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Contractile responses to sumatriptan and ergotamine in the rabbit saphenous vein: effect of selective 5-HT_{1F} receptor agonists and $PGF_{2\alpha}$

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1 Contractile responses to ergotamine, sumatriptan and the novel 5-HT_{1F} receptor agonists, LY334370 and LY344864 were examined using the rabbit saphenous vein.

2 Ergotamine ($pEC_{50} = 8.7 \pm 0.06$) was 30 fold more potent than 5-hydroxytryptamine (5-HT) ($pEC_{50} = 7.2 \pm 0.13$) and 300 fold more potent than sumatriptan ($pEC_{50} = 6.0 \pm 0.08$) in contracting the rabbit saphenous vein *in vitro*. The selective 5-HT_{1F} receptor agonists, LY334370 or LY344864 (up to 10^{-4} M), did not contract the rabbit saphenous vein.

3 The contractile response to ergotamine in this tissue resulted from activation of both $alpha_1$ and 5-$HT_{1B/1D}$ receptors based on the observation that prazosin (10^{-6} M), an α-adrenoceptor antagonist, and GR127935 (10^{-8} M) a 5-$HT_{1B/1D}$ receptor antagonist, dextrally shifted the contractile response to ergotamine. In contrast, prazosin (10^{-6} M) did not alter contraction to sumatriptan whereas GR127935 (10^{-8} M) was a potent antagonist ($-\log K_B = 10.0$) suggesting that sumatriptan-induced contraction of the rabbit saphenous vein was mediated only by activation of receptors similar or identical to 5-$HT_{1B/1D}$ receptors.

4 $PGF_{2\alpha}$ (3×10^{-7} M) produced a modest increase (approximately 5.0–10.0% maximum $PGF_{2\alpha}$ contraction) in saphenous vein force. Precontraction with $PGF_{2\alpha}$ (3×10^{-7} M) dramatically augmented the potency and maximal contractile response to sumatriptan ($pEC_{50} = 7.1$) and modestly enhanced the contractile potency of ergotamine ($pEC_{50} = 9.0$) in the rabbit saphenous vein. However, $PGF_{2\alpha}$ (3×10^{-7} M) only unmasked a contraction to the 5-HT_{1F} receptor agonists when concentrations exceeded 10^{-5} M, concentrations considerably higher than their 5-HT_{1F} receptor affinities.

5 LY334370 (10^{-6} M) pretreatment did not alter contraction to either sumatriptan or ergotamine and a higher concentration (10^{-5} M) of LY334370 or LY344864 inhibited contraction to sumatriptan.

6 Thus, activation of 5-HT_{1F} receptors will not induce vascular contraction (either alone or following modest tone with $PGF_{2\alpha}$) or augment contraction to other contractile agonists in the rabbit saphenous vein.

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Abbreviations: GR127935, N-[methoxy-3-(4-methyl-1-piperazinyl)phenyl]-2′-methyl-4′-(5-methyl-1 2,4-oxadiazol-3-yl) [1, 1-biphenyl]-4-carboxamide hydrochloride; 5-HT, 5-hydroxytryptamine, serotonin; LY334370, 4-fluoro-N-[-3-(1-methyl-piperidin-4-yl)-1H-indol-5-yl]-benzamide hydrochloride; LY344864, (R)-(+)-N-(3-Dimethylamino-1,2,3,4-tetrahydro-9H-carbazol-6-yl)-4-fluorobenzamide; $PGF_{2\alpha}$, prostaglandin $F_{2\alpha}$

Introduction

Both ergotamine and sumatriptan are antimigraine therapies that also contract human coronary arteries. In fact, ergotamine-induced coronary arterial contraction has been used as a diagnostic test to detect patients with Prinzmetal's angina (Mantle *et al*., 1981). In part, the vascular contractile effect of ergotamine and sumatriptan has been attributed to the ability of these agents to activate 5-$HT_{1B/1D}$ receptors in vascular tissue. In contrast to sumatriptan, ergotamine may also interact with α-adrenoceptors both as an agonist and/or antagonist dependent on the vascular bed (Silberstein, 1997). Recently, selective 5-HT_{1F} receptor agonists have been proposed as effective antimigraine therapies (Johnson *et al*., 1998) that possess minimal propensity to cause coronary arterial vasocontraction or to interact with α-adrenoceptors (Cohen & Schenck, 1999). However, data are emerging to suggest that induction of a modest degree of tone in vascular preparations can enhance the response to other vasocontractile agonists such as sumatriptan (MacLennan & Martin, 1992; MacLean *et al*., 1994; Yildiz & Tuncer 1995; Maassen VanDenBrink *et al*., 1996; Smith *et al*., 1996; Cohen & Schenck 1999). The interaction of 5-HT_{1F} receptor agonists with other vasoactive agents has not been extensively examined.

The rabbit saphenous vein is a convenient *in vitro* model for responses that mimic those observed with human cerebral and coronary blood vessels (Cohen *et al*., 1997). Using this preparation, the present studies were designed to explore (1) the receptors involved in ergotamine and sumatriptan-induced contraction of the rabbit saphenous vein, and (2) potential interactions of the 5-HT_{1F} receptor agonists with ergotamine and sumatriptan. LY344864 (Phebus *et al*., 1997) and LY334370 (Johnson *et al*., 1997) were used as our prototypic 5-HT_{1F} receptor agonists. For comparative purposes, the effect

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of $PGF_{2\alpha}$, an agent known to potentiate contractile responses to sumatriptan (Yildiz & Tuncer, 1994; Cohen & Schenck 1999) was also explored for its effect on vascular contraction to ergotamine and the 5-HT_{1F} receptor agonists.

Methods

Isolation of vascular tissue

Male New Zealand White rabbits (1.5 −3.0 kg) (Myrtles Rabbitry, Thompson Station, TN, U.S.A.) were sacrificed by a lethal dose of sodium pentobarbital (200 mg) injected into the ear vein. The saphenous vein was dissected free of connective tissue, cannulated *in situ* with polyethylene tubing (PE no 50), placed in petri dishes containing Krebs' bicarbonate buffer (see below), and ring preparations were obtained.

Tissues were mounted in organ baths containing 10 ml of modified Krebs' solution of the following composition (millimolar concentrations): NaCl, 118.2; KCl, 4.6; $CaCl_2$ $2H_2O$, 1.6; KH_2PO_4, 1.2; $MgSO_4$, 1.2; dextrose, 10.0; and $NaHCO_3$, 24.8. Tissue bath solutions were maintained at 37°C and aerated with 95% O_2 and 5% CO_2 (pH = 7.4). An initial optimum resting force of 4 g was applied to the rabbit saphenous vein as determined in preliminary length tension studies using KCl (67 mM) challenge. Isometric contractions were recorded as changes in grams of force on a Beckman Dynograph with Statham UC-3 transducers or with a Macintosh-Compatible Data Acquisition System (BIOPAC Systems, Inc., Santa Barbara, CA, U.S.A.). Tissues were allowed to equilibrate 1 to 2 h before exposure to compounds.

Experimental protocol

Cumulative agonist concentration-response curves were generated and no tissue was used to generate more than one agonist concentration-response curve. Tissues precontracted with $PGF_{2\alpha}$ (3×10^{-6} M) did not relax to acetylcholine (10^{-6} M) indicating the absence of an intact endothelium (removed by rotating a cannula in the lumen). In some experiments, tissues were precontracted [7.62 + 2.76% (n = 12) of a maximal KCl response] with $PGF_{2\alpha}$ (3×10^{-7} M) prior to initiating a response to sumatriptan, ergotamine, LY344864 or LY334370. Initial studies have documented that this minimal contractile concentration of $PGF_{2\alpha}$ markedly augmented contraction to sumatriptan in the rabbit saphenous vein (Cohen & Schenck, 1999). In other experiments, tissues were pre-exposed to vehicle, prazosin (10^{-6} M), GR127935 (10^{-8} M), the combination of prazosin and GR127935, LY344864 or LY334370 for 1 h prior to initiating a response to sumatriptan or ergotamine. All results are expressed as mean ± s.e.mean where n represents the number of tissues examined. 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 $PGF_{2\alpha}$ (3×10^{-7} M), force produced by the second agonist was measured using the precontracted force as baseline. The $-\log EC_{50}$ values (pEC_{50}) were determined by least-squares linear regression analysis of the linear portion of the generated concentration-response curves taking maximal response as 100%.

Drugs and solutions

Prostaglandin $F_{2\alpha}$ and acetylcholine chloride were purchased from Sigma Chemical Company (St. Louis, MO, U.S.A.) and ergotamine was purchased from Research Biochemicals, Inc. (Natick, MA, U.S.A.). Prazosin hydrochloride was a gift from Pfizer Laboratories (Groton, CT, U.S.A.). Sumatriptan, GR127935, LY334864 and LY334370 were provided by the Lilly Research Laboratories (Indianapolis, IN, U.S.A.). Stock solutions (10^{-2}–10^{-3} M) of GR127935, sumatriptan, LY334864 and LY334370 were prepared in de-ionized distilled water with 2–10% 0.1 N HCl. Prazosin and $PGF_{2\alpha}$ were prepared in de-ionized distilled water. Ergotamine (10^{-3} M) was prepared in 2% DSMO and 0.1 N HCl. Subsequent dilutions were prepared in de-ionized distilled water.

Results

Contractile responses to ergotamine, 5-HT, sumatriptan and 5-HT_{1F} receptor agonists

Ergotamine (pEC_{50} = 8.7 ± 0.06), 5-HT (pEC_{50} = 7.2 ± 0.13) and sumatriptan (pEC_{50} = 6.0 ± 0.08) produced concentration dependent contractile effects in the rabbit saphenous vein (Figure 1). Ergotamine was approximately 30 and 300 fold more potent than 5-HT and sumatriptan as a contractile agonist in the saphenous vein and produced a maximal response that was approximately 50% greater than that of sumatriptan. In contrast to these agonists that markedly contracted the rabbit saphenous vein, the selective 5-HT_{1F} receptor agonists did not significantly contract the rabbit saphenous vein in concentrations as high as 10^{-4} M (Figure 1).

Antagonism of contraction to ergotamine and sumatriptan

To understand further the receptors mediating the contractile responses to both ergotamine and sumatriptan, we examined the effect of prazosin (10^{-6} M) and the 5-$HT_{1B/1D}$ receptor antagonist GR127935 (10^{-8} M) on the responses to sumatriptan and ergotamine in the rabbit saphenous vein. Although prazosin did not alter the contractile response to sumatriptan (Figure 2), prazosin did inhibit the contractile concentration response to ergotamine in a biphasic fashion. Contraction to low concentrations ($<10^{-9}$ M) of ergotamine was not altered by prazosin. However, contraction to higher ergotamine

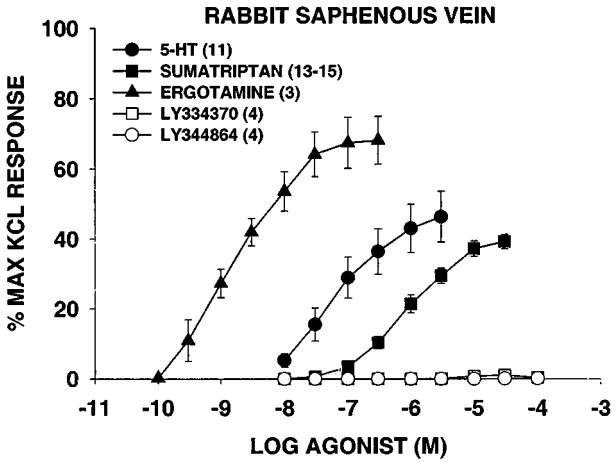


Figure 1 Comparative contractile response curves to ergotamine, 5-HT, sumatriptan, LY334370 and LY344864 in the rabbit saphenous vein. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.

concentrations ($>10^{-9}$ M) was dextrally shifted by prazosin (10^{-6} M). Thus, α_1-adrenoceptors are involved in vascular contraction to high concentrations ($>10^{-9}$ M) of ergotamine, but not in the contraction produced by low ergotamine concentrations (Figure 2).

In contrast, GR127935 produced a marked dextral shift in the contractile response to sumatriptan ($-\log K_B = 10.04 \pm 0.08$; $n=4$) suggesting that receptors similar to or identical to 5-HT$_{1B/1D}$ receptors participate in the vascular contractions produced by sumatriptan (Figure 3). However, GR127935 (10^{-8} M) had no effect on the contractile response to ergotamine in the absence of α-adrenoceptor blockade (Figure 3). In the presence of both antagonists, the response to ergotamine was shifted monophasically, consistent with the contractile response to ergotamine resulting from activation of both alpha and 5-HT$_{1B/1D}$ receptors in the rabbit saphenous vein (compare Figure 2, bottom panel and Figure 4).

Effect of PGF$_{2\alpha}$ to augment contractile responses

Because PGF$_{2\alpha}$ can augment contractile responses to sumatriptan (Yildiz & Tuncer, 1994; Cohen & Schenck 1999), we compared the effect of PGF$_{2\alpha}$ (3×10^{-7} M) precontraction on contractile responses to both ergotamine and sumatriptan. PGF$_{2\alpha}$ produced a profound augmentation of the contractile response to sumatriptan (pEC$_{50} = 7.08 \pm 0.01$ M) and a more modest augmentation of the contractile response to ergotamine (pEC$_{50} = 9.0 \pm 0.03$ M) (Figure 5). In contrast to these marked effects, pretreatment of tissues with PGF$_{2\alpha}$ (3×10^{-7} M) to produce a modest tone in the rabbit saphenous vein only enhanced the contractile response to the 5-HT$_{1F}$ receptor agonists when the concentration of the agonist was equal to or exceeded 10^{-5} M (Figure 6). In these high concentrations, it is likely that the 5-HT$_{1F}$ receptor agonists may be activating the 5-HT$_{1B/1D}$ contractile receptor in this preparation. Furthermore, even with vascular tone augmented by PGF$_{2\alpha}$, the potency of the 5-HT$_{1F}$ receptor agonists was considerably less than the contractile potency of sumatriptan alone.

Effect of 5-HT$_{1F}$ receptor agonists on contraction to sumatriptan and ergotamine

Lastly, we examined the effects of LY334370 pretreatment on the contractile responses to sumatriptan and ergotamine. LY334370 (10^{-6} M) neither augmented nor inhibited contraction to sumatriptan or ergotamine (data not shown). To examine the effects of these 5-HT$_{1F}$ receptor agonists further, we utilized even higher concentrations (10^{-5} M) of both LY334370 and LY344864 (Figure 7). In high concentrations,

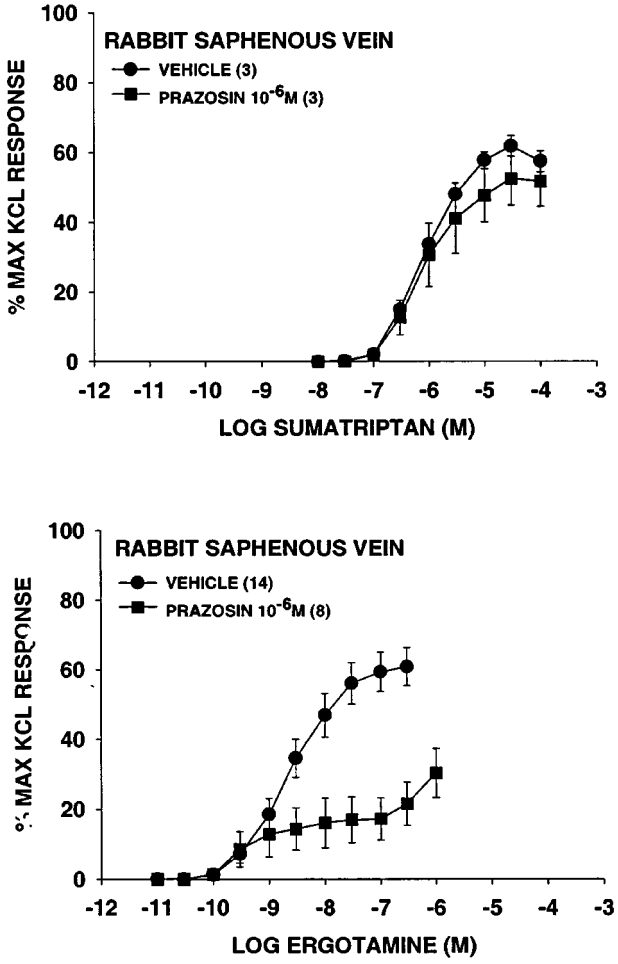


Figure 2 Effect of prazosin (10^{-6} M) on the contractile concentration response curves to sumatriptan (top) and ergotamine (bottom) in the rabbit saphenous vein. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.

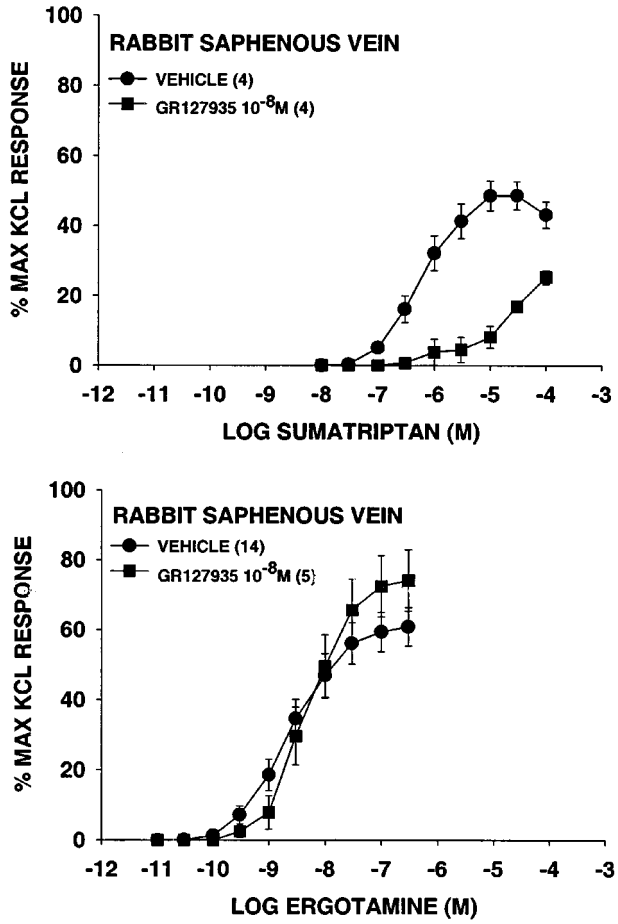


Figure 3 Effect of GR127935 (10^{-8} M) on the contractile concentration response curves to sumatriptan (top) and ergotamine (bottom) in the rabbit saphenous vein. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.

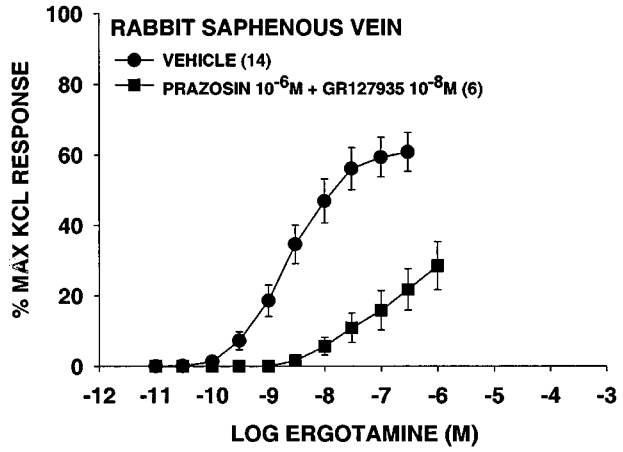
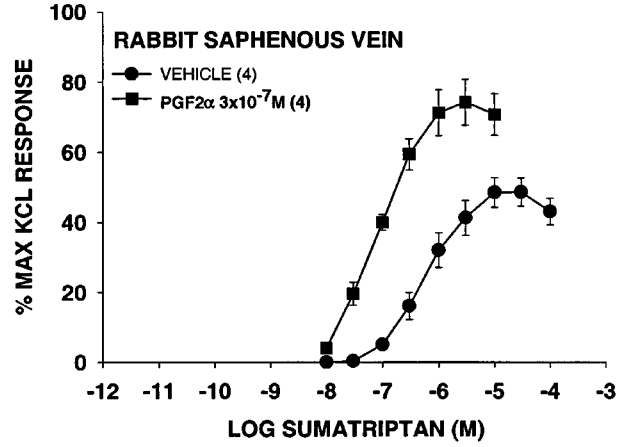


Figure 4 Effect of prazosin (10^{-6} M) and GR127935 (10^{-8} M) given together on the contractile concentration response curve to ergotamine in the rabbit saphenous vein. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.



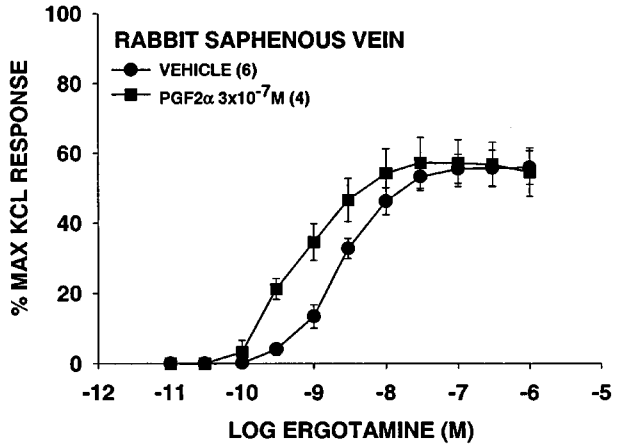
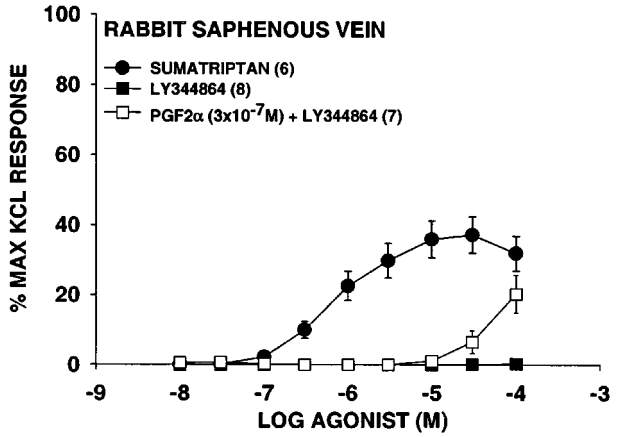


Figure 5 Effect of pre-contraction with $PGF_{2\alpha}$ (3×10^{-7} M) on the contractile concentration response curves to sumatriptan (top) and ergotamine (bottom) in the rabbit saphenous vein. Tissues were pre-contracted with $PGF_{2\alpha}$ to 13.4 ± 4.2 and 4.2 ± 1.6% of KCl maximum response for veins contracted with sumatriptan and ergotamine, respectively. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.



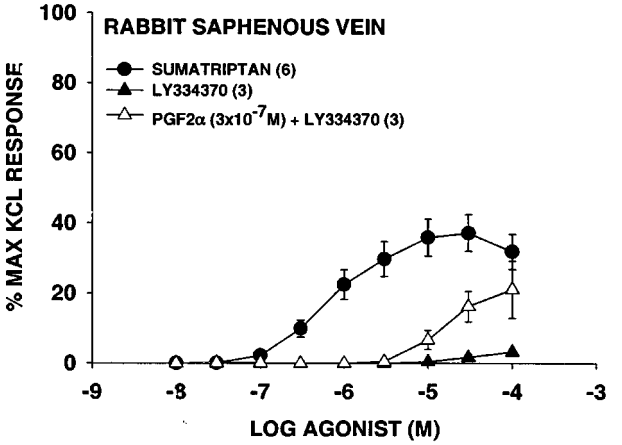


Figure 6 Effect of pre-contraction with $PGF_{2\alpha}$ (3×10^{-7} M) on the contractile concentration response curves to LY344864 (top) and LY334370 (bottom) in the rabbit saphenous vein. Tissues were pre-contracted with $PGF_{2\alpha}$ to 5.5 ± 1.2 and 6.6 ± 3.4% of KCl maximum response for veins contracted with LY344864 and LY334370, respectively. The concentration response curve to sumatriptan in the absence of augmentation is also shown. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.

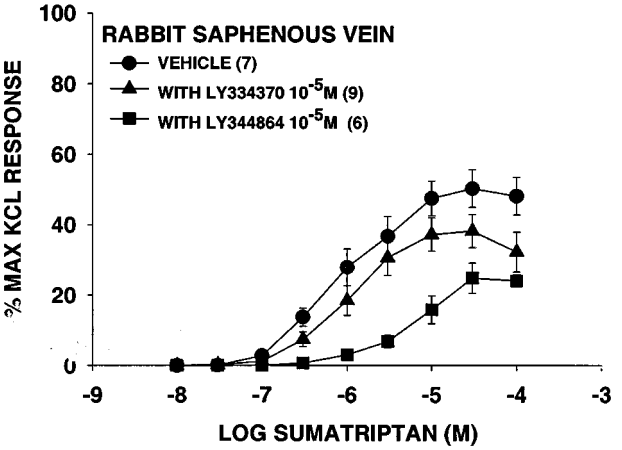


Figure 7 Effect of LY344864 (10^{-5} M) and LY334370 (10^{-5} M) on the contractile concentration response curve to sumatriptan in the rabbit saphenous vein. Points are mean values and vertical bars represent the standard error of the mean for the number of tissues indicated in parenthesis.

neither agonist (10^{-5} M) augmented the contractile response to sumatriptan. However, each agonist (10^{-5} M) inhibited the contractile response to sumatriptan.

Discussion

Although ergotamine and sumatriptan are efficacious in the treatment of migraine headache, the cardiovascular liabilities of these agents limit their more wide spread utility and acceptance (Yasue *et al*., 1981; Bax & Saxena, 1993; Chester *et al*., 1993; MacIntyre *et al*., 1993; Koh *et al*., 1994). Both sumatriptan and ergotamine are relatively potent agonists of coronary arterial vasoconstriction (Maassen VanDenBrink *et al*., 1998). This cardiovascular liability of these drugs has prompted the identification of alternative antimigraine therapy lacking vasoconstrictor potential. To this end, LY344864 and LY334370 were developed as prototypic high affinity and selective 5-HT$_{1F}$ receptor agonists. Although a recent report has emerged suggesting that LY334370 possesses significant 5-HT$_{1A}$ receptor effects (Dupuis *et al*., 1998), previous studies that also documented high 5-HT$_{1A}$ receptor affinity ($K_i = 12$ nM) in cloned cell lines did not detect marked *in vitro* or *in vivo* functional effects associated with 5-HT$_{1A}$ receptor activation (Overshiner *et al*., 1996). Nevertheless, both LY344864 and LY334370 were effective in inhibiting trigeminal-induced dural extravasation in animal models of migraine (Johnson *et al*., 1997; Phebus *et al*., 1997) and LY334370 demonstrated efficacy in clinical migraine (Offen *et al*., 1999).

With the identification of 5-HT$_{1F}$ receptor agonists and their utility in migraine, the rabbit saphenous vein, a tissue whose responses to sumatriptan are thought to mimic the responses to sumatriptan in human coronary arteries (Cohen *et al*., 1997), was used to understand whether 5-HT$_{1F}$ receptor agonists exhibit vasocontractile properties. Furthermore, the rabbit saphenous vein possesses α-adrenoceptors (Daly *et al*., 1988a,b) in addition to 5-HT$_{1B/1D}$ receptors which have been implicated in the vascular effects of ergotamine (Mikkelsen *et al*., 1981). Thus, the rabbit saphenous vein affords a model to understand the role of serotonergic versus α-adrenoceptors in the response to triptans, ergotamine and 5-HT$_{1F}$ receptor agonists.

Contraction to ergotamine resulted from activation of both alpha$_1$ and 5-HT$_{1B/1D}$ receptors in the rabbit saphenous vein. This conclusion was based on the demonstration that contraction to low concentrations of ergotamine (10^{-9} M and lower) was resistant to prazosin blockade, whereas contraction to higher concentrations of ergotamine was markedly inhibited by prazosin. Thus, in high concentrations, ergotamine contracted the rabbit saphenous vein by activation of α_1-adrenoceptors. Further evidence for this dual contractile mechanism was obtained by documenting a marked dextral shift in the contractile response to ergotamine by the combination of GR127935 and prazosin. Under these conditions, contraction to low concentrations of ergotamine was dramatically inhibited consistent with the finding that ergotamine has exceptionally high affinity for the cloned 5-HT$_{1B}$ ($K_i = 0.03$ nM) and 5-HT$_{1D}$ ($K_i = 0.07$ nM) receptors (Hamblin *et al*., 1992). These data underscore the marked heterogeneity in mechanisms of vasoconstriction to ergotamine. Previous studies in human blood vessels documented contractile responses to ergotamine that were resistant to α-adrenoceptor blockade but inhibited by 5-HT receptor antagonists (Mikkelsen *et al*., 1981). In contrast, *in vivo* studies using canine external carotid vasoconstriction revealed a marked contractile effect of ergotamine mediated by 5-HT$_{1B/1D}$ receptors as well as α_2-adrenoceptors, but not α_1-adrenoceptors (Villalon *et al*., 1999). Clearly, the effects of ergotamine are highly dependent upon the receptor densities present in specific vascular beds (Muller-Schweinitzer, 1982).

In contrast to the marked contractile potency of ergotamine in the rabbit saphenous vein, sumatriptan was approximately 300 fold less potent than ergotamine, producing a maximal response that was approximately 50% of the maximal contraction to ergotamine. Furthermore, sumatriptan was a highly selective agonist at the 5-HT$_{1B/1D}$ receptor in the rabbit saphenous vein based on the observation that prazosin (10^{-6} M) did not alter the contractile response to sumatriptan, whereas GR127935 (10^{-8} M) potently inhibited contraction to sumatriptan. These data are consistent with previous studies documenting the 5-HT$_{1B/1D}$ receptor interactions of sumatriptan (Razzaque *et al*., 1995; Terron 1996; Cohen *et al*., 1999).

The rabbit saphenous vein markedly contracted to sumatriptan, 5-HT and ergotamine, yet the selective 5-HT$_{1F}$ receptor agonists, LY334370 and LY344864 did not contract the rabbit saphenous vein from baseline force in concentrations up to 10^{-4} M. Although LY334370 and LY344864 did not contract the saphenous vein, 5-HT$_{1F}$ receptor mRNA has been detected in the rabbit saphenous vein (Bard *et al*., 1996) suggesting a potential role of 5-HT$_{1F}$ receptor protein in vascular tissue. To examine this further, we took advantage of the observation that vascular tissue can exhibit augmented contractile force to serotonergic agonists following exposure to low concentrations of other agonists (Stupecky *et al*., 1986; Yildiz *et al*., 1998). Based on this, we questioned whether the presence of a modest force in the tissue could unmask a contractile response to the 5-HT$_{1F}$ receptor agonists. PGF$_{2\alpha}$ (3×10^{-7} M) was used to induce a modest force (approximately 5–10% of its maximal response) in the saphenous vein prior to exposure either to sumatriptan, ergotamine or a 5-HT$_{1F}$ receptor agonist. In the presence of PGF$_{2\alpha}$ (3×10^{-7} M), the contractile response to sumatriptan was markedly augmented (see Figure 5). The effect of PGF$_{2\alpha}$ on sumatriptan-induced contraction in the saphenous vein is consistent with previous reports using rabbit mesenteric and iliac arteries (Yildiz & Tuncer, 1994).

In contrast, contraction to ergotamine was not markedly altered by preconstriction with PGF$_{2\alpha}$. It is possible that responses to ergotamine, which was an exceptionally potent contractile agonist in the rabbit saphenous vein, could not be further enhanced or alternatively, that PGF$_{2\alpha}$ can dramatically augment the contractile response mediated by 5-HT$_{1B/1D}$ receptors and only to a lesser extent, augment α-adrenoceptor responses in the rabbit saphenous vein. This later hypothesis is consistent with the idea that amplification occurs as a result of cross talk between two G-protein coupled receptors with Gi-coupled receptors able to amplify Gq-coupled responses (MacLean, 1999). Thus, PGF$_{2\alpha}$, which activates Gq-coupled responses is less likely or able to amplify responses which are also Gq-coupled such as the α_1-adrenoceptor component of ergotamine-induced contraction whereas PGF$_{2\alpha}$ is able to dramatically amplify the Gi-coupled sumatriptan response.

In spite of the marked augmentation of sumatriptan-induced contraction, PGF$_{2\alpha}$ (3×10^{-7} M) did not unmask contraction to either of the 5-HT$_{1F}$ receptor agonists in concentrations of 10^{-5} M or lower. These concentrations were sufficient to markedly stimulate 5-HT$_{1F}$ receptors with pK$_i$ = 8.8 and 8.2 for LY334370 and LY344864, respectively (Johnson *et al*., 1998). Only when concentrations exceeded 10^{-5} M, was there an apparent unmasking of a contractile

response to 5-HT$_{1F}$ receptor agonists. Under augmented conditions, the contractile response observed using high concentrations of 5-HT$_{1F}$ receptor agonists may reflect an improved sensitivity to detect the ability of high concentrations of these agents to activate 5-HT$_{1B/1D}$ or similar receptors in the rabbit saphenous vein.

Because responses to sumatriptan and to a lesser extent to ergotamine could be augmented in the rabbit saphenous vein, we examined the ability of LY334370 and LY344864 to enhance or augment the contractile response to sumatriptan and ergotamine in the rabbit saphenous vein. Pre-incubation with LY334370 (10^{-6} M) did not alter the contractile response to sumatriptan or ergotamine under conditions that resulted in augmented contraction by PGF$_{2\alpha}$. We extended these studies with a higher concentration of 5-HT$_{1F}$ receptor agonist (10^{-5} M) and again, no augmentation to sumatriptan-induced contraction occurred. In fact, LY344864 and LY334370 (10^{-5} M) modestly inhibited contraction to sumatriptan. Thus, these studies with two independent 5-HT$_{1F}$ receptor agonists are consistent with the contention that 5-HT$_{1F}$ receptor agonists do not exert marked effects on vascular smooth muscle contractility.

In summary, ergotamine and sumatriptan, like 5-HT, contracted the rabbit saphenous vein with contraction mediated by 5-HT$_{1B/1D}$ receptors for sumatriptan and by both 5-HT$_{1B/1D}$ and α_1-adrenoceptors for ergotamine. Contraction to ergotamine and sumatriptan was augmented by low concentrations of PGF$_{2\alpha}$. In contrast, the selective 5-HT$_{1F}$ receptor agonists, LY344864 and LY334370 did not contract the rabbit saphenous vein and only produced a small contraction in the presence of PGF$_{2\alpha}$ when their 5-HT$_{1F}$ receptor agonist concentration exceeded 10^{-5} M. Furthermore, 5-HT$_{1F}$ receptor agonists did not augment contractile response to sumatriptan, but rather, high concentrations (10^{-5} M) of LY344864 and LY334370 inhibited sumatriptan-induced contractility. These studies support the contention that selective 5-HT$_{1F}$ receptor agonists exert minimal, if any vascular contractile agonist efficacy, in marked contrast to sumatriptan and ergotamine.

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