mesentery after injections of 5-HT (McGregor and Smirk, 1970; Dohi and Lüscher, 1991). These authors studied the vasoconstrictor responses to intraluminal and extraluminal 5-HT in isolated mesenteric resistance arteries of Wistar–Kyoto rats and spontaneously hypertensive rats. The contractile effects on vascular smooth muscle of rat mesenteric resistance arteries are mediated by 5-HT_2 receptors.

The vasoconstrictor effect obtained with all the doses of 5-HT assayed was reduced by pretreatment with ritanserin, a selective 5-HT_2 receptor antagonist (Awouters et al., 1988) and was totally reproduced by administration of similar doses of a 5-HT_2 receptor agonist, α-methyl-5-HT. The present results are consistent with those reported for isolated mesenteric resistance arteries of rats (Kawasaki and Takasaki, 1984; Kawasaki et al., 1989). The 5-HT released from adrenergic nerves produces a vasoconstrictor effect in the perfused mesenteric vascular bed of the rat, which is mediated by activation of postsynaptic 5-HT_2 receptor. The contractile agonist profile in mesenteric arteries is in agreement with the notion of the 5-HT receptor being a member of the 5-HT_2 receptor family (Watts et al., 1995).

However, in the case of the dog, Shimamoto et al. (1993) reported that the vasoconstrictor effect induced by rauwolscine (it has affinity to both α_2 adrenoceptors and 5-$HT_{1\text{-like}}$ receptors) in dog mesenteric arteries should be attributed to the agonist action of rauwolscine at the 5-$HT_{1\text{-like}}$ receptor site, which is most probably a 5-HT_{1D} site. Those authors compared rauwolscine and 5-HT-induced responses under similar experimental conditions. They also studied the nature of the contractile response to rauwolscine, assessing several non-selective serotonergic receptor antagonists: methysergide (5-HT_1/5-HT_2 receptor antagonist), methiothepin (5-HT_1/5-HT_2 receptor antagonist), spiperone (5-HT_{1A}/5-HT_2 receptor antagonist), propranolol and pindolol (5-HT_{1A}/5-HT_{1B} receptor antagonists), mianserin (5-HT_1/5-HT_2 receptor antagonist) and ketanserin (5-HT_2 receptor antagonist). In contrast, our experiments revealed that the agonists of 5-HT_1 and 5-HT_3 receptors, 5-CT and *m*-CPBG, respectively, did not reproduce the vasoconstrictor effects induced by 5-HT. These results suggest that these types of receptors do not participate in this vasoconstrictor effect.

In the same way, Shimamoto et al. (1994) reported that in dog mesenteric arteries, the response to 5-HT is mediated through 5-$HT_{1\text{-like}}$ and 5-HT_2 receptors at low concentrations ($< 10^{-5}$ M) and through α_1-adrenoceptors at high concentrations ($> 10^{-5}$ M). For rabbit isolated mesenteric artery, Choppin and Connor (1995, 1996) demonstrated the existence of 5-$HT_{1\text{-like}}$ receptors that mediate vasoconstriction in this type of artery, assessing 5-HT and other 5-HT receptor agonists and non-selective 5-HT receptor antagonists. In that study, the relative order of agonist potencies observed (5-CT > 5-HT > RU 24969 = sumatriptan > 8-OH-DPAT) most closely resembles the 5-HT_{1D} recognition site. The authors demonstrated that the ineffectiveness of the 5-HT_{1A}/5-HT_{1B} antagonist pindolol and the weak effects of the 5-HT_{2A}/5-HT_{2C} antagonist ritanserin confirm the exclusion of 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2C} subtypes. In the same way, the 5-HT_{2A} receptor antagonist spiperone did not have antagonist properties and ketanserin had only weak inhibitory effects when tested against 5-HT-induced contractions. The results shown by these authors thus exclude a significant role for 5-HT_{2A} receptors in this vasoconstrictor effect of 5-HT.

These findings highlight the need to consider the species to be used very carefully when examining the pharmacology of different 5-HT receptors (Porter et al., 1999).

It is known that the cardiovascular effects of 5-HT are very complex because they involve vasodilatation or vasoconstriction, and hypotension or hypertension. Among other factors, the eventual response depends on the vascular bed in question, the dose of 5-HT employed, the pre-existing sympathetic vascular tone, the species used and the nature of 5-HT receptors involved (Saxena and Villalon, 1991).

α-Methyl-5-HT shows affinity for three subtypes of 5-HT_2 receptors (2A, 2B and 2C) with high affinity for the 5-HT_{2B} receptor subtype ($pK_A = 8.8$, Baxter et al., 1995).

The vasoconstrictor effect induced by 5-HT and α-methyl-5-HT was partially reproduced by intra-arterial administration of DOI, a non selective 5-HT_2 receptor agonist with a rank order of 5-HT_{2A} > 5-HT_{2B} > 5-HT_{2C} (Porter et al., 1999) and *m*-CPP, pointing to higher selectivity of 5-HT_{2C} receptors (relative efficacy of 65% at 5-HT_{2C} receptors but 25% at either 5-HT_{2A} or 5-HT_{2B} receptors). Similarly, the vasoconstrictor effect induced by α-methyl-5-HT was blocked by prior administration of ritanserin.

In order to elucidate the possible interaction between 5-HT and other neurotransmission systems, the animals were pretreated with non-serotonergic antagonists.

We analysed the effect of a cyclooxygenase inhibitor on the mesenteric vasoconstrictor effects of 5-HT and α-methyl-5-HT, using indomethacin at a dose commonly used to inhibit prostaglandin production. In the light of our results, we propose that 5-HT_2 receptor-mediated vasoconstriction in not dependent on an intact prostaglandin system. Likewise, this vasoconstriction is not dependent on the release of renin because the vasoconstriction was not modified by pretreatment with propranolol.

When the animals were pretreated with an angiotensin-converting enzyme inhibitor, enalapril, the vasoconstrictor effects induced by 5-HT or α-methyl-5-HT were not modified either. Thus, we propose that the vasoconstrictor effect of 5-HT is not mediated by a release of angiotensin II, which might cause an increase in mesenteric resistance (Kooy and Lewis, 1996).

A possible 5-HT or α-methyl-5-HT-induced release of NA from sympathetic nerve terminals cannot be proposed either. The α-adrenoceptor blockade elicited by prazosin had no effect on the mesenteric vasoconstriction induced by these 5-HT receptor agonists.

In conclusion, our observations suggest that under the experimental conditions used (in anaesthetised rats pretreated with atropine) the receptor subtype that elicits contraction to 5-HT in the in situ autoperfused rat mesenteric involves a mixed 5-HT_{2A}/5-HT_{2B}/5-HT_{2C} receptor, although mainly the 5-HT_{2B} and/or 5-HT_{2C} receptor subtype is involved. The vasoconstrictor effect induced by *m*-CPP (5-HT_{2C} receptor agonist) was non-significant and lower than that of α-methyl-5-HT, which reproduced the vasoconstrictor effect induced by 5-HT. In both cases, 5-HT and α-methyl-5-HT, the vasoconstrictor effect was blocked by the selective 5-$HT_{2B/2C}$ receptor antagonist, SB 206553. This antagonist exhibited high affinity for both the 5-HT_{2C} ($pK_i = 7{,}9$) and 5-HT_{2B} ($pA_2 = 8{,}9$) receptors (Kennett et al., 1996). In addition 5-HT has 300–1000-fold higher affinity for the 5-HT_{2B} receptor than for the 5-HT_{2A} receptor (Wainscott et al., 1996).

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References

Awouters, F., Niemen-Geers, C.J.E., Megens, A.A.H.P., Meert, T.J., Janssen, P.A.J., 1988. The pharmacological profile of ritanserin, very specific central serotonin S_2 antagonist. Drug Dev. Res. 1, 61–73.

Baxter, G., Kennett, G., Blaney, F., Blachburn, T., 1995. 5-HT_2 receptor subtypes: a family re-united? Trends Pharmacol. Sci. 16, 105–110.

Choppin, A., Connor, S.E., 1995. Presence of vasoconstrictor 5-HT_{1like} receptors revealed by precontraction of rabbit isolated mesenteric artery. Br. J. Pharmacol. 114, 309–314.

Choppin, A., Connor, S.E., 1996. Influence of vascular tone on vasoconstrictor responses to the 5-HT_{1like} receptor agonist sumatriptan in anaesthetised rabbits. Eur. J. Pharmacol. 304, 87–92.

Dohi, Y., Lüscher, T.F., 1991. Altered intra and extraluminal effects of 5-hydroxytryptamine in hypertensive mesenteric resistance arteries: contribution of the endothelium and smooth muscle. J. Cardiovasc. Pharmacol. 18, 278–284.

Jackson, E.K., Campbell, B., 1980. The in situ blood perfused rat mesentery; a model for assessing modulation of adrenergic neurotransmission. Eur. J. Pharmacol. 66, 217–224.

Kawasaki, H., Takasaki, K., 1984. Vasoconstrictor response induced by 5-hydroxytryptamine release from vascular adrenergic nerves by periarterial nerve stimulation. J. Pharmacol. Exp. Ther. 229, 816–822.

Kawasaki, H., Urabe, M., Takasaki, K., 1989. Presynaptic α_2-adrenoceptor modulation of 5-hydroxytriptamine and noradrenaline release from vascular adrenergic nerves. Eur. J. Pharmacol. 164, 35–43.

Kennett, G.A., Wood, M.D., Bright, F., Cilia, J., Piper, D.C., Gager, T., Thomas, D., Baxter, G.S., Forbes, I.T., Ham, P.A., Blackburn, T.P., 1996. In vitro and in vivo profile of SB 206553, a potent 5-$HT_{2C/2B}$ receptor antagonist with anxiolytic-like properties. Br. J. Pharmacol. 117, 427–434.

Kooy, N.W., Lewis, S.J., 1996. The peroxynitrite product 3-nitro-l-tyrosine attenuates the haemodynamic responses to angiotensin II in vivo. Eur. J. Pharmacol. 315, 165–170.

McGregor, D.D., Smirk, F.H., 1970. Vascular responses to 5-hydroxytryptamine in genetic and renal hypertensive rats. Am. J. Physiol. 219 (3), 687–690.

Meehan, A.G., Kreulen, D.L., 1990. Electrophysiological studies on the interaction of 5-hydroxytryptamine with sympathetic transmission in the guinea pig inferior mesenteric artery and ganglion. J. Pharmacol. Exp. Ther. 256 (1), 82–87.

Mohan Dhasmana, K., Zhu, N.Y., Cruz, S.L., Villalon, C.M., 1993. Gastrointestinal effects of 5-hydroxytriptamine and related drugs. Life Sci. 53, 1651–1661.

Porter, R.H.P., Benwell, K.R., Lamb, H., Malcolm, C.S., Allen, N.H., Revell, D.F., Adams, D.R., Sheardown, M.J., 1999. Functional characterization of agonists at recombinant human 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors in CHO-K1 cells. Br. J. Pharmacol. 128, 13–20.

Roth, B.L., Willins, D.L., Kristiansen, K., Kroeze, K., 1998. 5-Hydroxytryptamine$_2$-Family receptors (5-Hydroxytryptamine$_{2A}$, 5-hydroxytryp-tamine$_{2B}$, 5-hydroxytryptamine$_{2C}$): Where structure meets function. Pharmacol. Ther. 79 (3), 231–257.

Saxena, P.R., Villalon, C.M., 1991. 5-hydroxytryptamine. A chamaleon in the heart. Trends Pharmacol. Sci. 12, 223–227.

Shimamoto, Y., Shimamoto, H., Kwan, C., Daniel, E.E., 1993. Rauwolscine induces contraction in the dog mesenteric artery precontracted with KCl and endothelin-1: mediation via 5-hydroxytriptamine$_{1\text{-like}}$ receptors. J. Pharmacol. Exp. Ther. 264 (1), 201–209.

Shimamoto, Y., Shimamoto, H., Kwan, C., Daniel, E.E., 1994. Amplification of 5-hydroxyytryptamine-induced contractile responses via 5-hydroxytriptamine receptors and alpha-adrenoceptors in dog mesenteric artery and vein. J. Pharmacol. Exp. Ther. 268 (2), 779–784.

Taylor, E.M., Kaumann, A.J., 1994. Potentation of responses to sympathetic nerve stimulation and vasoconstrictor agents by SK and F 103829 in the feline mesenteric circulation. Br. J. Pharmacol. 111, 264–270.

Wainscott, D.B., Lucaites, V.L., Kursar, J.D., Baez, M., Nelson, D.L.,

1996. Pharmacological characterisation of the human 5-hydroxytryptamine$_{2B}$ receptor: evidence for species differences. J. Pharmacol. Exp. Ther. 276, 720–727.

Warner, T.D., 1990. Simultaneous perfusion of rat isolated superior mesenteric arterial and venous beds: comparison of their vasoconstrictor and vasodilator responses to agonists. Br. J. Pharmacol. 99, 427–433.

Watts, S.W., Gilbert, L., Webb, R.C., 1995. 5-hydroxytyptamine$_{2B}$ receptor mediates contraction in the mesenteric artery of mineralocorticoid hypertensive rats. Hypertension 26 (6), 1056–1059, (part 2).