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Trace amine-induced vasoconstriction of human mammary artery and saphenous vein

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ABSTRACT

Sympathomimetic amines, including β-phenylethylamine (PEA), constrict animal blood vessels but their mechanism of action is not now thought to be through α-adrenoceptors and release of noradrenaline but via trace amine-associated receptors (TAARs). This information is not available for human blood vessels. Functional studies were therefore performed on human arteries and veins to establish whether they constrict to PEA and whether any constrictions are adrenoceptor-mediated. Isolated internal mammary artery or saphenous vein rings were set up in Kreb's-bicarbonate solution at 37 ± 0.5 °C gassed with O_2:CO_2 (95:5) under class 2 containment. Isometric contractions were measured and cumulative concentration-response curves for PEA or the α-adrenoceptor agonist, phenylephrine were established. PEA showed concentration-related contractions. The maximum was significantly greater in arteries (1.53 ± 0.31 g, n = 9) than veins (0.55 ± 0.18 g, n = 10), but not when plotted as % of KCl contractions. PEA showed slowly developing contractions plateauing at 17,3 ± 3.7 min in mammary artery. The reference α-adrenoceptor agonist, phenylephrine, exhibited more rapid onset (peak 5.0 ± 1.2 min) but non-sustained contractions. In saphenous veins, PEA (62.8 ± 10.7%) and phenylephrine (61.4 ± 9.7%, n = 4) displayed the same maximum, but phenylephrine was more potent. The α_1-adrenoceptor antagonist, prazosin (1 μM), blocked phenylephrine contractions of mammary arteries but not PEA contractions in either vessel. PEA causes substantial vasoconstriction of human saphenous vein and mammary artery, which explains its vasopressor actions. This response, however, was not mediated via α_1-adrenoceptors, but likely due to TAARs. The classification of PEA as a sympathomimetic amine on human blood vessels is therefore no longer valid and requires revision.

1. Introduction

Trace amines such as β-phenylethylamine (PEA), octopamine and tyramine occur in the body in trace amounts and are widespread in our diet [1]. They cause vasoconstriction in animal isolated blood vessels including aortic rings from rats [2–4] guinea-pigs [2] and rabbits [2] and porcine coronary arteries [5]. This is reflected in vivo as increases in the blood pressure after intravenous administration of PEA or tyramine in rats [6–8], cats [6,9], dogs [10,11] and rabbits [12]. In humans, administration of the trace amines tyramine [13,14] and phenylpropanolamine [15] also increase blood pressure.

The conventionally accepted mechanism of action of these amines is that they are indirectly acting sympathomimetic amines releasing noradrenaline from sympathetic neurones onto vascular smooth muscle α_1-adrenoceptors causing vasoconstriction and a rise in blood pressure [16]. More recent evidence suggests, however, that this mechanism may not entirely explain the vasoconstriction. We have shown that vasoconstrictor responses to PEA of rat [4,17] and guinea-pig [18,19] isolated aorta and pig coronary artery [5] are not inhibited by the α_1-adrenoceptor antagonist, prazosin. On this evidence, we proposed that vasoconstrictions by PEA and other trace amines were due to stimulation of trace amine-associated receptors (TAARs). TAAR-1 has been identified from its mRNA by quantitative reverse transcription (RT)-PCR in the human brain and several peripheral tissues. Moderate or low levels were found in the stomach, kidney, lung and small intestine with lower levels expressed in the prostate, skeletal muscle and spleen [20].

Abbreviations: CRC, concentration-response curve; TAAR, trace amine-associated receptor; L-NAME, N^{ω}-nitro-L-arginine; NO, nitric oxide; NOS, nitric oxide synthase; PEA, β-phenylethylamine.

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In rat heart tissue, TAAR-1 has been detected by RT-PCR [21]. We have shown the presence of TAAR-1 receptor protein by Western blotting and mRNA by RT-PCR in rat aorta [4].

There is virtually no information on the responses to trace amines such as tyramine in human isolated blood vessels. For example, contractions of human isolated uterine artery to tyramine were inhibited by prazosin and inspection of the data indicates non-competitive and non-progressive antagonism [22]. Furthermore, there do not appear to be any reports of trace amine-associated receptor identification in human blood vessels. Functional studies were therefore undertaken to determine whether human isolated arteries (internal mammary artery) and veins (saphenous vein) contract in response to the trace amine PEA. A second objective was to determine whether any constriction was due to stimulation of α_1-adrenoceptors or if TAARs might be involved.

2. Materials and methods

2.1. Human tissues

This work received a favourable ethical opinion from the National Research Ethics Service, Newcastle and North Tyneside 2 Committee. The work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and their tissues. Informed consent to use their tissues was obtained from male and female patients prior to them undergoing surgery. Internal mammary arteries and saphenous veins surplus to coronary artery by-pass graft (CABG) surgery were used. Internal mammary arteries were sprayed with papaverine (3 mg ml^{-1} normal saline) after harvest, while the saphenous vein was perfused with and stored in heparinised Hartmann's solution. They were then transferred to Kreb's bicarbonate solution pre-gassed with O_2:CO_2 (95:5) for transport from the theatre to the laboratory at ambient temperature.

2.2. . Tissue set-up

Internal mammary arteries or saphenous veins were cleared of attached fat and cut into rings approximately 0.5 mm in length. They were set up under class 2 containment conditions in organ baths containing Krebs-bicarbonate solution maintained at 37 ± 0.5 °C with a circulator (type KD Grant Instruments, Cambridge, UK) and gassed with O_2:CO_2 (95:5) (BOC Gases, Guildford, UK). Fixed and mobile stainless steel wire hangers were passed through the ring, the fixed hanger being secured in a 50 ml organ bath. The Krebs bicarbonate buffer was made up in distilled water and had the following composition (mM): NaCl (118), $NaHCO_3$ (25), glucose (11.7), $MgSO_4.7H_2O$ (1.2), KH_2PO_4 (1.2), KCl (4.7) and $CaCl_2.2H_2O$ (2.5). A suture attached to the upper mobile hanger was connected to an isometric transducer (Dynamometer UF1, 57 g sensitivity range, Pioden Controls Ltd., Canterbury, UK). A resting tension of 1.5 g was applied to each ring and isometric tension recorded and displayed on a computer (Power Lab, Chart 5, ADInstruments, Chalgrove, Oxfordshire, UK).

2.3. Experimental protocols

After 1 h equilibration, a cumulative concentration-response curve (CRC) for β-phenylethylamine (PEA) or (−)-phenylephrine was obtained by addition of half logarithmic increments in concentration, each successive concentration being added after the peak effect was reached for the preceding concentration. The contraction to each concentration was allowed to develop fully which could take up to 20 min. The tissue was then washed and after approximately 15 min a second wash undertaken to restore baseline. A second CRC was then constructed in the presence of prazosin or vehicle which was left in contact with the tissue for 15 min before commencing the second CRC. At the end of each experiment, KCl (60 mM) was routinely added to achieve a maximum contraction.

2.4. Data processing and statistical analysis

Contractions at the plateau response to each concentration of agonist were measured from the baseline before the CRC. These were then expressed as a percentage of the contraction to KCl in each experiment, to normalize responses to the maximum contractility of each tissue. The mean responses (±SEM) were then plotted. Time courses for responses to PEA and phenylephrine at approximately the 50% of maximum were plotted by measuring the increase in tension from the previous dose maximum every 15 s for the first minute, every 30 s for the next 4 min and then every minute. These were plotted as a percentage of the maximum contraction to that concentration of agonist and the mean (±SEM) plotted against time. n values are the number of subjects providing mammary artery or saphenous vein. For some experiments n is less than 5 because of limited availability of suitable donor tissue. Maximum responses before and after inhibitors and at individual concentrations in the same tissue were compared by paired Student's *t*-tests, whereas responses in different tissues were compared by Student's unpaired *t*-tests.

2.5. Drugs used

Prazosin hydrochloride, (−)-phenylephrine hydrochloride and β-phenylethylamine hydrochloride (PEA) were obtained from Sigma-Aldrich (Poole, Dorset, UK). All chemicals for the Krebs-bicarbonate buffer were of analytical grade and were obtained from Fisher Scientific, Leicestershire, UK. PEA and phenylephrine were dissolved in distilled water. Prazosin hydrochloride was dissolved in dimethylsulfoxide (DMSO):distilled water (1:10) and further diluted 1 in 10 with DMSO:water (1:10).

3. Results

3.1. Effects of phenylephrine and PEA

PEA and phenylephrine showed concentration-related contractions of mammary artery (Fig. 1.) and saphenous vein.

PEA compared in artery and vein The contractions to PEA were significantly greater in the artery (1.53 ± 0.31 g, $n = 9$) than the vein (0.55 ± 0.18 g, $n = 10$) when plotted as g tension (Fig. 2A.). However, when plotted as % of the KCl maximum contraction (Fig. 2B.), the responses were not significantly different (vein 66.7 ± 9.5% n = 10; artery 74.7 ± 4.6% $n = 9$ at 3×10^{-3} M), indicating the overall greater contractility of this artery.

PEA and phenylephrine compared in saphenous vein ($n = 4$) PEA (62.8 ± 10.7%) and phenylephrine (61.4 ± 9.7%) displayed the same maximum responses at 3×10^{-3}M and 3×10^{-4}M, respectively, but phenylephrine was more potent (Fig. 3.).

3.2. Time courses of responses to phenylephrine and PEA

PEA displayed slowly developing contractions in both tissues which reached plateau effects at 13.9 ± 0.9 ($n = 9$) and 17.3 ± 3.7 min ($n = 6$) in saphenous vein and mammary artery, respectively (Fig. 4.). The reference α-adrenoceptor agonist, phenylephrine, however, showed a biphasic contraction with a rapid-onset contraction, followed by a slower phase contraction peaking at 5.0 ± 1.2 min ($n = 5$) in the mammary artery, which was not sustained (Fig. 4.).

3.3. Effects of prazosin on responses to phenylephrine and PEA

In the mammary artery, the selective α_1-adrenoceptor antagonist, prazosin (1 μM) shifted the CRC for phenylephrine to the right and reduced the maximum response to 44.8 ± 8.8 of the pre-prazosin maximum contraction ($n = 4$) (Fig. 5A.). Since a 50% of maximum response was not achieved in the presence of prazosin, the dose-ratio for

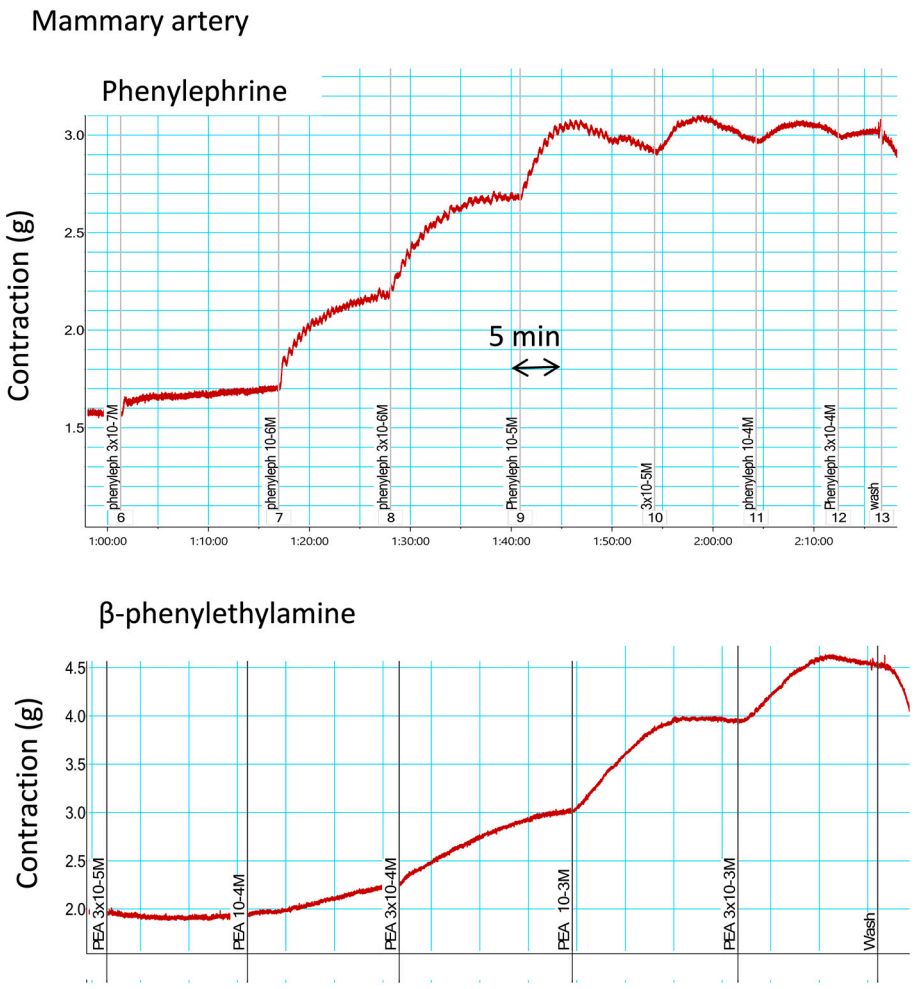

Fig. 1. Representative traces of contractions of human isolated internal mammary arteries to A. phenylephrine and B β-phenylethylamine (PEA). Phenylephrine and PEA were administered cumulatively in half logarithmic increments in concentration. The time scale for 5 min is shown and contractions are recorded in g tension.

the shift of the concentration-response curve (68.3 ± 35.3) was measured at the EC_{30} rather than the EC_{50}. This yielded a -logK_D value for prazosin of 7.65 ± 0.23. Prazosin, however, did not affect the contractions of the mammary artery to PEA (Fig. 5B.). Similarly, in the saphenous vein, prazosin (1 μM) did not block the contractions to PEA (Fig. 6A.). The DMSO vehicle for prazosin had no effect on PEA contractions in mammary artery (Fig. 5C.) or saphenous vein (Fig. 6B.).

4. Discussion

PEA contracted human isolated mammary artery and saphenous vein. This is the first demonstration of such contractions in any human blood vessels. PEA belongs to a group of biogenic amines known as trace amines [1]. PEA has also been characterized as an indirectly acting sympathomimetic amine causing increases in blood pressure by releasing endogenous noradrenaline [9]. The only previous studies on human blood vessels appear to have been performed using the related sympathomimetic amine, tyramine. Intravenous infusion [23] or oral administration [13] of tyramine causes increases in blood pressure. The tyramine pressor test has been used as an index of noradrenaline from sympathetic neurones and of sympathetic nerve function [24]. Tyramine infusion causes increases in systolic but not diastolic blood pressure and there is evidence of noradrenaline spillover suggesting a sympathomimetic action [23] The increase in blood pressure as attributed mainly, however, to increases in cardiac output since it was blocked by the β_1-adrenoceptor antagonist, bisoprolol [25]. Forearm blood flow has also been measured as an index of tyramine action on human blood vessels in vivo. In the paper by Jacob et al., [23], tyramine caused a paradoxical increase in forearm blood flow measured by plethysmography. In contrast, intra-arterial administration of tyramine to human forearm caused vasoconstriction and reduced forearm blood flow [26]. Tyramine also constricts blood vessels in the human hand as measured by plethysmography [27]. The responses to tyramine of human isolated blood vessels have rarely been examined – vasoconstrictor responses have been recorded in cerebral arteries [28] and posterior ciliary arteries [29]. Tyramine also constricts human isolated uterine arteries but the antagonism by prazosin was non-competitive and non-progressive [22]. All the aforementioned studies assumed that tyramine was acting as a sympathomimetic amine by releasing noradrenaline from endogenous storage sites. There are no previous studies with other trace amines in human isolated blood vessels, including PEA used in the present study. Other amines such as tryptamine would not be suitable because of introducing mixed activity, tryptamine stimulating 5-HT (serotonin) receptors as well as TAAR.

In the present study, the possible sympathomimetic mechanism of action of PEA was examined by measuring the antagonistic activity of the selective α_1-adrenoceptor antagonist, prazosin. Prazosin inhibited the contractions of the mammary artery to the reference α_1-adrenoceptor agonist phenylephrine, however, the rightwards shift of the concentration-response curve was not parallel as expected of a competitive antagonist. Instead, there was a suppression of the maximum response more representative of non-competitive antagonism. There is little information on the antagonism by prazosin in human isolated blood vessels. In human femoral arteries, prazosin

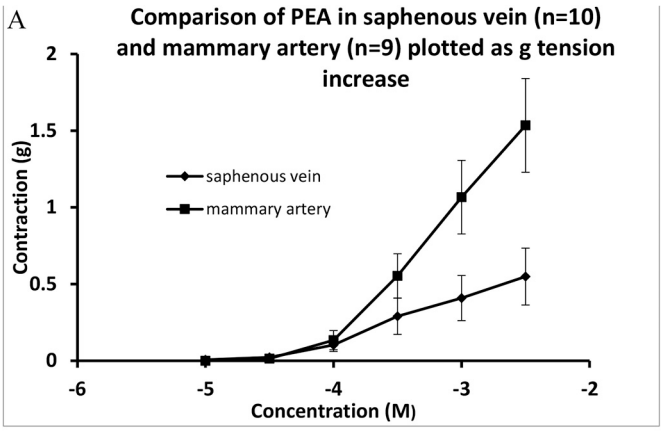

Fig. 2. Mean concentration-response curves for the contractions to β-phenylethylamine (PEA) compared in human internal mammary arteries (■)(n = 9) and saphenous veins (◆) (n = 10). Contractions are plotted as the mean ± SEM increases in tension above baseline expressed as either A g tension or B percentage of the contraction to KCl (60 mM).

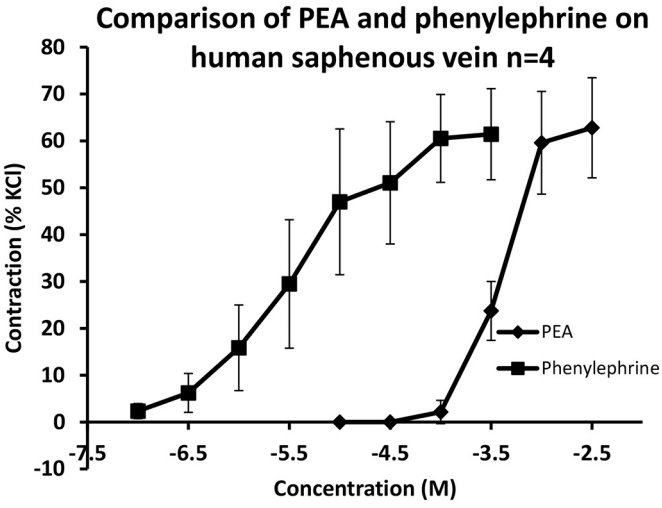

Fig. 3. Mean concentration-response curves (n = 4) for the contractions of human isolated saphenous vein to phenylephrine (■) and β-phenylethylamine (PEA)(◆). Contractions are plotted as the mean ± SEM increases in tension above baseline expressed as percentage of contraction to KCl (60 mM).

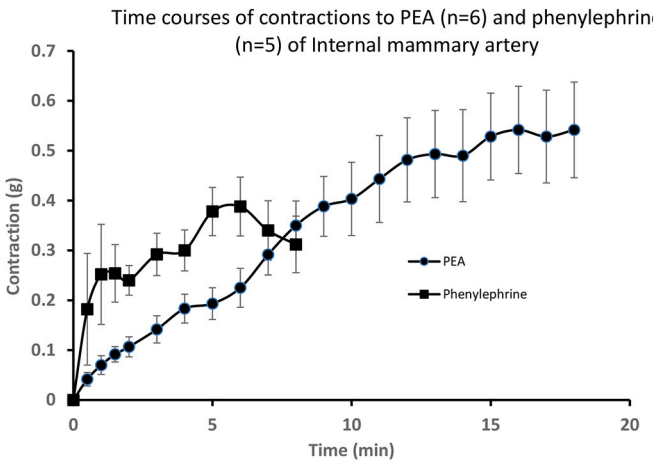

Fig. 4. Mean time courses for the contractions of human isolated internal mammary arteries to β-phenylethylamine (PEA) (3×10^{-4}M, n = 6, ◆) and phenylephrine (10^{-5} M, n = 5, ■). Contractions are plotted as the mean ± SEM increases in tension above baseline expressed as g tension.

inhibited noradrenaline contractions competitively but in veins it was a weak non-competitive antagonist [30]. In rat aorta, prazosin inhibited phenylephrine or noradrenaline contractions with pA_2 values of 9.9 (slope of Schild plot 1.15 ± 0.16) [31], 9.26 [32], 9.8 [33] and 9.66 ± 0,07 slope 1.02(0.922–1.117) [34]. In all these experiments, the endothelium was removed from the arteries. However, when the endothelium was left intact, the antagonism by prazosin was described as non-competitive but its removal converted it to a competitive antagonism [35]. Their study showed that when cyclic AMP levels were reduced with methylene blue, in intact aortae, the non-competitive antagonism by prazosin was converted to a competitive one. They suggested that this was due to cGMP altering agonist efficacy. These observations are consistent with the fact that in the present study the endothelium was not intentionally removed from the human veins and arteries and would appear to support the contention that it was still intact.

While prazosin antagonised the contractions of the human blood vessel to phenylephrine albeit non-competitively, it did not inhibit the contractions to PEA. This observation applied to both the mammary artery and saphenous vein. This indicates that the contractions to PEA are not mediated via α_1-adrenoceptors, which is in agreement with observations in isolated aortae of rats [4,17] and guinea-pigs [18,19] and pig coronary arteries [5]. Other potential receptors for mediating contractions to PEA and related trace amines, such as p-tyramine, have also been eliminated. For example, our previous studies have shown that antagonism of 5-HT_{2A} and 5-HT_{1D} receptors with ketanserin and methiothepin, respectively, failed to antagonise the contractions of porcine coronary arteries to β-PEA [5]. This indicates that 5-HT receptors are unlikely to be involved in the vasoconstriction of human arteries and veins. These observations and the incomplete antagonism by prazosin of contractile responses to PEA and p-tyramine in pig coronary vessels [5,36] have led to the conclusion that they are mediated via trace amine-associated receptor-1 (TAAR-1). TAAR-1 has been detected from mRNA by RT-PCR in rat heart [21] and from receptor protein by Western blotting and from mRNA by RT-PCR in rat aorta [4]. TAAR-1 have also been identified from mRNA in a number of human cardiovascular tissues including the kidney and spleen [20], but there is no information for human blood vessels. It would therefore be of interest to determine the expression of TAAR-1 in human mammary arteries and saphenous vein. The involvement of TAAR-1 in the functional contractile responses can only be confirmed by the use of antagonists of human TAAR-1. The only available antagonist, EPPTB (N-(3-ethoxy-phenyl)-4-pyrrolidin-1-yl-3-trifluoromethyl-benzamide), has activity at mouse receptors (Stalder et al. 2011, Revel et al. 2011) but not rat or human

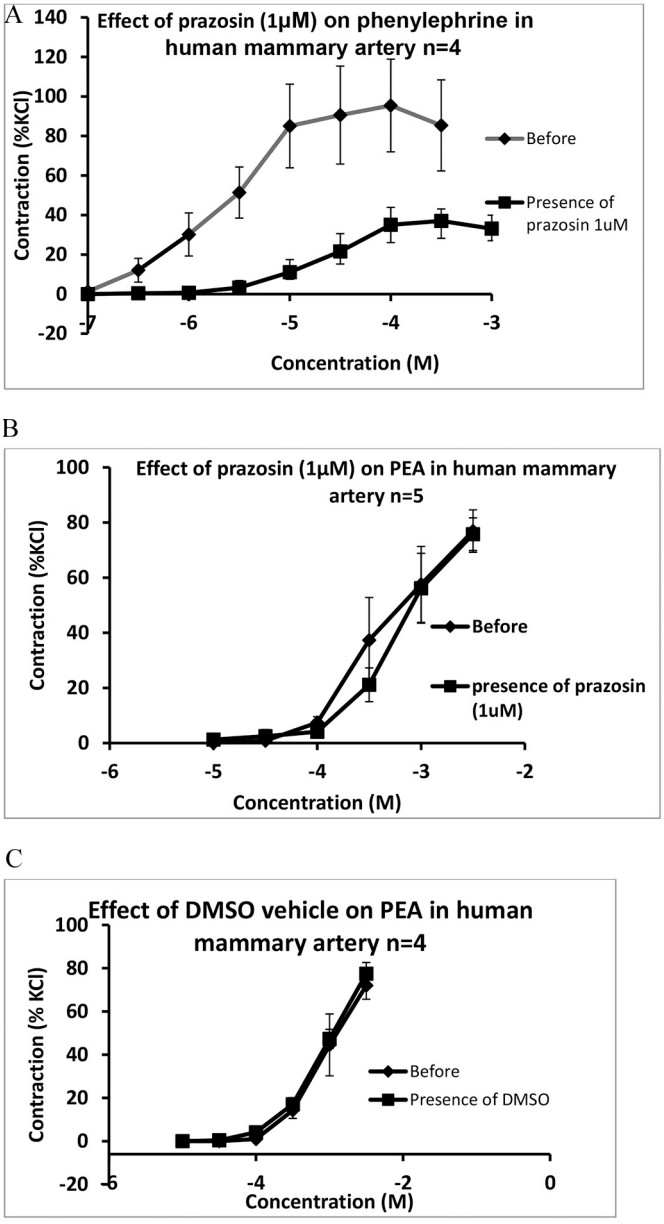

Fig. 5. Effect of prazosin (1 μM) on contractions of human isolated mammary arteries to phenylephrine and β-phenylethylamine (PEA). Concentration-response curves are plotted as the mean ± SEM increases in tension expressed as % of contraction to KCl 60 mM. Responses to A. phenylephrine (n = 4) and B. PEA (n = 5) are shown before (◆) and in the presence of prazosin (◆) and C. responses to PEA (n = 4) before (■) and in the presence of dimethylsulfoxide (DMSO, 1 in 10 distilled water)(■).

TAAR-1. It is not therefore suitable for examining human TAAR-1 function., It is likely, however, that the contractions of human mammary artery and saphenous vein to PEA are mediated via TAAR-1.

That the vasoconstrictions of these human blood vessels to PEA are different from those to the α_1-adrenoceptor agonist, phenylephrine, is further illustrated by the time-course of the contractions. The rate of onset of the contraction to phenylephrine was biphasic as reported for contractions of rat aorta to noradrenaline [37]. The initial fast component is attributed to the intracellular release of Ca^{2+} from the sarcoplasmic reticulum and is blocked by ryanodine. The secondary slow sustained contraction is due to influx of extracellular Ca^{2+} via Ca^{2+} channels and is inhibited by L-type Ca^{2+} channel blockers such as nifedipine [38]. The initial fast component of contraction of the

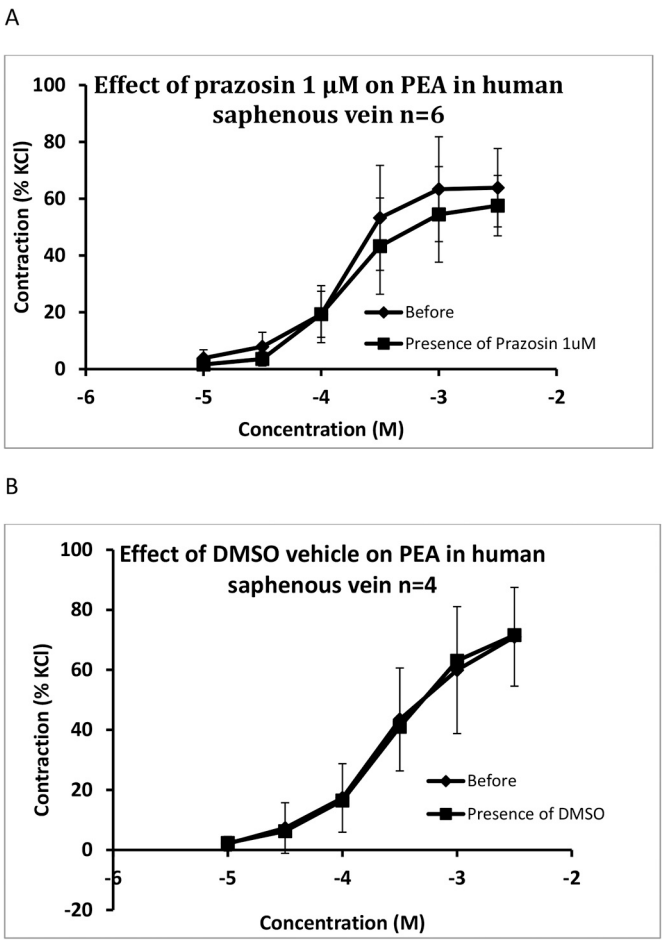

Fig. 6. Effect of prazosin (1 μM) on contractions of human isolated saphenous veins to β-phenylethylamine (PEA). Concentration-response curves are plotted as the mean ± SEM increases in tension expressed as % of contraction to KCl 60 mM. Responses to PEA are shown before (◆) and in the presence of (■) either A. prazosin (n = 6) or B. dimethylsulfoxide (DMSO, 1 in 10 distilled water)(n = 4).

mammary artery to phenylephrine was complete within 1 min and the slow secondary component was complete after 5 min. In contrast, the contraction to PEA had no apparent fast component suggesting that the TAAR-1 receptors mediating this contraction are not linked to the intracellular Ca^{2+} source. Instead, there was a slow onset single phase contraction which peaked later at 17 min in the mammary artery than the secondary phase of contraction to phenylephrine. We have reported previously the fast- and slow-onset contractions, respectively, to phenylephrine and PEA in guinea-pig aorta [19]. We have also shown that octopamine causes a fast onset contraction in guinea-pig aorta mediated via α_1-adrenoceptors and a slow-onset contraction when α_1-adrenoceptor are blocked [17]. The TAAR-1-mediated contractions of human blood vessels therefore appear to be coupled to the influx of extracellular Ca^{2+}.

An important issue is whether the concentrations in the circulation of trace amines like PEA reach levels required to induce the arterial and venous constrictions observed in this study. Basal plasma concentrations of tyramine are 2.6 μM in males and 2.34 μM in females [39]. Therefore normal circulating levels of tyramine are in low micromolar concentrations [40]. However, plasma levels of tyramine and PEA are elevated after meals rich in these amines and further raised in individuals in who MAO A and B activity is compromised or blocked [41]. Cloned trace amine-associated receptor-1 (TAAR-1) of human and rat are activated by submicromolar concentrations of PEA and tyramine. The EC50 for tyramine-induced cAMP accumulation at TAAR-1 expressed in cell lines

is 214 nM [1] and 324 ± 110 and 214 ± 67 nM, respectively, for PEA and tyramine cAMP accumulation [20]. However, EC50 values derived from binding data or generation of cAMP in cell lines would be several-fold less than those determined for a functional tissue response because of the signal amplification in coupling between receptor activation and the contractile response. The concentrations of trace amines required to induce constrictions of isolated blood vessels in our previous studies in pig coronary arteries are in the range 10-100 μM [5]. Here, in human artery and vein, contractions to PEA occurred at 100 μM. Thus, normal circulating levels of tyramine and β-phenylethylamine would appear to be within the required range to elicit responses via TAARs.

5. Conclusions

This study has shown for the first time that human artery (mammary artery) and vein (saphenous vein) are constricted by the sympathomimetic amine, PEA. However, this vasoconstriction is not mediated by α_1-adrenoceptors and therefore its former classification as a sympathomimetic amine is incorrect. The vasoconstriction is most likely mediated via trace amine-associated receptor-1. The textbook classification of PEA as a sympathomimetic amine is therefore no longer valid and requires revision.

Author contributions

KJB undertook the experiments, analysed the data and prepared the manuscript. DM provided the tissues and manuscript overview.

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CRediT authorship contribution statement

Kenneth J. Broadley: Conceptualization, Methodology, Investigation, Formal analysis, Data curation, Writing – original draft. **Dheeraj Mehta:** Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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