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Influence of vascular tone on vasoconstrictor responses to the 5-HT_1-like receptor agonist sumatriptan in anaesthetised rabbits

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Abstract

The cardiovascular profile of the 5-HT_1-like receptor agonist sumatriptan has been studied in anaesthetised rabbits pretreated with chlorisondamine (0.5 mg kg^{-1} i.v.) and enalapril (0.3 mg kg^{-1} i.v.) to eliminate autonomic reflexes and minimise endogenous vasoconstrictor tone. Under these conditions sumatriptan (2–100 μg kg^{-1} i.v.) produced modest increases in carotid vascular resistance but had no significant influence on heart rate, blood pressure or mesenteric vascular resistance. In a similarly pretreated group of animals in which vasoconstrictor tone was elevated by infusion of angiotensin (100 ng kg^{-1} min^{-1} i.v.) sumatriptan caused moderate increases in blood pressure (55 ± 5 to 65 ± 5 mm Hg after 25 μg kg^{-1} i.v.) and mesenteric vascular resistance (1.4 ± 0.2 to 1.6 ± 0.2 mm Hg min ml^{-1} after 25 μg kg^{-1} i.v.) and tended to produce a greater carotid vasoconstriction (3.6 ± 0.5 to 4.7 ± 0.7 mm Hg min ml^{-1} after 25 μg kg^{-1}). These effects were antagonised by methiothepin 0.3 mg kg^{-1} i.v. implying the involvement of 5-HT_1-like receptor stimulation. Hence, the presence of angiotensin produces a modest amplification of the vasoconstrictor effects of sumatriptan and, in particular, unmasks a constriction of the mesenteric vascular bed. The degree of synergy observed between these two vasoconstrictors was, however, less marked than might have been expected on the basis of previous isolated tissue studies.

Keywords: 5-HT_1-like receptor; Vasoconstriction; Sumatriptan; (Rabbit, anesthetised); Vasoconstrictor synergy; Vascular tone

1. Introduction

5-Hydroxytryptamine (5-HT) produces vasoconstriction, an effect which in certain vascular tissues involves stimulation of a receptor which has been characterised on functional/operational criteria as 5-HT_1-like (Bradley et al., 1986; Martin, 1994). 5-HT_1-like mediated vasoconstriction is subject to considerable species and tissue variation, the best known examples being cerebral and coronary vessels of rabbit, dog and primate (Parsons and Whaley, 1989; Connor et al., 1989). The identification of sumatriptan (Humphrey et al., 1988) a relatively selective 5-HT_1-like/5-HT_{1D} receptor agonist provides a useful research tool for investigation of the role of this receptor subtype, particularly in vivo. Studies of sumatriptan in intact anaesthetised dog, cat and pig have demonstrated a clearly defined increase in carotid vascular resistance resulting from constriction of arterio-venous anastamoses, but little effect on other vascular territories (Feniuk et al., 1989; Perren et al., 1989; Den Boer et al., 1992). However, in more recent anaesthetised dog studies, potent sumatriptan-induced renal vasoconstriction (Cambridge et al., 1995) and saphenous venoconstriction (Drieu la Rochelle and O'Connor, 1995) have also been reported.

We have investigated the vasoconstrictor profile of sumatriptan in anaesthetised rabbits. Our study was orientated particularly towards the evaluation of a possible influence of vascular tone on vasoconstrictor responsiveness to sumatriptan in an in vivo setting. Isolated tissue studies have demonstrated that 5-HT_1-like receptors mediating vasoconstriction may be functionally silent unless tissues are precontracted by another vasoconstrictor agent. In the case of the rabbit, such vasoconstrictor synergy involving 5-HT_1-like receptors has been reported for femoral (MacLennan and Martin, 1992), renal (Tadipatri et al., 1991; Choppin and O'Connor, 1994) and mesenteric (Choppin and O'Connor, 1995) arteries. It is, therefore, possible that in vivo the level of endogenous vascular tone may also in some way determine the functional importance of 5-HT_1-like receptors.

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To investigate this issue we have tested the effects of sumatriptan in anaesthetised rabbits using two different experimental conditions. In the first series of experiments pharmacological interventions (ganglion blockade + enalapril) were utilised with the objectives of reducing endogenous vasoconstrictor tone and reflex control of vascular tone to a minimum. In a second series of animals, vasoconstrictor tone was re-established in a controlled fashion by infusion of angiotensin II. We studied two vascular beds. The carotid, for which a vasoconstrictor response to sumatriptan is well-documented in larger species, and the mesenteric vascular bed. The choice of the latter was made based on isolated tissue studies showing that rabbit mesenteric arteries demonstrate prominent vasoconstrictor responses to sumatriptan only after precontraction with the thromboxane mimetic, 9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin $F_{2\alpha}$ (U46619) (Choppin and O'Connor, 1995).

2. Materials and methods

2.1. Surgical preparation

Male New Zealand white rabbits (2.0–2.5 kg) were anaesthetized with sodium pentobarbital (30 mg kg^{-1} i.v. followed by infusion of 24 mg kg^{-1} h^{-1}) and a tracheotomy was performed. Artificial ventilation was maintained via an Ugo Basile respiration pump at a rate of 30 strokes min^{-1} and a stroke volume of 15–17 ml min^{-1}. The effectiveness of this ventilation was regularly monitored by analysis of femoral arterial blood samples to ensure that blood gases (pO_2 and pCO_2) and pH were within normal limits. Body temperature was maintained at 40°C. Polyethylene cannulae (Clay Adams, Parippany, NJ) were inserted into a femoral artery to record the arterial blood pressure, from which was derived the heart rate, and into a femoral vein for drug administration.

Electromagnetic blood flow probes (Carolina Medical Electronics) were placed on the right common carotid artery and on the main mesenteric artery to measure the changes of blood flow in these vessels. Each animal was allowed to equilibrate for at least 1 h prior to starting the experimental studies. In order to quantify vasoconstriction or vasodilatation, percentage changes in vascular resistance were calculated for carotid and mesenteric beds (resistance was obtained by dividing mean arterial pressure by the mean blood flow).

2.2. Experimental protocol

Animals were divided randomly into three groups (n = 6–7). In all three groups endogenous vascular tone and reflexes were suppressed by pretreatment with the ganglion-blocker chlorisondamine (0.5 mg kg^{-1} i.v.) and the inhibitor of angiotensin converting enzyme enalapril (0.3 mg kg^{-1} i.v.) given at 10-min intervals. The following protocols were then undertaken.

Group 1 Ascending bolus i.v. doses of sumatriptan (2–100 μg kg^{-1}) given at 15-min intervals.

Group 2 Continuous infusion of angiotensin II (100 ng kg^{-1} min^{-1} i.v.) to provide and maintain vasoconstrictor tone. Ascending i.v. bolus doses of sumatriptan (2–100 μg kg^{-1}) given at 15-min intervals.

Group 3 Angiotensin infusion as in group 2. Administration of the 5-HT_1-like receptor antagonist methiothepin (0.3 mg kg^{-1} i.v.) followed 10 min later by ascending bolus i.v. doses of sumatriptan (2–100 μg kg^{-1}) given at 15-min intervals.

The choice of antagonist doses used was based on studies reported previously, e.g. Drieu la Rochelle and O'Connor (1995) (methiothepin) and Lefèvre-Borg et al. (1988) (enalapril and chlorisondamine).

2.3. Drugs

Sumatriptan succinate was synthesized within the Chemistry Department of Synthélabo Recherche. Sources of other compounds used were: methiothepin mesylate (RBI), chlorisondamine chloride (Ciba Geigy), enalapril maleate (Merck) and angiotensin II (Sigma). Doses of the above drugs were calculated as the free base, dissolved and diluted in distilled water and administered in saline.

2.4. Data analysis

Basal values of cardiovascular parameters were measured before each dose of sumatriptan and again at the time of peak vasoconstrictor effect. All values shown are mean values ± S.E.M. from n rabbits. Following each treatment, differences between vascular resistance recorded before and after each dose of sumatriptan were compared using an analysis of variance and an analysis of Winer after logarithmic transformation (Winer, 1971). When appropriate, Student-Newman-Keuls' multiple range test was performed. A value of $P < 0.05$ was taken to be statistically significant.

3. Results

Pretreatment with chlorisondamine (0.5 mg kg^{-1} i.v.) followed by enalapril (0.3 mg kg^{-1} i.v.) caused marked falls in mean arterial pressure, heart rate and mesenteric vascular resistance (Table 1) with a slight reduction in carotid vascular resistance. In the presence of chlorisondamine and enalapril (group 1) ascending bolus doses of sumatriptan (2–100 μg kg^{-1} i.v.) had no effect on heart rate, produced minor changes in mean arterial pressure (+2.5 ± 0.4 mm Hg after sumatriptan 25 μg kg^{-1} i.v.) and in mesenteric vascular resistance (Fig. 1) and modest

Table 1
Effects of pharmacological treatments on basal cardiovascular values

	CBF (ml min^{-1})	CVR (mm Hg min ml^{-1})	MBF (ml min^{-1})	MVR (mm Hg min ml^{-1})	MAP (mm Hg)	HR (beats min^{-1})
Group 1						
Control	19±2	4.4±0.8	47±2	1.6±0.1	76±4	311±11
After CHLOR + ENA	11±3	4.1±1.2	30±2	1.0±0.1	28±1	229± 8
Group 2						
Control	15±3	4.3±0.6	34±2	1.6±0.1	56±5	341±18
After CHLOR + ENA + ANG	17±3	3.8±0.6	37±4	1.6±0.2	55±4	311±21
Group 3						
Control	15±2	4.5±0.4	40±4	1.7±0.1	66±3	314±24
After CHLOR + ENA + ANG + MET	15±4	4.3±0.5	35±4	1.6±0.2	56±7	309±20

CHLOR, chlorisondamine 0.5 mg kg^{-1} i.v.; ENA, enalapril 0.3 mg kg^{-1} i.v.; ANG, angiotensin II 100 ng kg^{-1} min^{-1} i.v.; MET, methiothepin 0.3 mg kg^{-1} i.v.; CBF, carotid blood flow; CVR, carotid vascular resistance; MBF, mesenteric blood flow; MVR, mesenteric vascular resistance; MAP, mean arterial pressure; HR, heart rate.

increases in carotid vascular resistance which were dose-related up to 25 μg kg^{-1} and plateaued thereafter (Fig. 1).

In animals pretreated in identical fashion with chlorisondamine (0.5 mg kg^{-1} i.v.) and enalapril (0.3 mg kg^{-1} i.v.), continuous infusion of angiotensin (100 ng kg^{-1} min^{-1} i.v.) restored cardiovascular parameters to normal levels. No significant differences were evident between pre- and postdrug values (group 2, Table 1). The stimulant effects of angiotensin were well-maintained throughout the protocol, the values of mean arterial pressure, mesenteric vascular resistance and carotid vascular resistance in this group just before the first and last doses of sumatriptan being 55 ± 4 and 60 ± 4 mm Hg, 1.6 ± 0.2 and 1.5 ± 0.2 mm Hg min ml^{-1}, 3.8 ± 0.6 and 4.0 ± 0.6 mm Hg min ml^{-1}, respectively. Under these conditions, sumatriptan (2–100 μg kg^{-1} i.v.) produced more prominent dose-related carotid vasoconstriction and modest dose-related increases in mesenteric vascular resistance. Fig. 1 shows the comparison of sumatriptan-induced changes in carotid and mesenteric vascular resistances. The changes in mesenteric vascular resistance in angiotensin-treated animals (group 2) were significantly different when compared with group

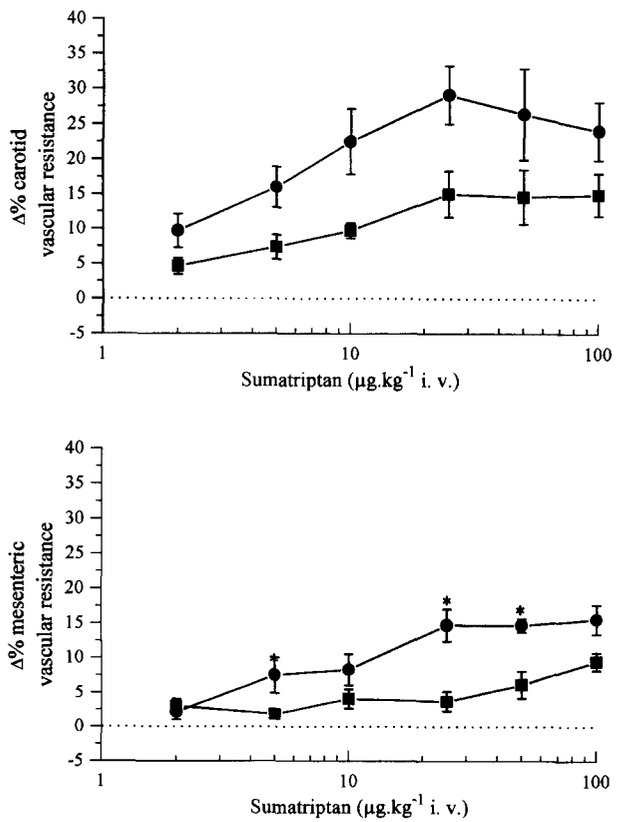

Fig. 1. The responsiveness of carotid and mesenteric vascular beds to sumatriptan (2–100 μg kg^{-1} i.v.) in the presence (●) or absence (■) of continuous infusion of angiotensin II (100 ng kg^{-1} min^{-1} i.v.) to elevate vascular tone. Both groups of animals were pretreated with chlorisondamine (0.5 mg kg^{-1} i.v.) and enalapril (0.3 mg kg^{-1} i.v.). Values shown are mean ± S.E.M. (n = 6–7). * P < 0.05 compared with the effect of the same dose of sumatriptan in the absence of angiotensin.

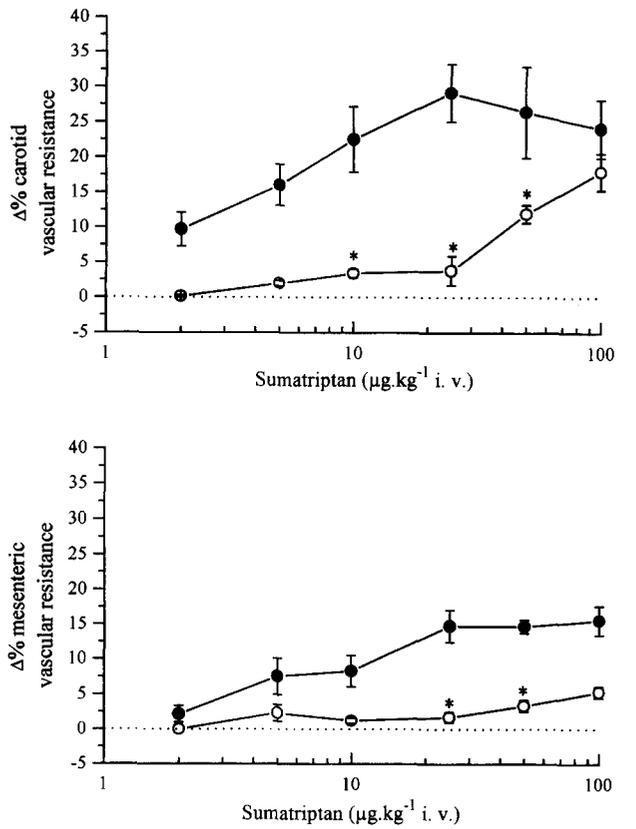

Fig. 2. Sumatriptan-induced changes in carotid and mesenteric vascular resistances in the presence (○) and absence (●) of methiothepin 0.3 mg kg^{-1} i.v. Both groups of animals were pretreated with chlorisondamine (0.5 mg kg^{-1} i.v.), enalapril (0.3 mg kg^{-1} i.v.) and angiotensin (100 ng kg^{-1} min^{-1} i.v.). Values shown are mean ± S.E.M. (n = 6–7). * P < 0.05 compared with the effect of the same dose of sumatriptan in the absence of methiothepin. Blood pressure and other cardiovascular parameters measured remained reasonably stable in the animals receiving methiothepin. Mean ± S.E.M. for each parameter just before the first dose of sumatriptan tested and just before the last dose tested were as follows: mean blood pressure 56 ± 7, 58 ± 8 mm Hg; heart rate 309 ± 20, 292 ± 19 bpm; carotid blood flow 15 ± 4, 21 ± 4 ml min^{-1}; mesenteric blood flow 35 ± 4, 35 ± 4 ml min^{-1}.

1 (P < 0.05). In group 2 sumatriptan produced increases in mean arterial pressure (55 ± 5 to 65 ± 5 mm Hg after sumatriptan 25 μg kg^{-1} i.v.) which were sometimes preceded by a transient fall in this parameter. Heart rate was not affected by sumatriptan administration.

In animals pretreated with chlorisondamine (0.5 mg kg^{-1} i.v.), enalapril (0.3 mg kg^{-1} i.v.) and angiotensin II (100 ng kg^{-1} min^{-1} i.v.), the administration of the 5-HT$_1$-like receptor antagonist methiothepin (0.3 mg kg^{-1} i.v.) did not modify basal cardiovascular parameters (group 3, Table 1). Notably, basal values of carotid and mesenteric vascular resistances were similar to those observed in group 2. Pretreatment with methiothepin produced a marked attenuation of the vasoconstrictor effects of sumatriptan. Fig. 2 shows that the response of carotid vascular resistance to sumatriptan was right-shifted ~ 20-fold. For example, the change in carotid vascular resistance pro-

duced by 25 μg kg^{-1} i.v. sumatriptan which was $+1.10 \pm 0.23$ mm Hg min ml^{-1} in group 2 was reduced to $+0.13 \pm 0.08$ mm Hg min ml^{-1} in the presence of methiothepin ($P < 0.05$). Similarly, the modest increases in mesenteric vascular resistance were virtually eliminated in methiothepin-treated animals. Methiothepin also antagonised sumatriptan-induced increases in mean arterial pressure. For example, after 25 μg kg^{-1} i.v. sumatriptan blood pressure increased from 55 ± 5 to 65 ± 5 mm Hg in group 2 compared with 55 ± 7 to 57 ± 8 mm Hg in group 3.

4. Discussion

The use of pithing or pharmacologically mediated blockade of autonomic ganglia to create an areflex animal model is a classical technique which has been widely used to study vascular responsiveness to vasoconstrictor agents, notably those acting via α-adrenoceptor stimulation. As one of our objectives was to reduce, to a minimum, endogenous vasoconstrictor tone, we also pretreated animals with enalapril to block generation of the potent vasoconstrictor angiotensin II. This seemed appropriate because the renin-angiotensin system is known to be activated by anaesthesia and surgical procedures (Pettinger et al., 1975), indeed, enalapril had significant cardiovascular effects in our model. Naturally, other endogenous vasoconstrictor mechanisms rest intact, for example those involving vascular endothelium, however, we considered that by inactivating the sympathetic nervous and renin-angiotensin systems we had eliminated the two major contributors to vasoconstrictor tone. An additional advantage of working in ganglion-blocked animals is elimination of possible sumatriptan-induced vasodilation mediated through stimulation of prejunctional 5-HT$_1$-like receptors on sympathetic nerve terminals (Molderings et al., 1990).

Under these experimental conditions, administration of the 5-HT$_1$-like receptor agonist sumatriptan produced no significant changes in blood pressure or mesenteric vascular resistance but a modest dose-related increase in carotid vascular resistance. The lack of a significant increase in blood pressure after administration of sumatriptan under conditions where vasoconstrictor tone is low and reflexes are absent indicates that 5-HT$_1$-like receptor stimulation does not produce systemic vasoconstriction in the rabbit. This observation is in keeping with the majority of data published in other species in vivo and in vitro (Saxena and Villalon, 1990) which shows that although 5-HT$_1$-like receptors may mediate constriction of certain conduit arteries, they have no major influence on systemic vascular resistance. By contrast, stimulation of the 5-HT$_2$ receptor subtype by 5-HT produces marked increases in blood pressure (+80 mm Hg) in ganglion-blocked animals (Saxena and Lawang, 1985). Man, where sumatriptan administration does increase blood pressure, may represent one of the exceptions to this rule (MacIntyre et al., 1992). It is, however, important to note that most of the in vivo data available with sumatriptan involves intact animals rather than the ganglion-blocked model used in our study. The dose-related increase in carotid vascular resistance observed after sumatriptan is consistent with observations reported in other species (Perren et al., 1989). This effect has been attributed to constriction of arterio-venous anastomoses mediated by 5-HT$_1$-like receptor stimulation. Our data indicate that sumatriptan-induced carotid vasoconstriction does not, therefore, show an absolute dependence on vascular tone provided by sympathetic nerves and endogenous angiotensin.

Infusion of angiotensin produced a sustained and stable increase in blood pressure and mesenteric vascular resistance. Since heart rate was also restored to normal values it seems that angiotensin provided combined vasoconstriction and cardiac stimulation. The primary objective of our study was to investigate whether administration of a vasoconstrictor (angiotensin), under conditions where endogenous vasoconstrictor activity was inhibited, would modify vascular reactivity to sumatriptan. This was in fact the case since, in the presence of angiotensin, sumatriptan produced small increases in blood pressure, a more pronounced carotid vasoconstriction although the differences were not statistically significant, and a small constriction of the mesenteric vascular bed, a territory which had been unresponsive to sumatriptan in the absence of exogenous angiotensin. Sumatriptan-induced increases in carotid and mesenteric resistances occurred over the dose range 2–25 μg kg^{-1} i.v. which is in good agreement with other reports of sumatriptan-induced vasoconstriction in vivo (Drieu la Rochelle and O'Connor, 1995). Furthermore, they were markedly inhibited by the 5-HT$_1$-like/5-HT$_2$ receptor antagonist methiothepin. Although the relative lack of selectivity of methiothepin means that it is not the ideal tool to confirm that these responses were 5-HT$_1$-like receptor mediated, this seems the only reasonable explanation given the low potency of sumatriptan for 5-HT$_2$ receptors (Humphrey et al., 1988).

Thus, in the presence of angiotensin, administration of sumatriptan causes moderate local and systemic vasoconstriction through 5-HT$_1$-like receptor stimulation. Our study presents the first evidence in vivo that supplementary vasoconstrictor tone can amplify 5-HT$_1$-like receptor mediated vasoconstriction and may, as in the case of the mesenteric vascular bed, uncover functional responses which are not evident under different experimental conditions. However, it has to be stated that the degree of amplification produced by angiotensin was small and probably not of major physiological significance. The extent of the vascular synergy between angiotensin and sumatriptan observed in this in vivo study appears much less marked than that shown in vitro. For example, in quiescent isolated rabbit mesenteric arteries sumatriptan was inactive up to 10^{-4} M, whereas in tissues modestly precontracted with U46619, sumatriptan produced concentration-related con-

tractions with a maximum response which exceeded that of potassium chloride 80 mM and an EC_{50} of 2×10^{-7} M (Choppin and O'Connor, 1995). There are, of course, many differences between these in vitro and in vivo settings which could explain this discrepancy. Possibly the most important of these is that the isolated mesenteric artery is a conduit vessel whereas mesenteric vascular resistance as measured in the anaesthetised rabbit reflects primarily the reactivity of small mesenteric arterioles. The choice of exogenous vasoconstrictor agent may also be important, although we have observed a synergy between angiotensin and sumatriptan in vitro (unpubl. obs.) and isolated tissue studies suggest that spasmogens of many different mechanistic classes are capable of 'unmasking' 5-HT_1-like mediated vasoconstriction (Choppin and O'Connor, 1993). However, it is not always possible to translate such studies directly to the in vivo setting since some of the agents commonly used for this purpose in vitro (e.g. potassium chloride, U46619) are unsuitable for use in vivo because of the likelihood of adverse effects. Additional in vivo studies will be required to determine whether the protocol used in the present study was optimal for investigating the phenomenon of vascular synergy as concerns vasoconstrictor 5-HT_1-like receptors.

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