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Effects of SL 65.0472, a novel 5-HT receptor antagonist, on 5-HT receptor mediated vascular contraction

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Abstract

5-Hydroxytryptamine (5-HT) contracts vascular smooth muscle and pharmacological and molecular biological data suggest that these effects are mediated primarily by stimulation of 5-HT_{1B} and 5-HT_{2A} receptor subtypes. We have studied the properties of 7-fluoro-2-oxo-4-[2-[4-(thieno[3,2-*c*] pyridin-4-yl) piperazin-1-yl] ethyl]-1,2-dihydroquinoline-1-acetamide (SL 65.0472), a novel 5-HT receptor antagonist, in isolated vascular preparations contracted by 5-HT or sumatriptan. In canine isolated saphenous vein strips (putatively 5-HT_{1B}-mediated contraction), SL 65.0472 antagonised sumatriptan-induced contractions in a competitive manner (pA_2 8.17 ± 0.36). 5-HT contracts rabbit aorta by stimulation of 5-HT_{2A} receptors. SL 65.0472 displaced the 5-HT concentration response curve in rabbit aorta rightwards with a significant reduction in maximum. The apparent pK_B value was 8.58 ± 0.18. 5-HT-induced contractions of human coronary arteries are mediated by a mixed population of 5-HT_{1B} and 5-HT_{2A} receptors. SL 65.0472 produced rightward parallel shifts of the 5-HT concentration response curves in all tissues studied (pA_2 8.8 ± 0.14, $n = 7$). In conclusion, SL 65.0472 is a potent antagonist of vascular smooth muscle contraction in vitro mediated by 5-HT receptor stimulation.

Keywords: SL 65.0472; Vasoconstriction; 5-HT_{1B} receptor; 5-HT_{2A} receptor

1. Introduction

5-Hydroxytryptamine (5-HT) contracts vascular smooth muscle by stimulation of multiple receptor subtypes (Saxena and Villalon, 1990). The two receptors most consistently implicated in these functional effects are 5-HT_{2A} receptors and a subtype initially classified as 5-HT_{1-like} (Bradley et al., 1986) but now considered likely to be the 5-HT_{1B} receptor (previously 5-$HT_{1D\beta}$, Hartig et al., 1996). 5-HT_{2A} receptors are responsible for contractions observed in several tissues including rabbit aorta and dog femoral artery (Apperley et al., 1980; Feniuk et al., 1985) and are characterised by their high sensitivity to antagonism by 5-HT_{2A} receptor antagonists such as ketanserin.

The 5-$HT_{1B/1D}$ receptor-agonist sumatriptan (Humphrey et al., 1988) contracts canine saphenous vein, human basilar artery (Parsons et al., 1989) and human coronary artery (Kaumann et al., 1994). These effects of sumatriptan and structurally related compounds (e.g. eletriptan) are resistant to block by ketanserin but are antagonised by 5-$HT_{1B/1D}$ receptor antagonists such as 2-methyl-4-(5-methyl-[1,2,4]oxadiazol-3-yl)-biphenyl-4-carboxylic acid[4-methoxy-3-(4-methyl-piperazin-1-yl)-phenyl]-amide (GR 127935, Clitherow et al., 1994) or *N*-[4-methoxy-3-(4-methyl-piperazin-1-yl)phenyl]-3-methyl-4-(4-pyridyl)-benzamide (GR 125743 Gupta et al., 1999). Lack of antagonism by relatively high concentrations of ketanserin is an important element in the pharmacological characterisation of these responses in human tissues. Ketanserin, in addition to potently blocking 5-HT_{2A} receptors, discriminates between human 5-HT_{1D} and 5-HT_{1B} receptors, showing moderate affinity for the 5-HT_{1D} subtype (pK_i 7.17)

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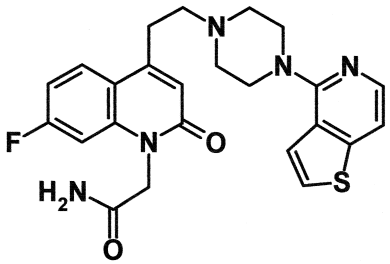

Fig. 1. The chemical structure of SL 65.0472 (7-fluoro-2-oxo-4-[2-[4-(thieno[3,2-*c*] pyridin-4-yl) piperazin-1-yl] ethyl]-1,2-dihydroquinoline-1-acetamide).

but very poor affinity for the 5-HT_{1B} subtype (pK_i 5.29, Zgombick et al., 1995). In addition, recent molecular biology studies have demonstrated abundant expression of 5-HT_{1B} receptor mRNA in vascular tissues which contract to sumatriptan, notably, canine saphenous vein (Sgard et al., 1996a), human temporal artery (Verheggen et al., 1998) and human coronary artery (Nilsson et al., 1999). By contrast, 5-HT_{1D} receptor mRNA was absent or only weakly expressed in these tissues.

Vasoconstrictor 5-HT_{1B} receptors may be more widespread than previously thought since a number of vascular tissues which do not respond to sumatriptan under quiescent conditions demonstrate prominent contractions to this 5-$HT_{1B/1D}$ agonist in the presence of threshold levels of another vasoconstrictor. Examples of this phenomenon include guinea pig iliac artery (Sahin-Erdemli et al., 1991), rabbit renal artery (Choppin and O'Connor, 1994), rabbit mesenteric artery (Choppin and O'Connor, 1995) and rabbit ear artery (Movaheddi and Purdy, 1997). The presence of 5-HT_{1B} mRNA and the absence of 5-HT_{1D} mRNA has been demonstrated in rabbit mesenteric artery tissue (Hinton et al., 1999).

In this paper, we report the properties of 7-fluoro-2-oxo-4-[2-[4-(thieno[3,2-*c*] pyridin-4-yl) piperazin-1-yl] ethyl]-1,2-dihydroquinoline-1-acetamide (SL 65.0472, Fig. 1), a novel 5-HT receptor antagonist (Berry et al., 2000; O'Connor et al., 2000), in isolated vascular tissues. We have selected for this study tissues used classically to evaluate vasoconstrictor effects mediated by 5-HT receptor stimulation, i.e. canine saphenous vein (a tissue with a putative 5-HT_{1B}-mediated response), rabbit aorta (a tissue showing a 5-HT_{2A}-mediated response) and, human coronary artery, a tissue where the contractile response to 5-HT is believed to involve a mixed population of 5-HT_{1B} and 5-HT_{2A} receptors (Kaumann et al., 1994).

2. Methods

The animals used in these experiments were treated in accordance with ethical guidelines edited by the European community (EC directive 86/609), the council of Europe (Convention ETS 123) and the French government (decree of 19.10.87).

2.1. Canine isolated saphenous vein

Saphenous veins were removed from Beagle or Anglopoitevin dogs (ECDL, either sex, 25–34 kg) anaesthetised with pentobarbital (35 mg/kg, i.v.). Helical strips approximately 0.4 cm in width and 0.5 cm in length were prepared by mounting the vein on metal cannula and then suspended in 20-ml tissue baths containing Krebs' solution of the following millimolar composition: NaCI 118.0; KCI 4.7; $MgCI_2$ 1.2; $CaCI_2$ 2.6; $NaHCO_3$ 25.0; glucose 11.1; ascorbic acid 0.11; (pH 7.4; 37°C) and aerated continuously with 95% O_2–5% CO_2. Endothelial integrity was not verified. The solution also contained atropine 1 μM (to inhibit muscarinic receptors); ketanserin 1 μM (to inhibit 5-HT_{2A} receptors); mepyramine 1 μM (to inhibit histamine H_1 receptors).

Contractile responses were recorded isometrically using Hugo Sachs model 351 force-displacement transducers (March Hugstentten, Germany), connected to a Gould 2400S polygraph (Courtaboeuf, France). Optimal responses were obtained when the tissues were subjected to an initial tension of 2 g. Data acquisition was performed automatically using the JAD.2 Notocord software (Croissy, France) on a PC Compaq (Houston, USA).

Strips were allowed to equilibrate for 30 min with several washes before exposure to a 3 μM noradrenaline challenge to test the viability of the preparation. Following a 30-min resting period, the first concentration–response curve to sumatriptan was obtained by exposing the preparations to cumulative additions of the compound until the maximal response was obtained. Another resting period with several washes allowed the strips to return to the basal tension. Then, an antagonist compound was added to the bath and left in contact with the tissue for 15 min prior to the second concentration–response curve to sumatriptan. Preliminary experiments have shown reproducibility of the contractile effect of two consecutive concentration–response curves to sumatriptan under control conditions in the same tissue (pD_2 values of 6.26 and 6.22 for first and second concentration–response curves; data not shown). A single antagonist concentration was tested per tissue.

2.2. Rabbit isolated aorta

Male white rabbits (New Zealand, Lebeau, France) weighing 2.4–3.1 kg were sacrificed by 6% pentobarbitone sodium injection (5 ml) in the ear vein. Thoracic aortas were removed, cleared of fat and adhering connective tissue. Tissues were cut into circular rings 4–5 mm in width. Each vascular ring was suspended between two stainless steel wire hooks in 20-ml tissue baths containing

modified Krebs' solution of the following millimolar composition: NaCI 118; KCI 4.7; $MgSO_4$ 1.2; KH_2PO_4 1.2; $CaCI_2$ 2.5; $NaHCO_3$ 25; glucose 11; with 1 μM phentolamine and 1 μM propanolol in order to inhibit α- and β-adrenoceptors, respectively, 6 μM cocaine to prevent uptake of 5-HT, 0.1% ascorbic acid; pH 7.4; 37°C, and aerated continuously with 95% O_2–5% CO_2. Endothelial integrity was not verified. Changes in tissue isometric force were measured using Grass type 9B73W force displacement transducers (Quincy, USA) and recorded on a Grass 79D polygraph (Quincy).

Aortic rings were allowed to equilibrate for 1 h under a resting tension of 2 g before exposure to pargyline (500 μM) for 30 min in order to irreversibly inhibit monoamine oxidase activity. At the end of this incubation period, tissues were washed several times in order to remove excess pargyline. To establish viability, vessels segments were contracted two times with KCI at a concentration of 60 mM, the second contraction being used as a reference contraction with which to compare agonist responses. Only one concentration–response curve to 5-HT was performed in each tissue to avoid any risk of desensitisation. Antagonists were added to the bath and left in contact with the tissue for 30 min prior to the 5-HT concentration–response curve.

2.3. Human isolated coronary artery

Human coronary arteries were obtained from four human hearts explanted from patients undergoing heart transplantation in the Service de Chirurgie Cardiovasculaire of Professeurs Gandjbakhch and Pavie (La Pitié-Salpètrière Hospital, Paris, France). Patients were 39 to 49 years old, three males and one female. All coronary arteries showed intermittent macroscopic atherosclerotic lesions. Right coronary and left interventricular coronary arteries were dissected from fresh hearts, placed in ice-cold sodium chloride solution and transported to the laboratory where they were transferred into modified Krebs' solution of the following miliimolar composition: NaCl 118; KCl 5.0; $CaCl_2$ 2.25; $MgSO_4$ 0.5; $NaHPO_3$ 1; $NaHCO_3$ 29; glucose 10; EDTA 0.04; ascorbic acid 0.2 to prevent oxidation of 5-HT; with 1 μM prazosin in order to block α_1-adrenoceptors and 6 μM cocaine to prevent uptake of 5-HT; pH 7.4; 37°C. Within 8 h of artery removal, helical strips ($n = 15$) approximately 0.4 cm in width and 0.5 cm in length cleared of fat and connective tissue, were suspended in 20 ml tissue baths and aerated continuously with 95% O_2–5% CO_2. Endothelial integrity was not verified, Chester et al. (1990) were unable to demonstrate 5-HT-induced vasorelaxation in precontracted human coronary arteries. Contractile responses were recorded isometrically using Hugo Sachs model 351 force-displacement transducers (March Hugstentten), connected to a Gould TA11 polygraph (Courtaboeuf). Optimal responses were obtained when the tissues were subjected to an initial tension of 2 g. Strips were allowed to equillibrate for 30 min with several washes before exposure to several KCl 123 mM challenges to test the viability of the preparation, the last contraction being used as a reference contraction (taken as 100%). Only one concentration–response curve to 5-HT was performed in each tissue to avoid risk of desensitization. Antagonists were added to the bath and left in contact with the tissue for 30 min prior to the 5-HT concentration–response curve. Data acquisition was performed automatically using the JAD 2 Notocord software (Croissy) on a PC Compaq.

2.4. Data analysis

In canine saphenous vein studies, responses were expressed as a percentage of the maximum contraction obtained with the first concentration response curve to sumatriptan taken as 100%. In rabbit aorta and human coronary artery studies, responses were expressed as the percentage of the maximal contraction obtained with the last challenge to KCI taken as 100%. Results are expressed as mean ± S.E.M.

The statistical comparison of sigmoid curves was carried out according to the extra sum of squares principle (De Lean et al., 1978) using the ALLFIT program to calculate EC_{50} (concentration of agonist that produced half-maximal response) and E_{max} (maximal effect) values.

To evaluate antagonist affinity in rabbit aorta and human coronary artery, pA_2 values were calculated according to the following equation (Furchgott, 1972): $pA_2 = -\log[\text{antagonist}]M + \log(\text{concentration ratio} - 1)$ where concentration ratio is the EC_{50} value of the agonist in the presence of the antagonist divided by the EC_{50} value of the agonist in control tissues. In canine saphenous vein, pA_2 values were calculated using the Schild plot method (Arunlakshana and Schild, 1959). In the case of noncompetitive antagonism (displacement with reduction of the E_{max}) apparent pK_B values were calculated using a RS/1 procedure (BBN software) (Kenakin, 1993).

2.5. Drugs

The following drugs were used: pentobarbitone (Sanofi Libourne, France), atropine (Prolabo, Paris, France) 5-HT creatinine sulfate, propranolol, ascorbic acid, noradrenaline obtained from Sigma, (St Louis, USA), cocaine obtained from Coopération Pharmaceutique Française (Paris, France), phentolamine mesylate obtained from RBI (Natick, USA), ketanserin, pargyline, sumatriptan, mepyramine, methiothepin, prazosin and SL 65.0472 were prepared by the Department of Chemistry, Synthélabo (Chilly-Mazarin, France). Stock solutions were made up in distilled water

except ketanserin, SL 65.0472 and methiothepin, which were dissolved in dimethyl sulfoxide (100%). Dilutions were made in distilled water.

3. Results

3.1. Canine isolated saphenous vein

Sumatriptan caused a concentration-related contraction of the canine isolated saphenous vein with an EC_{50} value of 0.35 ± 0.02 μM ($n = 14$). Under the same conditions, SL 65.0472 up to 1 μM was devoid of any direct effect on the saphenous vein (data not shown).

Exposure of canine saphenous vein strips to SL 65.0472 (0.01–0.1 μM) significantly shifted to the right the concentration–response curve to sumatriptan without reducing the maximal effect (Fig. 2). The slope of the regression line derived from Schild plot analysis was 1.18 (not significantly different from unity). The pA_2 value obtained from this Schild plot was 8.17 ± 0.36.

Under the same experimental conditions, methiothepin, the reference 5-HT_1 receptor antagonist, also shifted to the right the concentration–response curve to sumatriptan without reducing the maximal effect (data not shown). The slope of the Schild plot was 1.03 (not significantly different from unity). The pA_2 value was 8.43 ± 0.18.

3.2. Rabbit isolated aorta

5-HT caused concentration-dependent contractions of rabbit aorta rings with an EC_{50} of 1.11 ± 0.23 μM ($n = 9$) and E_{max} of $74 \pm 6\%$ compared to the KCI challenge.

In a previous study, we have demonstrated that SL 65.0472 1 μM does not modify KCl-induced contraction of rabbit aorta. Exposure of rabbit aorta rings to SL 65.0472 (0.01–1 μM) significantly displaced to the right the concentration–response curve to 5-HT, with a slight but significant reduction of the maximal effect at the higher antagonist concentrations. E_{max} values were $74 \pm 6\%$ (control), $65 \pm 3\%$ (SL 65.0472 0.01 μM), $61 \pm 4\%$ (SL 65.0472 0.1 μM, $p < 0.01$) and 50 ± 12 (SL 65.0472 1 μM, $p < 0.01$). The apparent pK_B value was 8.58 ± 0.18 (Fig. 3).

Under the same experimental conditions, ketanserin caused concentration-dependent rightward shifts of the concentration response curve to 5-HT without significantly changing the maximal effect (curves not shown). E_{max} values were $74 \pm 6\%$ (control), $77 \pm 5\%$ (ketanserin 0.1 μM), $62 \pm 10\%$ (ketanserin 0.3 μM) and $87 \pm 8\%$ (ketanserin 1 μM). The calculated pA_2 value was 7.90 ± 0.12 ($n = 3$).

3.3. Human isolated coronary artery

5-HT contracted human coronary arteries in a concentration-dependent manner with an EC_{50} of 0.110 ± 0.014 μM (4 patients; $n = 5$ tissues) and an E_{max} of $74 \pm 12\%$ compared to the KCl challenge.

Exposure to SL 65.0472 (0.03 μM), displaced the concentration–response curve to 5-HT in all tissues tested (4 patients; $n = 7$). The shifts were monophasic and parallel, allowing calculation of a pA_2 value of 8.8 ± 0.14. The effect was constant and reproducible and no regional differences were detected between the various tissues (Figs. 4 and 5).

The antagonist properties of ketanserin (0.03 μM) were evaluated in coronary arteries from two patients and gave

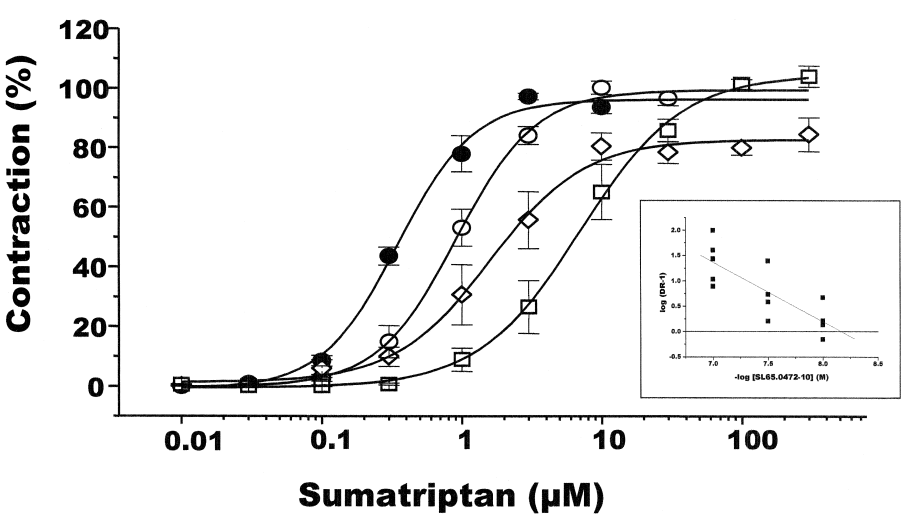

Fig. 2. Contractile concentration–response curves to sumatriptan in isolated canine saphenous vein tissues in the presence and absence of SL 65.0472, with the corresponding Schild plot shown as an insert. (●) Control, (○) 0.01, (◇) 0.03, (□) 0.1 μM SL 65.0472. Results are expressed as percentage of the E_{max} of the first concentration–response curve to sumatriptan taken as 100%. Each point represents mean ± S.E.M. of 4 to 14 preparations.

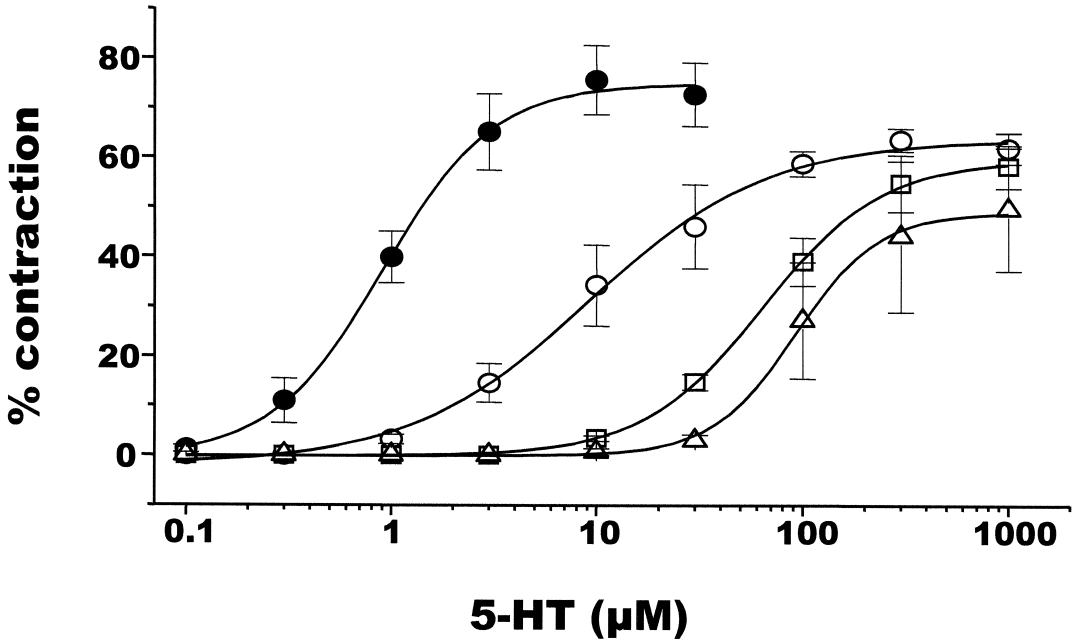

Fig. 3. Contractile concentration–response curves to 5-HT in isolated rabbit aorta tissues in the presence and absence of SL 65.0472. (●) control, (○) 0.01, (□) 0.1, (△) 1 μM SL 65.0472. Results are expressed as percentage of the E_{max} of the second challenge to KCI taken as 100%. Each point represents mean ± S.E.M. of four to nine preparations.

different results according to the patient. In the first patient, ketanserin significantly shifted to the right the concentration–response curve to 5-HT, without changing the maximal effect (data not shown, pA_2 8.7). In the second

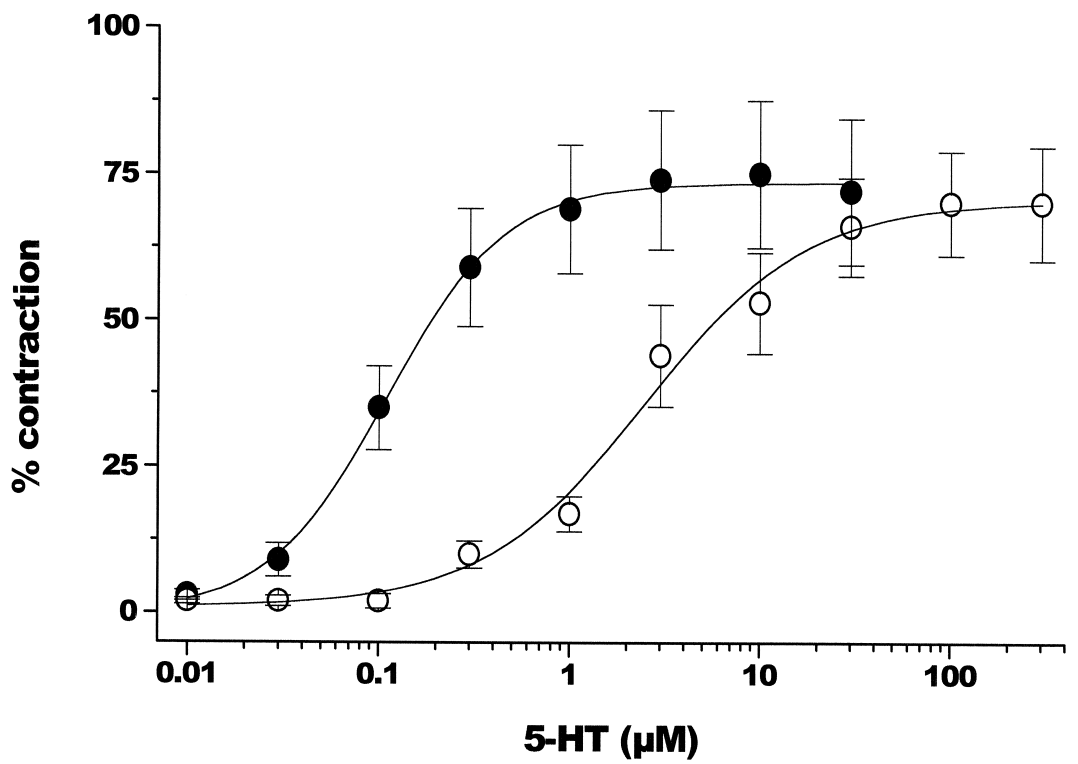

Fig. 4. Contractile concentration response curve to 5-HT in isolated human coronary artery tissues in the presence and absence of SL 65.0472 (0.03 μM). (●) control (n = 5 tissues, four patients), (○) SL 65.0472 0.03 μM (n = 7 tissues, four patients). Results are expressed as a percentage of the E_{max} to the second challenge with KCl taken as 100%. Each point represents mean ± S.E.M.

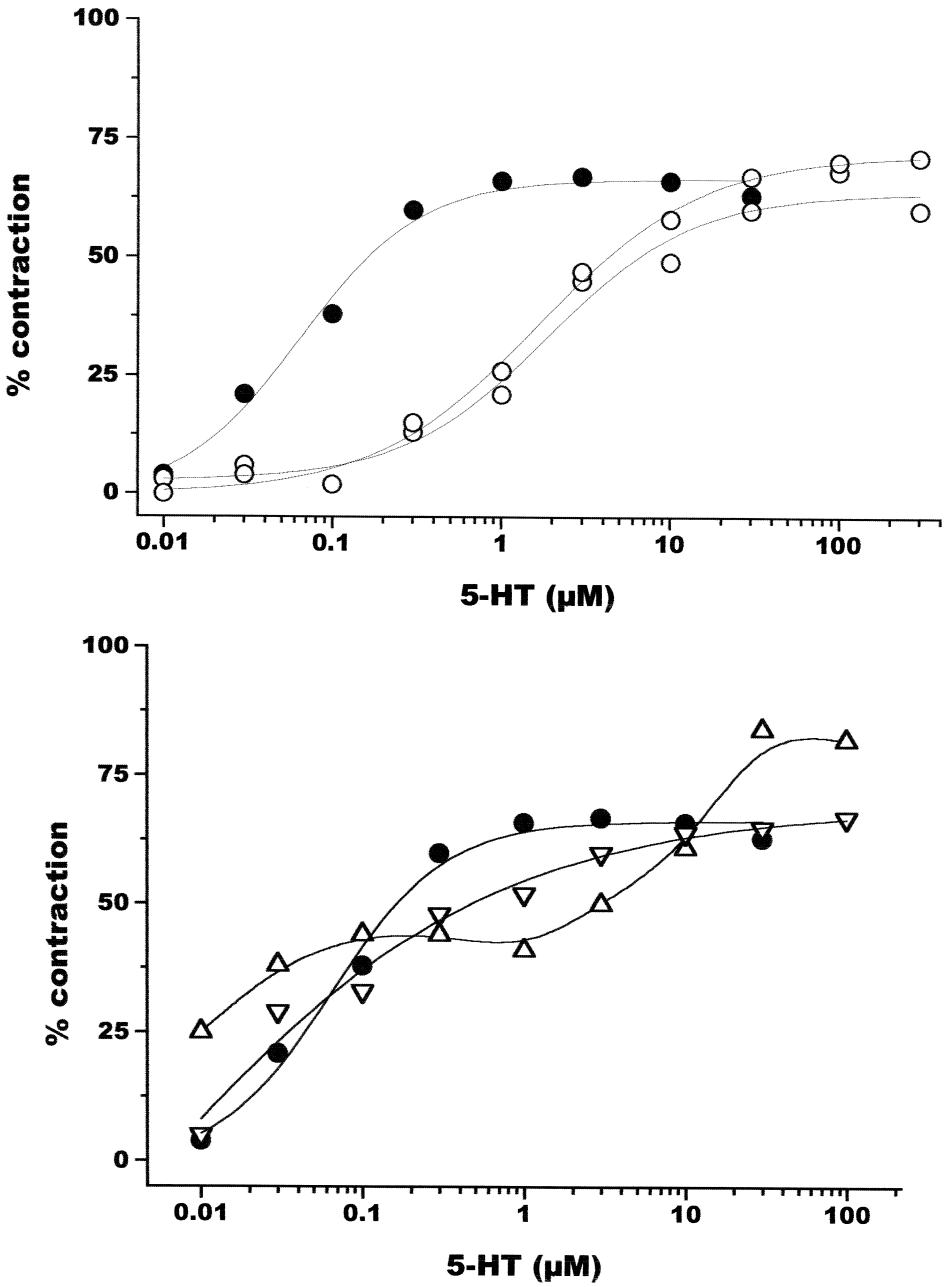

Fig. 5. Comparison of the effects of SL 65.0472 0.03 μM (○) (upper panel) and ketanserin 0.03 μM (△) (lower panel) on contractile responses to 5-HT in individual human coronary artery preparations taken from the same patient. Control tissue (●). Results are expressed as a percentage of the E_{max} to the second challenge with KCl taken as 100%.

patient, exposure to ketanserin evoked a biphasic curve to 5-HT with no antagonism at low concentrations of agonist in one tissue, whereas in the other tissue responses to 5-HT were resistant to ketanserin treatment (Fig. 5).

4. Discussion

This study has investigated the functional effects of SL 65.0472 at 5-HT receptors mediating contraction in three isolated vascular preparations. SL 65.0472 demonstrated antagonist properties in each preparation with high affinity (pA_2/pK_B values in the range 8–9). In view of the receptor types thought to be involved in these tissues, our data indicate that SL 65.0472 antagonises functional responses mediated by stimulation of 5-HT_{1B} and 5-HT_{2A} receptors.

In canine saphenous vein preparations the agonist potency of sumatriptan (EC_{50} value) and the antagonist affinity of methiothepin measured in our study are in good agreement with the initial characterisation of this model (Humphrey et al., 1988). RT-PCR (reverse transcriptase

polymerase chain reaction) studies using saphenous vein tissue obtained from our own laboratory have identified the presence of 5-HT_{1B} receptor mRNA but the absence of 5-HT_{1D} receptor mRNA (Sgard et al., 1996a). SL 65.0472 was characterised as a competitive antagonist in this model with a potency similar to that of methiothepin. The absence of a direct effect of SL 65.0472 on basal saphenous vein tone suggests that this compound has no intrinsic activity at 5-HT_{1B} receptors. In rabbit isolated aorta, SL 65.0472 blocked 5-HT_{2A} receptor-mediated contractions with a potency which was at least equivalent to that of ketanserin. Unlike ketanserin, the antagonist effects of SL 65.0472 were associated with a modest decrease in maximum response, indicating a noncompetitive component of its action.

We performed an evaluation of the effects of SL 65.0472 in human coronary artery tissues for two reasons. Firstly, this preparation is of obvious pathophysiological interest in the context of cardiovascular disease. Secondly, it represents an example of a well-characterised mixed population of 5-HT_{1B} and 5-HT_{2A} receptors. 5-HT and sumatriptan contract human coronary artery (Chester et al., 1990; Bax et al., 1993; Kaumann et al., 1994). In an extensive analysis based on agonist and antagonist responsiveness, Kaumann et al. (1994) concluded that the non-5-HT_{2A} receptor component was likely to be mediated by 5-HT_{1B} receptors. Using a two-receptor model, these authors also concluded that, overall, 5-HT_{1B} receptors made the major contribution (71%) to 5-HT contractions (vs. 29% mediated by 5-HT_{2A} receptors). Recent molecular biological studies are consistent with the pharmacological characterisation of this mixed receptor population. RT-PCR products corresponding to human 5-HT_{2A} and 5-HT_{1B} receptors were found to be strongly expressed in human coronary arteries (Ishida et al., 1999; Nilsson et al., 1999). Using a ribonuclease protection assay, Ishida et al. (1999) demonstrated 5-HT_{1B} and 5-HT_{2A} receptor signals in all patients examined (14/14) whereas neither 5-HT_{1A}, 5-HT_{1D} nor 5-HT_{2B} receptor signals were detected. Following immunohistochemical studies to measure the expression of receptor proteins, specific 5-HT_{1B} receptor immunoreactivity was observed in the coronary artery smooth muscle cell layer whereas 5-HT_{1D}-receptor immunoreactivity was absent (Nilsson et al., 1999). In the present study, the potency of 5-HT to contract human coronary artery preparations was equivalent to that reported by other investigators (Bax et al., 1993; Kaumann et al., 1994). SL 65.0472 (0.03 μM) produced a marked rightward shift of the 5-HT concentration response curve corresponding to a pA_2 value of 8.8 ± 0.14. It is interesting to note that in each of the seven tissues exposed to SL 65.0472 the displaced 5-HT concentration response curve was approximately sigmoid and monophasic. Given the molecular biological and pharmacological evidence indicating not only a mixed population of 5-HT_{1B} and 5-HT_{2A} receptors in human coronary arteries but a significant contribution of the 5-HT_{1B} subtype, it is reasonable to conclude that the effects of SL 65.0472 observed in our study result from block of both receptor subtypes. Because of the difficulty of obtaining fresh human coronary artery tissue, we were unable to perform a complete comparative study with ketanserin. However, in coronary artery strips obtained from one patient ketanserin failed to antagonise 5-HT-induced contractions over the first part of the concentration response curve, resulting in curves which were complex and probably representative of multiple receptors. By contrast, in tissues from the same patient, SL 65.0472 displaced the full 5-HT concentration response curve rightwards. These results are consistent with the existence of a significant ketanserin-resistant but SL 65.0472-sensitive component in this patient which, presumably, is mediated by 5-HT_{1B} receptor stimulation.

There is growing evidence that 5-HT_{1B} receptor-mediated vasoconstriction may be functionally important in man. In addition to human coronary artery, sumatriptan contracts other isolated human vascular tissues such as pulmonary artery (MacLean et al., 1996) and internal mammary artery (Yildiz et al., 1996). Furthermore, administration of sumatriptan to man causes increases in blood pressure, total peripheral resistance and pulmonary vascular resistance accompanied by reductions in large coronary artery diameter (MacIntyre et al., 1992, 1993). SL 65.0472, by virtue of its ability to block vasoconstrictor 5-HT_{1B} and 5-HT_{2A} receptor responses at nanomolar concentrations, could have utility for the treatment of conditions in which local release of 5-HT following platelet aggregation results in vasospasm. In this context, we have demonstrated in in vivo models that SL 65.0472 inhibits 5-HT-induced vasoconstriction and has potent antithrombotic properties (Berry et al., 2000; O'Connor et al., 2000). Ligand binding studies (unpublished) show that SL 65.0472 possess high affinity for several 5-HT_1 and 5-HT_2 receptor subtypes but has no affinity for 5-HT_3 or 5-HT_4 receptors. In the three vascular preparations used in this study, methiothepin would be expected to present a similar profile to SL 65.0472. However, unlike methiothepin, SL 65.0472 shows excellent haemodynamic tolerance in vivo (probably due to its relatively modest adrenoceptor activities) and does not readily penetrate the CNS (unpublished data). Based on these characteristics, SL 65.0472 is of potential therapeutic interest for the treatment of cardiovascular diseases. Previous 5-HT receptor antagonists developed for this purpose (e.g. ketanserin) are 5-HT_{2A} receptor-selective and, therefore, unlike SL 65.0472, cannot oppose vasoconstriction mediated by 5-HT_{1B} receptor stimulation.

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