Triptan-induced contractile (5-HT$_{1B}$ receptor) responses in human cerebral and coronary arteries: relationship to clinical effect

Lars EDVINSSON*, Erik UDDMAN*, Angelica WACKENFORS*, Anthony DAVENPORT†, Jenny LONGMORE‡ and Malin MALMSJÖ*

Abstract

Triptans are agonists at 5-HT$_{1B}$ and 5-HT$_{1D}$ (where 5-HT is 5-hydroxytryptamine; serotonin) receptors and cause vasoconstriction of isolated blood vessels. The aim of the present study was to determine vasoconstrictor potency (EC$_{50}$) of triptans in human coronary and cerebral arteries and to examine whether there was any relationship with the maximal plasma concentrations (C$_{max}$; nM) of the drugs achieved following oral administration of clinically relevant doses to man using values reported in the literature. We also examined the expression of 5-HT$_{1B}$ receptors in atherosclerotic and normal coronary arteries. The vasocontractile responses to sumatriptan, rizatriptan or eletriptan were characterized by in vitro pharmacology. The ratio of C$_{max}$/EC$_{50}$ was calculated. 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors were visualized by immunohistochemical techniques in coronary arteries. Sumatriptan, rizatriptan and eletriptan were powerful vasoconstrictors in cerebral artery. The rank order of agonist potency was eletriptan = rizatriptan = sumatriptan. In the coronary artery, the triptans were weaker vasoconstrictors. The rank order of potency was similar. In cerebral artery the ratio of C$_{max}$/EC$_{50}$ was not significantly different from unity, indicating a relationship between these two parameters. In general for the coronary artery, the ratios were significantly less than unity, indicating no direct relationship. Immunohistochemistry showed expression of 5-HT$_{1B}$ receptors in the medial layer, but did not reveal any obvious difference in 5-HT$_{1B}$ receptor expression between normal and atherosclerotic coronary arteries. The results support the notion that triptans are selective vasoconstrictors of cerebral arteries over coronary arteries and that there is a relationship between vasoconstrictor potency in cerebral arteries and clinically relevant plasma levels.

Introduction

The drugs used currently that act as acute abortive antimigraine therapies are defined as agonists at 5-HT$_{1B}$/1D receptors (where 5-HT is 5-hydroxytryptamine; serotonin) [1]. These drugs cause vasoconstriction in human blood vessels both in vitro and in vivo [2–7], although early haemodynamic studies have shown a selective action in causing vasoconstriction in the cranial vascular bed compared with peripheral arteries [8]. The original concept of sumatriptan was to design a selective 5-HT$_{1D}$-receptor agonist (with the 5-HT$_{1B}$ receptor

Key words: cerebral artery, coronary artery, 5-HT (5-hydroxytryptamine) receptor, plasma concentration, in vitro pharmacology, smooth muscle, triptan.

Abbreviation: 5-HT, 5-hydroxytryptamine.

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being the rat homologue). Subsequently, molecular cloning revealed that the 5-HT1D and 5-HT1B receptors were receptor subtypes (as opposed to species homologues). Human 5-HT1D and 5-HT1B receptors are closely related and therefore sumatriptan and other drugs in this class (triptans) have similar activity on both human receptor subtypes [9]. The triptans also have high affinity for the 5-HT1F subtype of receptors, but functional receptor subtypes [9].

Coronary arteries vasoconstrictor responses to triptans that in human blood vessels (including cranial and therefore sumatriptan and other drugs in this class (triptans) have similar activity on both human receptor subtypes [9]).

The aim of the present study was to characterize further the triptan-induced contractile responses in human small cerebral and coronary arteries and to relate their contractile responses to the reported plasma levels of these drugs obtained after administration in clinically relevant doses in man. Since triptans are contra-indicated in patients with known cardiovascular disease, we also examined the same relationship for coronary arteries and whether there was any overt change in the expression of 5-HT1B receptor immunoreactivity (and therefore potential vasoreactivity) in coronary heart disease.

**METHODS**

**Tissue samples**

Cerebral (cortex) arteries were obtained from adult patients (n = 13; six males and seven females) undergoing neurosurgery for an intracranial tumour or removal of an epileptic cortical region. Coronary (epicardial) arteries (n = 12; five males and seven females) were obtained from adult patients undergoing surgery for valvular disease due to aortic stenosis (n = 4) or removed from the explanted heart in conjunction with heart transplantation due to cardiomyopathy (n = 8). The vessels were macroscopically normal with no visible atheromatosis. All vessels were placed in bicarbonate buffer solution (119 mM NaCl, 15 mM NaHCO3, 4.6 mM KCl, 1.2 mM MgCl2, 1.2 mM NaH2PO4, 1.5 mM CaCl2 and 5.5 mM glucose, pH 7.4) aerated with 5% CO2 in O2 giving a pH of 7.4, and immediately transported to the laboratory for investigation. The arteries were carefully dissected free from the pia-arachnoid membrane or connective tissues under a microscope.

Informed consent was obtained from the patients for removal of the tissue used in the study. The Human Ethics Committee of the University of Lund, Sweden approved the study.

**Drugs**

The following agents were used in the experiments: sumatriptan (a gift from GlaxoWellcome, Stevenage, U.K.), eletriptan and rizatriptan (both synthesized by Medicinal Chemistry, Merck, Sharp & Dohme, Harlow, U.K.). SB224289 was a gift from Dr A. Maassen Van Den Brink, University Medical Centre, Rotterdam, The Netherlands. All the drugs were dissolved in 0.9% saline.

The concentrations are expressed as the final molar concentration in the tissue bath.

**Vasomotor responses**

The vessels were dissected free under a microscope and cut into cylindrical segments (1–2 mm long, 0.5–1 mm in outer diameter for cerebral and 0.5–2 mm for coronary arteries with macroscopically intact endothelium). After removal, the vessels were immediately immersed into an ice-cold bicarbonate buffer solution and transported to the laboratory (within 1 h) for preparation for the pharmacological study. The segments were mounted on two metal prongs, one of which was connected to a force displacement-transducer (FT03C; Grass Inc.), and the other to a displacement device. The position of the holder could be changed by means of a movable unit allowing fine adjustments of vascular tension by varying the distance between the metal prongs. The software program Chart® (AD Instruments) recorded the experiments continuously. The mounted specimens were immersed in temperature-controlled (37°C) tissue baths containing a bicarbonate buffer solution. The buffer solution was gassed continuously with 5% CO2 in O2 giving a pH of 7.4. The segments were loaded under an initial resting tension of 1 mN and they were allowed to stabilize at this tone for 1 h. The resting tone for small human arteries of the present size was determined in previous experiments on length–tension relationships in Ca2+-free conditions, and vessels were contracted by KCl depolarization [4,5].

The contractile capacity of each vessel segment was examined by exposure to a KCl-rich (60 mM) buffer solution which had the same composition as the standard buffer solution, except that NaCl was exchanged for an equimolar concentration of KCl. These contractions served as internal standards and were set at 100%. When two reproducible contractions had been achieved
(variation <10 %), the vessels were used for further studies.

Vasoconstrictor effects of the agonists were examined by obtaining cumulative concentration–effect curves for each of the triptan drugs. One or two concentration–response curves per artery segment was obtained for each patient, and the mean of these was used as one value for this patient. There was no desensitization when repeating agonist doses. In a subset of tests (n = 3), the endothelium was removed mechanically using a small wooden stick and the effect of sumatriptan examined as above. For the experiments with an antagonist (SB 224289, a selective 5-HT1B blocker) [2,21], matched pairs were always studied in parallel, i.e. one segment received agonist only and the other segments from the same vessel received agonist plus antagonist (30 min beforehand) at the selected concentration.

**Immunocytochemistry procedure for tissue sections**

Control arteries were obtained from six donors without any obvious atheromatosis, aged 20–59 years (three males and three females; three with dilated cardiomyopathy, one with cystic fibrosis and two normal hearts considered not suitable for transplantation). ‘Diseased’ arteries were obtained from 12 male donors, aged 44–59 years undergoing transplantation for ischaemic heart disease. The Local Research Ethics Committee (H97/252) approved the collection of this material, and informed consent was given from the patients for removal of the tissue. Arteries were dissected from the hearts and frozen in liquid nitrogen. Tissue sections (10 µm) were prepared on a cryostat (Brights). The sections were brought to room temperature and immersed in PBS/Tween 20 buffer [0.1 M PBS (pH 7.4) containing 0.1 % Tween 20] and 5 % (w/v) non-fat milk (Marvel; 1 h at room temperature), transferred to the same buffer containing the primary 5-HT1B- or 5-HT1D-receptor antibodies (1:300 and 1:100 dilutions respectively; Santa Cruz Laboratories [6]) or antisera to α-actin (smooth muscle cell marker; 1:1000 dilution; saturated humidity, overnight at 4 °C; Biogenesis). Details on the immunocytochemical procedures and controls have been reported previously [4–6]. For quantification studies, the sections were washed in PBS/Tween 20 buffer, incubated in PBS/Tween 20 buffer containing 5 % (w/v) non-fat milk and the secondary antibody ([35S]-labelled goat anti-rabbit IgG; 0.1 mCi/ml, saturated humidity, 1 h at room temperature). Following washing in PBS/Tween 20 buffer, the sections were rinsed in water, air dried and exposed to film (Hyperfilm-β-Max) for 7–10 days. Measurements of absorbance were made using an MCID M2 image analysis system (Imaging Res). For immunocytochemical localization studies, a biotinylated goat anti-rabbit secondary antibody/Avidin-Biotin Complex was used (Vectastain Elite Kit) with di-amino benzidine solution (0.0025 %) as the chromagen. A Leica (DMRB) microscope with brightfield was used. Detailed methodologies have been reported previously [6,7].

**Analysis of data**

The contractile response to each agonist was expressed as a percentage of the KCl-evoked contraction. The GraphPad Prism program (GraphPad Software Inc.) was used to obtain a fitted curve to calculate $E_{\text{max}}$ (maximum contraction) and pEC50 values (negative logarithm of the molar concentration of agonist inducing half of the maximum response). Data are expressed as means ± SD confidence limits, and n refers to the number of patients from whom the vessels were collected. Comparison between groups of data was carried out using Student’s t test (comparing two groups) and ANOVA with Bonferroni correction (comparing more than two groups); *P* < 0.05 indicated a significant difference.

We calculated the ratio of $C_{\text{max}}$/EC50, where $C_{\text{max}}$ is the maximum plasma concentration of the drug obtained after oral administration of clinically relevant doses to man (using values reported in the literature) taking into account the free pharmacologically active fraction of the drug using plasma protein binding values reported previously (see Table 2 for references). pEC50 is vasoconstrictor potency determined in isolated arteries (present study) and derived from the curve-fitting procedure which provides an estimation of the error of the pEC50 value which was used to put an error value on the $C_{\text{max}}$/EC50 ratio. Obviously the time point for the $C_{\text{max}}$ differs between triptans; the highest value was used in the calculation as this is usually regarded as the $C_{\text{max}}$.

**RESULTS**

**In vitro pharmacology: vasoconstrictor effects of agonists**

The agonists produced vasoconstriction of human isolated cerebral arteries and the concentration–effect curves are shown in Figure 1, and the $E_{\text{max}}$ and EC50 values are given in Table 1. The agonists produced mean contractions that varied between 45–61 % of the contractions elicited by 60 mM KCl. There was considerable variation across individual segments in the size of the maximum contraction to each of the agonists and this was also consistent with the considerable inter-individual variations, but no systematic relationship between responses and type of operation (results not shown). Rank order of agonist potency order was not different: eletriptan = rizatriptan = sumatriptan. The mean contractile force was not different among the triptans (*P* > 0.05). The triptan responses were antagonized by the selective 5-HT1B antagonist SB 224289 (10−6 M) in a competitive manner (results not shown).
Concentration–effect curves for eletriptan, rizatRIPTAN and sumatriptan in human isolated cerebral (upper panel) and coronary (lower panel) arteries

Contractile responses were expressed as a percentage of the contraction evoked by 60 mM KCl (= 100 %). Points represent means ± S.E.M. Curves were fitted to the mean data points using non-linear regression analysis (Graph Pad Prism).

Table 1  Contractile responses to 5-HT receptor agonists (triptans) in human cerebral and coronary arteries

Data are expressed as means ± 95 % confidence limits. pEC50 = –log concentration of the EC50; Emax, maximum contraction induced by the agonists tested. There was no difference in pEC50 or in Emax as seen between the triptans for each artery group; however, each triptan was significantly more potent in cerebral compared with coronary arteries (*P < 0.05).

<table>
<thead>
<tr>
<th>Artery</th>
<th>n</th>
<th>pEC50</th>
<th>Emax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>3</td>
<td>6.8 ± 0.4 *</td>
<td>50 ± 10 %</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>8</td>
<td>7.8 ± 0.4 *</td>
<td>61 ± 12 %</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>10</td>
<td>7.2 ± 0.3 *</td>
<td>45 ± 11 %</td>
</tr>
<tr>
<td>Coronary artery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>12</td>
<td>5.7 ± 0.1</td>
<td>41 ± 1 %</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>6</td>
<td>5.7 ± 0.1</td>
<td>26 ± 1 %</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>5</td>
<td>5.8 ± 0.1</td>
<td>35 ± 2 %</td>
</tr>
</tbody>
</table>

KCl (60 mM) and the triptans produced vasoconstrictor effects in human isolated coronary arteries. There was no obvious difference between arteries from valvular operations and heart transplantation cases. The concentration–effect curves are shown in Figure 1, and the Emax and EC50 values are given in Table 1. Mechanical removal of the endothelium (n = 3) did not result in enhanced responses to sumatriptan (results not shown). All triptans produced a significant and equally strong contraction with a concentration–effect curve that reached a clear maximum, hence it was possible to estimate EC50 values. The rank order of agonist potency was eletriptan = rizatriptan = sumatriptan. The EC50 values for triptans in cerebral arteries were significantly more potent than those seen for the respective triptan in the coronary arteries (P < 0.05; Table 1). SB 224289 (10^-6 M) antagonized the sumatriptan concentration–response relationship (n = 3; results not shown).

Comparison with plasma concentration

The Cmax/EC50 ratios for cerebral and coronary artery are shown in Table 2. Zolmitriptan data were obtained from the literature [4,5]. For cerebral arteries, the Cmax/EC50 ratios were, in general, not significantly different from unity, indicating a relationship between these two parameters. For coronary arteries, the ratios for the triptans were significantly less than unity, showing no direct relationship between Cmax and EC50, and for these triptans the coronary artery ratio was lower than the ratios obtained in the cerebral artery. For each triptan, the ratio was significantly lower for coronary arteries compared with the cerebral artery (P < 0.05).

Immunostaining

The immunostaining in representative sections from normal and diseased coronary arteries of relatively large diameter (approx. 4 mm) is shown in Figure 2. The morphology was dramatically different between the two groups (shown using haematoxylin/eosin stain), with the diseased arteries showing luminal occlusion, atherosclerotic plaques and necrotic tissue. In normal arteries the smooth muscle layer was well defined (using the anti-α-actin antibody) and expressed 5-HT1B-receptor immunoreactivity, but not 5-HT1D-immunoreactivity (in agreement with previous studies [4–6]). In general, a similar pattern was seen in diseased arteries, although the proteinous/charged nature of the atherosclerotic lesions caused non-specific staining. Therefore for the quantification studies using the radiolabelled secondary antibody, densitometric measurements were carefully made in areas of normal smooth muscle cells. ‘Normal’ was defined by simultaneous visualization of chromogenic 5-HT1B receptor immunoreactivity in areas outside the necrotic parts of the lesions and which showed densely packed smooth muscle nuclei of normal appearance...
Calculation of $C_{\text{max}}$  

**Table 2** Calculation of $C_{\text{max}}$/EC$_{50}$ ratios

$C_{\text{max}}$ is the maximum plasma concentration observed following administration of clinically relevant doses [1,3,25] and taking into account the calculation of the free pharmacologically active fraction ($C_{\text{max}}$ free) in the presence of plasma protein binding (using values reported in the literature). pEC$_{50}$ is vasoconstrictor potency determined in the present study using isolated cerebral and coronary arteries. Two doses of zolmitriptan are included, since clinical use instructs the patient to start with the 2.5 mg dose and then go to the 5 mg as required. Data for zolmitriptan are from [4,5]. $P < 0.05$ between cerebral and coronary artery ratio, as determined by Student’s $t$ test. p.o., per os; s.c., subcutaneously.

<table>
<thead>
<tr>
<th>Triptan</th>
<th>References</th>
<th>Clinical dose</th>
<th>$C_{\text{max}}$ total (nM)</th>
<th>Plasma protein binding (%)</th>
<th>$C_{\text{max}}$ free (nM)</th>
<th>pEC$_{50}$ (logM)</th>
<th>Mean ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>[22]</td>
<td>100 mg p.o.</td>
<td>142</td>
<td>14%</td>
<td>122</td>
<td>6.8 ± 0.4</td>
<td>0.77 (0.11–5.63)</td>
</tr>
<tr>
<td></td>
<td>[34]</td>
<td>6 mg s.c.</td>
<td>244</td>
<td></td>
<td>210</td>
<td>1.33 (0.30–5.89)</td>
<td>0.11 (0.08–0.57)</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>[23,35]</td>
<td>10 mg p.o.</td>
<td>74</td>
<td>14%</td>
<td>66</td>
<td>7.2 ± 0.3</td>
<td>1.05 (0.23–4.88)</td>
</tr>
<tr>
<td></td>
<td>[34]</td>
<td>2.5 mg p.o.</td>
<td>9</td>
<td>25%</td>
<td>7</td>
<td>7.2 ± 0.3</td>
<td>0.11 (0.02–0.60)</td>
</tr>
<tr>
<td></td>
<td>[34]</td>
<td>5 mg p.o.</td>
<td>18</td>
<td></td>
<td>14</td>
<td>7.2 ± 0.3</td>
<td>0.11 (0.02–0.60)</td>
</tr>
<tr>
<td>Eletriptan</td>
<td>[34]</td>
<td>40 mg p.o.</td>
<td>213</td>
<td>86%</td>
<td>30</td>
<td>7.8 ± 0.4</td>
<td>1.89 (0.23–15.83)</td>
</tr>
</tbody>
</table>

(determined using the haematoxylin counterstain). Given the above caveats, the absorbance measurements were $0.103 ± 0.010$ for normal arteries ($n = 22$ sections from six donors) and $0.088 ± 0.007$ for diseased arteries ($n = 45$ sections from 12 donors; $P$ values were not significantly different).

**DISCUSSION**

Studies using isolated blood vessels provide a robust quantitative pharmacological comparison of drugs and may identify subtle differences between triptans. These differences are of scientific interest since, in theory, all triptans belong to the same class (i.e. 5-HT$_{1B/1D}$ receptor agonists) and therefore would be expected to have similar pharmacological actions. It is important to remember that any differences detected using in vitro studies should not be extrapolated and used as predictors or comparators of drug effects when administered to man. In addition, analysis of multiple segments (within individuals) in a large population of cerebral [22] and omental arteries [23] revealed considerable inter-individual variability. This may account for variability among patients to respond to triptans, possibly due to differences in receptor expression. It has been shown that the 5-HT$_{1B}$ receptor protein is expressed not only in the smooth muscle, but also on the endothelium of both cerebral and coronary arteries [4,5]. Also, 5-HT$_{1B}$ receptor mRNA has the same localization, as shown by in situ hybridization on human middle meningeal and coronary arteries [2]. In the present study, the mechanical removal of the endothelium did not alter the contractile responses to sumatriptan in a major way, even though the selective luminal application of sumatriptan may relax the rat middle cerebral artery [24].

Comparison of vasoconstrictor potency showed that rizatriptan, sumatriptan and eletriptan as well as zolmitriptan were more powerful vasoconstrictors in human isolated cerebral arteries than in coronary arteries, being at least 3-fold more potent (Table 2). This agrees well with data from other studies comparing middle meningeal (dural) and coronary arteries [3,25]. Pharmacological analyses with 5-HT$_{1B/1D}$ selective blockers have revealed that the triptans act via the 5-HT$_{1B}$ subtype of receptors in human arteries [4,5,7,25,26]. The potency of rizatriptan determined in the present study is similar to that reported by Longmore et al. [7]. For the coronary artery, the potency is approx. 3–10-fold lower, which agrees well with previous reports [7,25]. The reason for the higher potency of triptans in cerebral and middle meningeal arteries compared with coronary arteries is not known, but could be due to at least two differences; firstly, according to receptor modelling of Black and Leff [27], there might be a higher number of 5-HT$_{2A}$ receptors in intracranial vessels compared with peripheral arteries in man. This concept has been studied in some detail for endothelin receptors where up-regulated contractions correlated with enhanced translation of ET$_B$ receptor mRNA [28]. In immunohistochemical studies with 5-HT$_{1B}$-selective antibodies, the staining seemed denser in cerebral [5] compared with coronary arteries [4]. Secondly, there are few, if any, 5-HT$_{2A}$ receptors in intracranial vessels. In coronary arteries, the 5-HT$_{2A}$ receptor population dominates [4], and their presence might obscure the 5-HT$_{1B}$ receptor contraction. In addition, there may be potential differences in the coupling of the 5-HT$_{1B}$ receptors between cerebral and coronary arteries. The methods employed in our present study do not damage the endothelium, as demonstrated by specific analysis with immunocytochemistry [4,5], and hence cannot explain the difference in responsiveness to triptans between the two vascular regions. Specific antagonism using either a 5-HT$_{1B/1D}$ blocker or a specific 5-HT$_{1B}$ antagonist supports further the identity of the receptor under study [2,4,5,21].
Calculation of the $C_{\text{max}}/EC_{50}$ ratios allowed the examination of the relationship between clinically relevant plasma levels and vasoconstrictor potency. In general for the cerebral artery, the $C_{\text{max}}/EC_{50}$ ratios were not significantly different from unity, indicating a relationship between these two parameters. The concentration of the triptans at their peak in plasma when given as shown in Table 2 hits the concentration–effect curve at around the $EC_{50}$ for cerebral arteries and, hence, suggests a meaningful concentration. Thus it suggests that, following administration of these triptans to migraineurs, plasma concentrations are likely to be achieved that cause contraction of the cranial/cerebral arteries, and this may be an important therapeutic mechanism for this class of drugs. The question of whether triptans have effects on cerebrovascular smooth muscle is intriguing and still under debate, since they may be prevented from entry by the blood/brain barrier. It is known that triptans are poor in penetrating the blood/brain barrier [24], but the large arteries belonging to the circle of Willis behave differently. Friberg et al. [29] have shown changes in artery diameter by transcranial laser Doppler studies, but there was no effect of cerebral blood flow after sumatriptan. This is supported by novel data on the calcitonin gene-related peptide antagonist BIBN4096BS, which has an acute antimigraine effect [30], but does not pass the blood/brain barrier in rat in vivo experiments [31]. Thus these data question a central effect of the triptans. In coronary arteries, sumatriptan, rizatriptan and eletriptan were significantly weaker and less potent vasoconstrictors, with the $C_{\text{max}}/EC_{50}$ ratios significantly less than 1 and, hence, the coronary artery ratios were lower than those obtained for cerebral arteries. This indicates that circulating plasma levels fall below or only at the start of the concentration–response relation of the drugs required to produce contraction in coronary arteries. By and large, the same conclusion was reached by Maassen Van Den Brink et al. [3,25].

There still exists some concern about coronary vaso-reactivity and the potential cardiovascular adverse events following administration of triptans to migraineurs. Intracoronary 5-HT caused vasodilatation at concentrations up to $10^{-5}$ M, whereas a higher dose gave constriction in healthy coronary vessels [32]. Interestingly, 5-HT only resulted in constriction of vessels from subjects with stable angina pectoris. This suggested a role of platelet 5-HT in myocardial ischaemia. It does not provide a clue as to which receptor subtype this may occur with; however, the 5-HT$_2$ subtype dominates in human coronary arteries [4,33]. Saxena and co-workers [3,25] have provided some perspectives on these concerns, stating that triptans are weak constrictors in coronary arteries and probably produce small changes in coronary artery diameter with a small impact on coronary blood flow, which, in healthy subjects, would be of little clinical consequence, since they act, by and large, only on the 5-HT$_{1B}$ subtype of receptors. However, small contractions would have proportionally greater impact in diseased artery where there is luminal occlusion and the presence of areas of normal and therefore contractable smooth muscle areas [3,25]. This point is clearly demonstrated in the present study. For this reason, triptans, which are all 5-HT$_{1B/1D}$ receptor agonists and belong to the same class, are contra-indicated in migraineurs with known or suspected coronary artery disease.
risk factors. In the present study, we confirmed the presence of 5-HT1B receptor immunoreactivity, but not 5-HT1D receptor immunoreactivity in coronary vascular smooth muscle [4,7]. The quantitative densitometry measurements (although with caveats) suggest that, where ‘normal’ areas of smooth muscle are present within atherosclerotic areas in coronary arteries, there is no proliferation of 5-HT1B receptor immunoreactivity and this would imply that there is no hyper-responsiveness of diseased arteries to triptans. The hyper-reactivity to 5-HT noted by McFadden et al. [32] might relate to proliferation of 5-HT2A receptors. This was not the target for the present study. This is supported by previous studies [3,7] which report similar vasoconstrictor potency values for triptans in isolated coronary arteries with intact endothelium obtained from ‘healthy’ individuals (e.g. obtained after sudden death and accident victims) or ‘worst-case scenario’ arteries (endothelium denuded) obtained from diseased ex-planted hearts. As studied in a subpopulation in the present study, removal of the endothelium did not elicit a hyper-response to sumatriptan.

In conclusion, the present study shows that triptans are potent vasoconstrictors in human cerebral arteries and there is an approximate 1:1 (unity) relationship between vasoconstrictor potency measured in these arteries and the clinically relevant plasma levels of these drugs. This agrees well with data comparing middle meningeal and coronary arteries [3,25]. This suggests that vasoconstriction of cerebral and meningeal arteries may contribute to the therapeutic action of this class of drugs. On the other hand, the relationship between vasoconstrictor potency in coronary arteries and plasma levels is much lower than unity. This again is consistent with the clinical profile, where triptans are considered safe drugs with a low incidence of serious coronary side effects. In addition, the present results also suggest that there is no proliferation of 5-HT1B receptor expression in diseased coronary arteries. However, in cases where there is significant luminal occlusion, vasoconstriction may reduce coronary blood flow, thus supporting the contra-indication of triptans in migraineurs with known or suspected risk factors for coronary artery disease.

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