Amplification of sumatriptan-induced contraction in rabbit saphenous vein but not in basilar artery

ANINDYA BHATTACHARYA, KATHRYN W. SCHENCK, AND MARLENE L. COHEN
Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana 46285
Submitted 18 April 2002; accepted in final form 4 October 2002

Bhattacharya, Anindy, Kathryn W. Schenck, and Marlene L. Cohen. Amplification of sumatriptan-induced contraction in rabbit saphenous vein but not in basilar artery. Am J Physiol Heart Circ Physiol 284: H719–H726, 2003; 10.1152/ajpheart.00345.2002.—The modulation of serotonin (5-HT1B/1D) receptor-induced vascular contractility by histamine and U-46619 was compared in the rabbit basilar artery and saphenous vein. In the saphenous vein, histamine (5 × 10⁻⁷ M) significantly increased the potency (from pEC₅₀ of 6.0 to 6.8) and efficacy (from 52.3% to 88.2%) of sumatriptan. Likewise, U-46619 (3 × 10⁻⁹ M) also increased the potency (from pEC₅₀ of 5.9 to 6.6) and efficacy (from 51.8% to 92.1%) of sumatriptan in the saphenous vein. In contrast, equieffective concentrations of histamine (10⁻⁷ M) and U-46619 (5 × 10⁻⁹ M) failed to amplify contraction to sumatriptan in the basilar artery. Contraction to sumatriptan was inhibited by nitrendipine (10⁻⁷ M) in the basilar artery but not in the saphenous vein, suggesting that different contractile signaling mechanisms are operating in these tissues. Furthermore, U-46619- and thrombin-induced contractility in the basilar artery were also not amplified by histamine, suggesting that lack of amplification of contraction in the basilar artery was not restricted to sumatriptan but was rather a characteristic of this cerebral vessel. These data suggest that in the in vivo plasma milieu sumatriptan will more markedly contract the peripheral saphenous vein than the basilar artery, a cerebral blood vessel.

SUMATRIPTAN is an antimigraine drug (20) with a high affinity for serotonin 5-HT₁B and 5-HT₁D receptors (27). The antimigraine efficacy of sumatriptan has been attributed, in part, to its ability to activate central vascular 5-HT₁B/₁D receptors (8). However, much of the information on the vascular effects of sumatriptan has been derived from studies using peripheral vascular serotonin receptors. For example, sumatriptan-induced peripheral vascular contraction has been widely studied in the rabbit saphenous vein (9), femoral artery (4), mesenteric artery (5), and iliac artery (36). Because the cardiovascular liabilities of sumatriptan may be related to its ability to constrict coronary arteries (23), sumatriptan has also been studied in coronary arteries from dogs (21) and humans (1). In contrast, the cerebral vascular effects of sumatriptan have been less extensively studied (3, 16, 17).

Modest increases in vascular tone with threshold concentrations of vascular contractile agonists such as prostaglandin, angiotensin, histamine, endothelin, or adrenergic agonists are known to increase sumatriptan-induced vascular contractility (35). Whereas this amplifying effect is well established in peripheral blood vessels (7, 9, 21, 22), amplification of serotoninergic responses in cerebral vessels is considerably more controversial. Some limited studies have examined the ability of contractile agonists to amplify serotonin-induced contraction in cerebral arteries from several species with conflicting results (2, 12, 18, 19). For example, endothelin did not potentiate serotonin-induced contraction in the basilar artery (19), whereas in pial arteries both endothelin and U-46619 augmented serotonin-induced vasoconstriction (18). Likewise, histamine potentiates serotonin-induced contraction of the rabbit basilar artery (2), whereas histamine did not augment vascular contraction to serotonin in the sheep middle cerebral artery (12). In contrast, in peripheral vascular beds, serotoninergic contractility was almost always augmented in the presence of vascular tone (7, 9, 22, 25, 36).

Because serotonin may activate multiple receptors, the present study focused on the amplification of sumatriptan (selective 5-HT₁B and 5-HT₁D receptor agonist)-induced cerebrovascular contractility. This study was designed to address the following questions. First, will the induction of modest tone amplify the contractile responses to sumatriptan similarly in the peripheral saphenous vein and in the cerebral basilar artery from the same species? Second, is amplification or lack thereof in cerebral arteries restricted to sumatriptan or common to other contractile agonists? Finally, does sumatriptan-induced contraction utilize a similar calcium source in these two vessels?

For these studies, we used a modest and equieffective concentration of both U-46619 and histamine to amplify sumatriptan-induced force in both the basilar artery and saphenous vein from the rabbit. The basilar artery was used to represent a cerebral blood vessel,
whereas the saphenous vein provided a peripheral model with similar responsiveness to coronary arteries (8). U-46619 and histamine were selected as representative contractile agonists that have been shown to potentiate contractile responses of peripheral vessels (2, 7). Histamine and U-46619 were selected as the amplifying agonists because during vascular lesions associated with atherosclerosis, thromboxane A2 and histamine are released from aggregating platelets (13, 28). During myocardial infarction and angina, plasma concentrations of thromboxane and histamine are increased (29, 31). Thromboxane concentration has also been reported to increase during migraine attacks (32). Thus these endogenous ligands may act in concert to augment vasoconstrictor effects of sumatriptan, especially under conditions of vascular injury. Finally, nitrendipine was used to block extracellular calcium influx to compare the calcium source required for contraction to sumatriptan in these blood vessels.

Our data suggest that augmentation of sumatriptan-induced contractility differed between these vessels. Whereas sumatriptan-induced contraction was augmented in the saphenous vein, the basilar artery did not exhibit any such amplification. Lack of amplification of sumatriptan-induced contractility in the basilar artery was not specific to sumatriptan and may be related to differences in the use of extracellular calcium by intracellular signaling cascades.

METHODS

Isolation of the rabbit saphenous vein and basilar artery. Male New Zealand White rabbits (2.0–3.0 kg, Harlan Sprague-Dawley; Indianapolis, IN) were euthanized by intravenous injection of pentobarbital sodium (65–100 mg/kg) into the ear vein. The saphenous vein and/or basilar artery were dissected free of connective tissue and cannulated with 99.9% platinum wire (32 gauge for the saphenous vein, 36 gauge for the basilar artery) in petri dishes containing Krebs bicarbonate buffer (see below for composition). All tissues were denuded of vascular endothelium by rotating the platinum wires along the luminal surface of the blood vessels. To test for the presence of endothelium, PGF2α (3 × 10⁻⁶ M) and histamine (10⁻⁶ M) were used to contract the saphenous vein and basilar artery, respectively, before the addition of cholinergic agonist. Endothelial denudation was confirmed in every tissue by the inability of carbamylcholine (10⁻⁶ M) or acetylcholine (10⁻⁶ M) to relax the precontracted saphenous vein and basilar artery, respectively.

Tissues were mounted in organ baths containing 10 ml of modified Krebs solution of the following composition (in mM): 118.2 NaCl, 4.6 KCl, 1.6 CaCl₂·2H₂O, 1.2 KH₂PO₄, 1.2 MgSO₄, 10.0 dextrose, and 24.8 NaHCO₃. Tissue bath solutions were maintained at 37°C and aerated with 95% O₂-5% CO₂ (pH = 7.4). An initial optimum force of 4 and 0.5 g was applied to the rabbit saphenous vein and basilar artery, respectively. Isometric contractions were recorded as changes in grams of force as measured with Sensotec transducers coupled to MP100 data-acquisition software (BIOPAC Systems; Santa Barbara, CA).

Experimental protocol. Each tissue was initially challenged with KCl (67 mM) to confirm tissue viability. Cumulative concentration-response curves were generated to sumatriptan, histamine, or U-46619, and no tissue was used to generate more than one agonist concentration-response curve. In experiments that examined the effect of precontraction, tissues were precontracted with threshold concentrations of histamine (saphenous vein: 5 × 10⁻⁷ M; basilar artery: 10⁻⁷ M) or U-46619 (saphenous vein: 5 × 10⁻⁸ M; basilar artery: 3 × 10⁻⁹ M) before a response was initiated to sumatriptan, U-46619, or thrombin. For studies with nitrendipine, tissues were incubated for 30–60 min with 10⁻⁷ M nitrendipine and then challenged with either sumatriptan or vehicle.

Data analysis. All results are expressed as means ± SE, where n represents the number of animals. The data are expressed as a percentage of the response to a maximal contractile concentration of KCl (67 mM) administered initially in each tissue. In tissues precontracted with histamine, U-46619, or thrombin, force produced by the second agonist was measured using the precontracted force as the baseline. EC₅₀ values (−log EC₅₀ or pEC₅₀) were determined by a three-parameter logistic nonlinear model. Statistical significance (P < 0.05) was determined by Student’s t-test using SigmaStat software.

Drugs and solutions. Histamine, PGF₂α, carbamylcholine, acetylcholine, and U-46619 were purchased from Sigma (St. Louis, MO). Human α-thrombin was purchased from Enzyme Research (South Bend, IN). Nitrendipine and sumatriptan were provided by Lilly Research Laboratories (Indianapolis, IN). All compound solutions were made fresh daily before the start of each experiment.

RESULTS

Comparison of histamine, U-46619, and sumatriptan-induced contractions between basilar artery and saphenous vein. Contraction to histamine, U-46619, and sumatriptan was distinctly different between the rabbit basilar artery and saphenous vein (Fig. 1 and Table 1). Histamine, U-46619, and sumatriptan were significantly more potent (P < 0.05) in contracting the basilar artery than the saphenous vein (Table 1). However, histamine and U-46619 produced significantly greater maximal contraction in the saphenous vein than in the basilar artery (see Table 1). The most marked difference between these two blood vessels resided in the contraction to U-46619, which maximally contracted the saphenous vein to about three times the force generated in the basilar artery. Thus histamine-, U-46619-, and sumatriptan-induced contractions differed between these two tissues from the rabbit.

Effect of histamine precontraction on the potency and efficacy of sumatriptan in the rabbit saphenous vein and basilar artery. Previous studies in the rabbit saphenous vein demonstrated that contraction to sumatriptan was amplified by threshold concentrations of PGF₂α (9). In this study, we systematically compared the effect of histamine- and U-46619-induced precontraction on sumatriptan-dependent vasoconstriction in both the saphenous vein and basilar artery.

For this purpose, equieffective concentrations of histamine were used to precontract the saphenous vein (5 × 10⁻⁷ M) and the basilar artery (10⁻⁷ M) (see Fig. 1). In the saphenous vein, histamine, like PGF₂α (9), markedly amplified sumatriptan-induced contraction (Fig. 2A). Precontraction with histamine significantly increased both the potency and efficacy of sumatriptan in the saphenous vein (see Table 2 for comparison of pEC₅₀ and maximum contractile responses). In con-
trast, histamine precontraction did not amplify sumatriptan-induced contraction in the basilar artery (Fig. 2B and Table 3).

**Effect of U-46619 precontraction on the potency and efficacy of sumatriptan in the rabbit saphenous vein and basilar artery.** To determine whether the difference observed between the basilar artery and saphenous vein with regard to amplification was restricted to histamine, the effect of precontraction with threshold and equieffective concentrations of U-46619 in the saphenous vein (5 × 10⁻⁹ M) and basilar artery (3 × 10⁻⁹ M) was also examined (see Fig. 1). As observed with histamine, U-46619 amplified sumatriptan-induced contraction in the saphenous vein (Fig. 3A and Table 2) but not in the basilar artery (Fig. 3B and Table 3). The potency and efficacy of sumatriptan increased significantly (P < 0.05) in the U-46619-precontracted saphenous vein (Table 2).

**Effect of nitrendipine on sumatriptan-induced contraction in the saphenous vein and basilar artery.** To study the role of voltage-gated calcium channels in sumatriptan-induced contraction, nitrendipine was used to block the entry of extracellular calcium in both the saphenous vein and basilar artery. Nitrendipine (10⁻⁷ M) did not alter sumatriptan-induced contraction in the saphenous vein (Fig. 4A). In contrast, nitrendipine precontraction did not amplify sumatriptan-induced contraction in the basilar artery (Fig. 4B and Table 3).

### Table 1. Pharmacological differences between the rabbit saphenous vein and basilar artery

<table>
<thead>
<tr>
<th>Agonist</th>
<th>n</th>
<th>pEC₅₀</th>
<th>Maximal Contraction, %KClₙ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saphenous vein</td>
<td>7</td>
<td>5.3 ± 0.06</td>
<td>187.9 ± 4.7*</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>4</td>
<td>5.9 ± 0.07*</td>
<td>164.9 ± 8.5</td>
</tr>
<tr>
<td>U-46619</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saphenous vein</td>
<td>5</td>
<td>7.0 ± 0.14</td>
<td>183.1 ± 15.6*</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>4</td>
<td>7.7 ± 0.16*</td>
<td>56.7 ± 3.0</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saphenous vein</td>
<td>12</td>
<td>5.9 ± 0.05</td>
<td>52.1 ± 2.8</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>14</td>
<td>6.5 ± 0.05*</td>
<td>43.0 ± 3.5</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of tissues. *P < 0.05.
Fig. 2. Effect of histamine on sumatriptan-induced contraction in the rabbit saphenous vein (A) and rabbit basilar artery (B). The saphenous vein was precontracted by histamine (5 × 10⁻⁷ M) to 14.9 ± 1.8% of KCl-induced force, followed by cumulative addition of sumatriptan (A). The basilar artery was precontracted by an equieffective concentration of histamine (1 × 10⁻⁷ M) to 14.4 ± 3.4% of KCl-induced force, followed by cumulative addition of sumatriptan (B). Contraction was plotted as a percentage of KCl (67 mM)-induced maximal force in the saphenous vein (5.0 ± 0.28 g) and basilar artery (0.40 ± 0.05 g). Tissues were denuded of endothelium, and loss of endothelium was assessed by the inability of acetylcholine (10⁻⁶ M) or carbamylcholine (10⁻⁶ M) to induce relaxation in the basilar artery (2.5 ± 1.2% relaxation) and saphenous vein (5.4 ± 1.1% relaxation), respectively. Points represent mean contractile values, and the vertical lines are SEs for the number of animals (number of tissues in parentheses).

Table 2. Contraction to sumatriptan (alone and augmented) in the rabbit saphenous vein

<table>
<thead>
<tr>
<th>Agonist Treatment</th>
<th>n</th>
<th>Sumatriptan, pEC50</th>
<th>Maximal Contraction, %Maximal KCl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>5</td>
<td>6.0 ± 0.08</td>
<td>52.3 ± 4.9</td>
</tr>
<tr>
<td>+histamine (5 × 10⁻⁷ M)</td>
<td>7</td>
<td>6.8 ± 0.06*</td>
<td>88.2 ± 3.3*</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>7</td>
<td>5.9 ± 0.08</td>
<td>51.8 ± 3.6</td>
</tr>
<tr>
<td>+U-46619 (5 × 10⁻⁹ M)</td>
<td>7</td>
<td>6.6 ± 0.09*</td>
<td>92.1 ± 10.0*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of tissues. *P < 0.05.

Table 3. Contraction to sumatriptan (alone and with histamine and U-46619) in the rabbit basilar artery

<table>
<thead>
<tr>
<th>Agonist Treatment</th>
<th>n</th>
<th>Sumatriptan, pEC50</th>
<th>Maximal Contraction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sumatriptan</td>
<td>3</td>
<td>6.4 ± 0.15</td>
<td>42.3 ± 6.8</td>
</tr>
<tr>
<td>+histamine (10⁻⁷ M)</td>
<td>4</td>
<td>6.4 ± 0.22</td>
<td>34.6 ± 9.4</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>4</td>
<td>6.8 ± 0.32</td>
<td>37.2 ± 8.6</td>
</tr>
<tr>
<td>+U-46619 (3 × 10⁻⁹ M)</td>
<td>4</td>
<td>6.6 ± 0.09</td>
<td>46.9 ± 9.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of tissues. No statistical differences (P < 0.05) occurred between mean values.
DISCUSSION

Cerebral vasoconstriction may play an important role in the antimigraine efficacy of sumatriptan (15). On the other hand, peripheral coronary vasospasm is thought to underlie the chest pressure and cardiac effects observed in patients undergoing triptan therapy (23). Thus sumatriptan-activated vascular receptors are targets for both therapeutic effects and side effects associated with migraine therapy. We systematically studied the saphenous vein as a model for coronary arterial responses (8) and the basilar artery from the same species to minimize the difficulty in interpreting and comparing results from tissues obtained from multiple species. Furthermore, we used equieffective contractile concentrations of histamine and U-46619 to contract the saphenous vein and basilar artery to minimize any differential effect of precontracted tone on subsequent contraction to sumatriptan.

Histamine, U-46619, and sumatriptan differed in potency between the basilar artery and saphenous vein (Fig. 1 and Table 1). The greater potency of sumatriptan in the rabbit basilar artery than in the saphenous vein was also observed between the dog basilar artery and saphenous vein (14). U-46619 exhibited greater contractile force in the saphenous vein than in the basilar artery. U-46619-induced maximal contraction was also greater in the human coronary artery (22) and dog saphenous vein (21) than in the rat basilar artery (10). Thus U-46619 appears to be a more efficacious contractile agonist of peripheral than cerebral blood vessels.

Serotoninergic contractility in the peripheral vasculature is synergistically modulated by multiple agonists (35), and amplified responses to sumatriptan are independent of precontracting substance (36). For example, in the rabbit femoral artery (4), serotonin-induced contractility was augmented by phenylephrine. Sumatriptan-induced vascular contraction in the rabbit saphenous vein was amplified by modest increase in PGF2α-dependent tone (9) and was also augmented by angiotensin, norepinephrine, histamine, and KCl in

![Fig. 3. Effect of U-46619 on sumatriptan-induced contraction in the rabbit saphenous vein (A) and rabbit basilar artery (B). The saphenous vein was precontracted by U-46619 (5 × 10^-9 M) to 17.2 ± 3.5% of KCl-induced force, followed by cumulative addition of sumatriptan (A). In the basilar artery, equieffective U-46619 (3 × 10^-9 M) was used to precontract tissues to 11.4 ± 3.1% of KCl-induced force, followed by sumatriptan (B). Contraction was plotted as a percentage of KCl (67 mM)-induced maximal force in the saphenous vein (4.7 ± 0.30 g) and basilar artery (0.62 ± 0.06 g). Tissues were denuded of endothelium, and loss of endothelium was assessed by the inability of acetylcholine (10^-6 M) or carbamylcholine (10^-6 M) to induce relaxation in the basilar artery (4.1 ± 1.8% relaxation) and saphenous vein (1.6 ± 0.9% relaxation), respectively. Points represent mean contractile values, and the vertical lines are SEs for the number of animals (number of tissues in parentheses).]

![Fig. 4. Effect of nitrendipine on sumatriptan-induced contraction in the saphenous vein (A) and basilar artery (B) of the rabbit. Tissues were equilibrated with nitrendipine (10^-7 M) or vehicle before cumulative addition of sumatriptan. Points represent mean contractile values, and the vertical lines are SEs. Number of tissues is in parentheses.]
the rabbit iliac artery (36). Similarly, U-46619 (7) and endogenous thromboxane (22) amplified sumatriptan-induced contraction in human coronary arteries, although U-46619 failed to potentiate sumatriptan-induced contraction in the dog coronary artery (21). Likewise, in the bovine pulmonary artery (25) and in the rabbit mesenteric artery (5), U-46619 also amplified sumatriptan-induced contraction. Consistent with these published data using peripheral vasculature, histamine and U-46619 increased the potency and efficacy of sumatriptan in the rabbit saphenous vein in this study (Figs. 2 and 3 and Table 2).

Unlike amplification to serotonin and sumatriptan observed in peripheral vessels, conflicting reports exist with regard to agonist-induced serotoninergic augmentation in cerebral vessels. For example, U-46619 and histamine amplified serotonin-induced vasoconstriction in the human pial artery and rabbit basilar artery, respectively (2, 18), whereas endothelin failed to augment contraction in the rat basilar artery (19). Furthermore, histamine failed to elicit any additional serotoninergic contractility in the rabbit basilar artery (30). One reason for these discrepancies may be related to the ability of serotonin to interact with multiple contractile receptors and the diversity of serotoninergic receptor density in blood vessels (33). Thus we used the more selective 5-HT1B/1D agonist sumatriptan in this study, because amplification of 5-HT1B/1D receptors is well established in peripheral vessels (35). Endothelium integrity may also modulate serotoninergic contractility (12, 26, 30) and amplification. In fact, histamine amplification of serotonin-induced contraction occurred in basilar arteries with an intact endothelium (2) but not when the endothelium was removed (30). The use of endothelial denuded basilar arteries in the present study eliminated this added variable. To our knowledge, this is the first study to document the inability of agonists to amplify sumatriptan-induced contraction in the basilar artery.

Although histamine and U-46619 augmented contraction to sumatriptan in the saphenous vein, amplification did not occur in the basilar artery (Figs. 2 and

---

**Fig. 5.** Effect of histamine on U-46619-induced (A) and thrombin-induced (B) contraction in the rabbit basilar artery. The basilar artery was precontracted by histamine (1 × 10⁻⁷ M) to 12.1 ± 1.7% of KCl-induced force, followed by either a cumulative addition of U-46619 or a single concentration of thrombin. Contraction was plotted as a percentage of KCl (67 mM)-induced maximal force (0.5 ± 0.04 g). Tissues were denuded of endothelium, and loss of endothelium was assessed by the inability of acetylcholine (10⁻⁶ M) to induce relaxation in the basilar artery (1.3 ± 0.6% relaxation). Points represent mean contractile values, and the vertical lines are SEs for the number of animals (number of tissues in parentheses).
3 and Table 3), consistent with previous studies using other agonists (19, 30). Several explanations may be advanced for the marked contractile augmentation observed in the saphenous vein but not in the basilar artery. First, lack of augmentation could have resulted from an inability of the basilar artery to contract further to agonists because maximum contraction occurred to the contractile agonist used. However, histamine maximally contracted the basilar artery to considerably greater force than sumatriptan and U-46619 (Fig. 1), suggesting that augmentation of U-46619 or sumatriptan-induced contraction was physiologically possible under the in vitro conditions of these studies. Thus contractile force can be greater in the basilar artery, yet induction of modest tone by contractile agonists did not augment agonist-induced tone.

Activation of different signaling cascades each capable of contributing to the same cellular effect has been proposed as an explanation for such amplifying phenomenon (24). For example, responses mediated by G\textsubscript{i}-coupled receptors in the rat tail artery were potentiated, and the efficacy was augmented by agents that couple to G\textsubscript{q}-stimulated phospholipase C activity (35). In the saphenous vein, sumatriptan-induced contraction may be coupled to inhibition of adenylyl cyclase, as previously proposed (34), which can be potentiated by agonists like histamine and U-46619 activating G\textsubscript{q}-coupled pathways. In contrast, in the basilar artery, sumatriptan has been reported to increase diacylglycerol and protein kinase C (6) and may increase extracellular calcium influx via G\textsubscript{q}-coupled pathways that would not be potentiated by agonists that also activated G\textsubscript{i} proteins. The effect of nitrendipine on the cerebral basilar artery (Fig. 4) indicated that extracellular calcium influx was critical to sumatriptan-induced contraction in this tissue but not in the peripheral saphenous vein. Other studies (11) have documented the ability of sumatriptan to cause a slow increase in intracellular calcium via phosphatase activation and not a G\textsubscript{i0}-coupled pathway in trigeminal neurons. The possibility that sumatriptan activates a signaling cascade in brain neurons and cerebral blood vessels that differs from peripheral tissues and thus is not amenable to augmentation is suggested by the present study.

In summary, the present studies document several differences in the effects of contractile agonists between the peripheral saphenous vein and a cerebral vessel, the basilar artery, from the rabbit. First, although sumatriptan and histamine produced a similar contractile profile between the basilar artery and saphenous vein, U-46619 was markedly more effective as a contractile agonist in the saphenous vein than in the basilar artery. Second, and perhaps most importantly, the induction of modest tone by agonists such as histamine and U-46619 augmented contraction to sumatriptan in the saphenous vein but not in the basilar artery, perhaps related to differences in calcium utilization and G protein involvement in these vessels. Should the response of the basilar artery reflect responses of other cerebral blood vessels, in particular those important to migraine therapy, based on our data, we speculate that at doses of the triptans required for antimigraine efficacy a more pronounced contractile response may occur in peripheral blood vessels resembling the saphenous vein than in cerebral vessels.

We are grateful to Kirk W. Johnson and David Nelson for reviewing this manuscript. The authors thank Priscilla Kirsch and Carla Maxey for expert administrative assistance.

Present address of A. Bhattacharya: Roche Bioscience, 3401 Hillview Ave., Palo Alto, CA 94304.

REFERENCES


