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Inhibition of noradrenaline release in the rat vena cava via prostanoid receptors of the EP_3-subtype

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1 In segments of the rat vena cava preincubated with [^{3}H]-noradrenaline and superfused with physiological salt solution (containing desipramine and corticosterone), we studied the effects of prostaglandins of the D, E and F series, of a prostacyclin analogue and a thromboxane-mimetic and of subtype-selective prostaglandin E-receptor (EP-receptor) ligands on the electrically (0.66 Hz)-evoked tritium overflow.

2 The electrically-evoked tritium overflow was inhibited by prostaglandin E_2 (maximum inhibition by about 80%; pIC_{40} 7.49). The effect of prostaglandin E_2 was not affected by rauwolscine, which, by itself, increased the evoked overflow; the α_2-adrenoceptor antagonist was added to the superfusion medium in all subsequent experiments. Indomethacin failed to affect either the evoked tritium overflow or its inhibition by prostaglandin E_2.

3 The inhibitory effect of prostaglandin E_2 on the electrically-evoked tritium overflow was not altered by the EP_1-receptor antagonist, AH 6809 (6-isopropoxy-9-oxoxanthene-2-carboxylic acid) at a concentration at least 30 fold higher than its pA_2 value at EP_1-receptors. The following compounds mimicked the effect of prostaglandin E_2 showing the following rank order of potencies: misoprostol (EP_2-/EP_3-receptor agonist) $\simeq$ sulprostone (EP_1-/EP_3-receptor agonist) $\simeq$ prostaglandin E_1 = prostaglandin E_2 >> iloprost (EP_1-/IP-receptor agonist) = prostaglandin $F_{2\alpha}$. The evoked overflow was not affected by high concentrations of prostaglandin D_2 or the thromboxane-mimetic U46619 (9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin $F_{2\alpha}$).

4 The present results suggest that the postganglionic sympathetic nerve fibres innervating the rat vena cava are endowed with presynaptic EP_3-receptors. They are not tonically activated by endogenously formed products of cyclo-oxygenase and do not interact with the presynaptic α_2-adrenoceptors.

Keywords: Rat vena cava; postganglionic sympathetic neurones; noradrenaline release; presynaptic EP_3-receptors; presynaptic α_2-receptors; receptor interactions; prostaglandin E_2; sulprostone; misoprostol; indomethacin

Introduction

Prostaglandin E_2 (PGE_2) inhibits noradrenaline release from the vascular postganglionic sympathetic nerve endings (for review, see Hedqvist, 1977; Starke, 1977; Güllner, 1983; Malik & Sehic, 1990). No information is so far available with respect to the prostaglandin E-receptor subtype involved in this effect in vascular tissues (EP_1, EP_2 or EP_3; for review of prostaglandin E (PGE)-receptor subtypes, see Coleman *et al.*, 1990). We, therefore, decided to address this question using the rat vena cava. Furthermore, the effects of prostaglandins of the D and F series and of an analogue of prostacyclin and a thromboxane A_2-mimetic on noradrenaline release were studied. Finally, the inhibitory effect of PGE_2 on noradrenaline release was also examined in vascular segments in which formation of endogenous prostaglandins was inhibited by indomethacin or in which the presynaptic α_2-adrenoceptors on the postganglionic sympathetic nerve fibres (Göthert & Kollecker, 1986) were blocked by rauwolscine.

A preliminary account of the present results was given to the 33rd Spring Meeting of the Deutsche Gesellschaft für Pharmakologie und Toxikologie (Malinowska & Schlicker, 1992).

Methods

Cranial segments of the inferior vena cava from male Wistar rats were ligated at both ends and incubated for 30 min with physiological salt solution (37°C; for composition, see below) containing [^{3}H]-noradrenaline 0.1 μmol l^{-1} (specific activity 43.7 Ci $mmol^{-1}$). The veins were mounted vertically in an organ bath, between two parallel platinum electrodes (1.5 cm long), and under a tension of 0.5 g. The adventitial surface was superfused with [^{3}H]-noradrenaline-free physiological salt solution of 37°C at 2 ml min^{-1}. The composition of the solution was (mmol l^{-1}): NaCl 118, NaH_2PO_4 1.2, $NaHCO_3$ 25.0, KCl 4.7, $CaCl_2$ 1.6, $MgSO_4$ 1.2, glucose 11.0, ascorbic acid 0.3, Na_2EDTA 0.03 (aerated with 95% O_2 and 5% CO_2). The solution contained desipramine 0.6 μmol l^{-1} and corticosterone 40 μmol l^{-1} (for inhibition of neuronal and extraneuronal noradrenaline uptake, respectively) throughout the superfusion. Five periods (duration 6 min each) of electrical stimulation (rectangular pulses of 100 mA and 0.3 ms; 0.66 Hz) were applied to each vein after 93 (S_1), 117 (S_2), 141 (S_3), 165 (S_4) and 189 (S_5) min of superfusion. The superfusate was collected in 3 or 6 min fractions. The radioactivity in the superfusate samples and veins was determined by liquid scintillation counting.

Calculations and statistics

Tritium efflux was calculated as the percentage of tritium present in the vein at the start of the respective collection period. Basal ^{3}H efflux was expressed as the percentage of tritium efflux during the collection period immediately before S_2 (t_2), S_3 (t_3), S_4 (t_4) and S_5 (t_5). Stimulation-evoked ^{3}H overflow was calculated by subtraction of the basal efflux (assumed to decrease linearly from the collection period before to that 12–15 min after the start of stimulation) from the total efflux during stimulation and the subsequent 6 min

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and was expressed as a percentage of tissue tritium at the start of stimulation. In order to quantify the effects of prostanoids (added to the medium in three increasing concentrations 9 min before and during S_3, S_4 and S_5) on basal and evoked overflow, the ratios t_3/t_2, t_4/t_2 or t_5/t_2 and S_3/S_2, S_4/S_2 or S_5/S_2 obtained in the presence of the drug under study were compared to the corresponding ratios obtained in its absence. For quantification of the effects of rauwolscine, indomethacin and AH 6809 (added to the medium from 27 min before S_2 onward), the percentage of ^3H efflux during t_2 or the tritium overflow evoked by S_2 in veins exposed to the drug under study was compared to the respective parameter in untreated veins.

Results are given as means ± s.e.mean. Student's t test for unpaired data was used for comparison of mean values. If two or more experimental series were compared to the same control series, the t test was subjected to Bonferroni's procedure.

Drugs

The following drugs were used: (−)-[ring-2,5,6-^{3}H]-noradrenaline (NEN, Dreieich, Germany); AH 6809 (6-isopropoxy-9-oxoxanthene-2-carboxylic acid; Glaxo, Ware, England); corticosterone, prostaglandin D_2, E_1, E_2, $F_{2\alpha}$ (Sigma, Munich, Germany); desipramine hydrochloride (CIBA-Geigy, Wehr, Germany); iloprost, sulprostone (Schering, Berlin, Germany); indomethacin (MSD Sharp & Dohme, Munich, Germany); misoprostol (Searle, Skokie, IL, U.S.A.); rauwolscine hydrochloride (Roth, Karlsruhe, Germany); U46619 (9,11-dideoxy-11α,9α-epoxymethano-prostaglandin $F_{2\alpha}$; Biosigma, Munich, Germany). Stock solutions were prepared with water (AH 6809, desipramine, rauwolscine), saline (iloprost; ampoules provided by the manufacturer), 1,2-propanediol (corticosterone), ethanol (indomethacin, misoprostol, PGD_2, PGE_1, PGE_2, $PGF_{2\alpha}$, sulprostone) or dimethylsulphoxide (U46619) and diluted with physiological salt solution to the concentration required. The solvents did not affect basal and evoked tritium overflow.

Results

Basal tritium efflux

The percentage of tritium efflux during t_2 and the ratios t_3/t_2, t_4/t_2 and t_5/t_2 (t_n/t_2) were used for quantification of basal ^3H efflux (for further details, see Methods). The percentage of tritium efflux during t_2 was not affected by rauwolscine 1 μmol l^{-1}, indomethacin 3 μmol l^{-1} or AH 6809 10 μmol l^{-1} (Table 1). The ratios t_3/t_2, t_4/t_2 and t_5/t_2 were 0.96 ± 0.03, 0.88 ± 0.02 and 0.85 ± 0.03, respectively, in 7–9 control experiments (i.e. prostanoids absent) performed on vascular segments exposed to rauwolscine. These ratios were not changed by omission of rauwolscine or by addition of indomethacin or AH 6809 (results not shown). The ratio t_n/t_2 was not affected by most of the prostanoids or slightly decreased (by up to 27%; results not shown). Since preliminary experiments had shown that sulprostone 1 μmol l^{-1} markedly increased basal efflux, only lower concentrations of this prostanoid (1–100 nmol l^{-1}) were examined in subsequent experiments.

Electrically-evoked tritium overflow

Tritium overflow evoked by S_2 and the ratios S_3/S_2, S_4/S_2 and S_5/S_2 (S_n/S_2) were used for quantification of evoked overflow (for further details, see Methods). Tritium overflow evoked by S_2 was increased by rauwolscine 1 μmol l^{-1} (by 277%), but not further affected by indomethacin 3 μmol l^{-1} or AH 6809 10 μmol l^{-1} (Table 1). The ratios S_3/S_2, S_4/S_2 and S_5/S_2 were 1.03 ± 0.04, 1.01 ± 0.06 and 0.93 ± 0.07 in the control series mentioned above. These ratios were not affected by omission of rauwolscine or addition of indomethacin or AH 6809 (results not shown). In the following paragraphs, the S_n/S_2 ratios obtained in the presence of prostanoids are given, expressed as percentages of the respective control values.

The electrically evoked ^3H overflow was inhibited by PGE_2 10–1000 nmol l^{-1} in a concentration-dependent manner; essentially the same concentration-response curve was obtained for the prostanoid both in the absence and presence of rauwolscine 1 μmol l^{-1} (Figure 1a). All further experiments were therefore performed in the presence of rauwolscine. Indomethacin 3 μmol l^{-1}, added to the superfusion medium to inhibit the production of endogenous prostaglandins, had no significant effect on the concentration-response curve to PGE_2 (Figure 1b).

In another series of experiments, the effects of prostaglandins D_2 and $F_{2\alpha}$ and of iloprost and U46619 were studied (Figure 2, open symbols). $PGF_{2\alpha}$ and iloprost inhibited the electrically-evoked tritium overflow only at concentrations > 100 nmol l^{-1}. PGD_2 and U46619 failed to affect the evoked overflow even at concentrations of up to 1 μmol l^{-1}.

Next, experiments were carried out to investigate the involvement of prostaglandin EP-receptor subtypes in the effect of PGE_2. The concentration-response curve for PGE_2 was not affected by a high concentration (10 μmol l^{-1}) of the EP_1-receptor antagonist AH 6809 (Figure 1c). Amongst a range of prostaglandin E analogues tested, PGE_1, the EP_2-/EP_3-receptor agonist, misoprostol and the EP_1/EP_3-receptor agonist, sulprostone were found to be as potent as PGE_2 (Figure 2, closed symbols).

Table 1 Effect of rauwolscine, indomethacin and AH 6809 on the basal and electrically (0.66 Hz)-evoked tritium overflow from superfused rat vena cava segments preincubated with [^{3}H]-noradrenaline

Drug(s) (μmol l^{-1})	n	*Basal ^3H efflux* (t_2)[a] (expressed as % of tissue tritium × min^{-1})	*Evoked ^3H overflow* (S_2) (expressd as % of tissue tritium[b])
–	13	0.25 ± 0.02	0.92 ± 0.07
Rauwolscine 1	50	0.23 ± 0.01	3.47 ± 0.16*
Rauwolscine 1 + indomethacin 3	16	0.21 ± 0.01	2.77 ± 0.21
Rauwolscine 1 + AH 6809 10	13	0.17 ± 0.01	2.95 ± 0.33

The veins were superfused with isotope-free physiological salt solution containing desipramine 0.6 μmol l^{-1} plus corticosterone 40 μmol l^{-1}. Rauwolscine, indomethacin and/or AH 6809 were added to the medium from 27 min before S_2 onward. Five 6 min periods of transmural electrical stimulation (S_1–S_5) were administered to each vein. Means ± s.e.mean of n experiments.
*$P < 0.001$, compared to the rauwolscine-free value.
[a]t_2 represents the 3 min period of superfusate sampling immediately before S_2.
[b]Evoked overflow in excess of basal efflux.

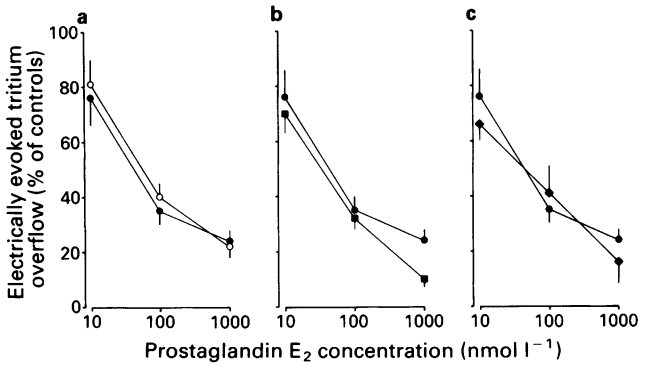

Figure 1 The effect of prostaglandin E_2 on the electrically-evoked ^3H overflow from rat vena cava segments preincubated with [^3H]-noradrenaline. Mean inhibitory concentration-effect curves to prostaglandin E_2 in the absence (open symbols) and presence (closed symbols) of rauwolscine 1 μmol l^{-1} (●); rauwolscine + indomethacin 3 μmol l^{-1} (■); or rauwolscine + AH 6809 10 μmol l^{-1} (◆). All points are means from 4–9 experiments with s.e.mean shown by vertical lines. All values below 75% were significantly different ($P \leq 0.05$) from the corresponding controls (prostaglandin E_2 absent).

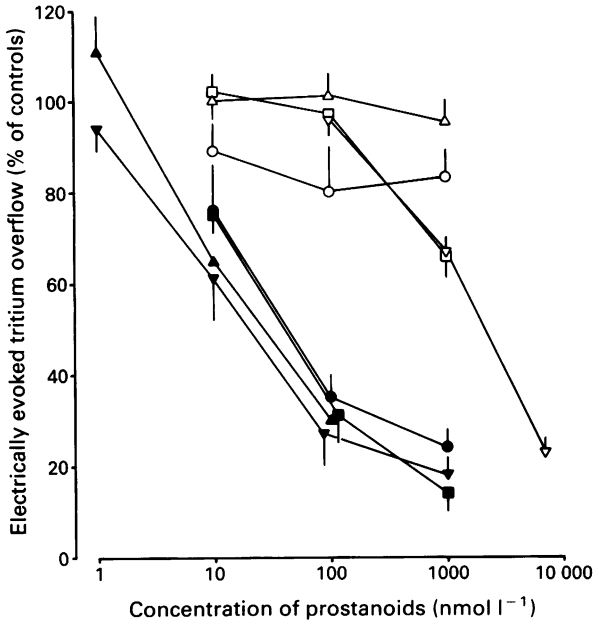

Figure 2 The effect of prostanoids on the electrically-evoked ^3H overflow from rat vena cava segments preincubated with [^3H]-noradrenaline. Mean inhibitory concentration-effect curves to prostaglandin E_2 (●); prostaglandin E_1 (■); misoprostol (▼); sulprostone (▲); prostaglandin D_2 (○); prostaglandin $F_{2\alpha}$ (□); iloprost (▽) and U46619 (△). Each point is the mean from 5–9 separate experiments with s.e.mean shown by vertical lines (not shown are the s.e.mean values for sulprostone 10 nmol l^{-1}, 100 nmol l^{-1} and prostaglandin $F_{2\alpha}$ 100 nmol l^{-1}, which were 15, 8 and 4% of controls, respectively). All values below 75% were significantly different ($P \leq 0.05$) from the corresponding controls.

Since the maximum inhibitory effect of PGE_2 and related compounds was about 80%, pIC_{40} values were determined to quantify the potencies of the 8 drugs (Table 2). The following rank order of potencies was obtained: misoprostol $\simeq$ sulprostone $\simeq$ PGE_1 = PGE_2 >> $PGF_{2\alpha}$ = iloprost >> PGD_2 or U46619.

Table 2 Potencies of prostanoids for their inhibitory effect on the electrically-evoked ^3H overflow from superfused rat vena cava segments preincubated with [^3H]-noradrenaline

Prostanoid	*pIC_{40}*
Misoprostol	7.97
Sulprostone	7.85
Prostaglandin E_1	7.66
Prostaglandin E_2	7.61[a]
Iloprost	5.87
Prostaglandin $F_{2\alpha}$	~5.8[b]
Prostaglandin D_2	<6.0
U46619	<6.0

pIC_{40} values were determined from the concentration-response curves shown in Figure 2.
[a]The pIC_{40} value for prostaglandin E_2 was 7.49 in the absence of rauwolscine (Figure 1a), 7.74 in the presence of rauwolscine plus indomethacin (Figure 1b) and 7.76 in the presence of rauwolscine plus AH 6809 (Figure 1c).
[b]Approximate value, obtained by extrapolation.

Discussion

In the present study, superfused segments of the rat vena cava preincubated with [^3H]-noradrenaline were used for the analysis of prostanoid-induced effects. The electrically-evoked tritium overflow in this tissue was shown to be Ca^{2+}-dependent and tetrodotoxin-sensitive and may be assumed to represent quasi-physiological noradrenaline release from the postganglionic sympathetic nerve fibres (Göthert & Kollecker, 1986). A variety of presynaptic receptors have been shown to occur in this tissue, including inhibitory α_2-adrenoceptors (Göthert & Kollecker, 1986), 5-HT_{1B}- (Molderings *et al.*, 1987) and $GABA_B$-receptors (Schneider *et al.*, 1991) or facilitatory β_2-adrenoceptors and angiotensin II-receptors (Göthert & Kollecker, 1986).

As expected, noradrenaline release in the rat vena cava was inhibited by PGE_2 and PGE_1. Iloprost, which is a stable analogue of prostacyclin (the principal product of arachidonic acid released in response to adrenergic nerve stimulation in blood vessels; for review, see Malik & Sehic, 1990), was markedly less potent than PGE_2 in inhibiting noradrenaline release. $PGF_{2\alpha}$ (which has been shown previously to inhibit or facilitate noradrenaline release from blood vessels; for review, see Starke, 1977; Malik & Sehic, 1990) was also markedly less potent than PGE_2 in inhibiting noradrenaline release in the rat vena cava. PGD_2 (which increased noradrenaline release in dog mesenteric arteries; Nakajima & Toda, 1984) and U46619 were ineffective in the present model, even at high concentrations. The data therefore implicate a role for EP-receptors in prostanoid-induced inhibition of electrically-evoked noradrenaline release.

Next, the question was addressed as to which subtype of EP-receptor (according to the classification of Coleman *et al.*, 1990) is involved in the inhibitory effect of PGE_2 and PGE_1 on noradrenaline release in the rat vena cava. The effect of PGE_2 was mimicked by the EP_1-/EP_3-receptor agonist, sulprostone and the EP_2-/EP_3-receptor agonist, misoprostol, which were both at least as potent in this respect as PGE_2. Iloprost, which is equipotent with PGE_2 at EP_1-receptors and markedly less potent than PGE_2 at EP_2- and EP_3-receptors (Sheldrick *et al.*, 1988), was 55 fold less potent than PGE_2 in the present model. Moreover, the EP_1-receptor antagonist, AH 6809, at a concentration which was at least 30 fold higher than its pA_2 value at EP_1-receptors (Coleman *et al.*, 1985), failed to affect the concentration-response curve of PGE_2. Taken together, these data suggest that the effect of PGE_1 and PGE_2 is mediated via EP_3-receptors. The same holds true for the presynaptic receptor for PGE_2 on postganglionic sympathetic nerve fibres innervating non-vascular

tissues, namely the rat trachea (Racké *et al.*, 1991), the guinea-pig vas deferens (Coleman *et al.*, 1987) and atrium (Beckman & Knirk, 1991; Mantelli *et al.*, 1991), and the human iris-ciliary body (Ohia & Jumblatt, 1991).

Our data obtained with $PGF_{2\alpha}$, PGD_2 and U46619 can be easily reconciled with the view that the sympathetic nerve endings are endowed with presynaptic EP_3-receptors and that additional presynaptic receptors for prostanoids, e.g. FP-receptors, are lacking. Thus, the potencies of these drugs in inhibiting noradrenaline release in the present model are in good agreement with their potencies in contracting the chick ileum (an EP_3-receptor containing preparation; Coleman *et al.*, 1990). The equipotent concentrations ($PGE_2 = 1$) were 116, >1500 and >400, respectively, in the chick ileum and ~ 65, $\gg 41$ and $\gg 41$, respectively, in the present model.

To answer the question as to whether noradrenaline release, under the experimental conditions of the present study, is also inhibited by endogenously formed arachidonic acid metabolites, experiments with indomethacin were carried out. If the EP_3-receptors were tonically activated by endogenous prostanoids, one would expect that noradrenaline release would be increased by indomethacin (due to interruption of an inhibitory effect produced by endogenous prostanoids); moreover, one would expect that the inhibitory effect of exogenously added PGE_2 on noradrenaline release would be enhanced since the exogenously added prostaglandin has to compete for the EP_3-receptor only with a small amount of endogenously formed prostanoids. The lack of effect of indomethacin on noradrenaline release, and its modulation by PGE_2 argue against a tonic activation of the EP_3-receptors by endogenous prostanoids. These findings are at variance with results reported for several other vascular preparations (for review, see Hedqvist, 1977; Starke, 1977; Malik & Sehic, 1990).

Finally, the question was addressed as to whether an interaction occurs between the EP_3-heteroreceptors and the α_2-autoreceptors. Interactions between presynaptic EP- and α_2-receptors have been shown to occur on peripheral (Hedqvist, 1974; Ohia & Jumblatt, 1990) and central noradrenergic neurones (Allgaier *et al.*, 1989). In the latter studies, blockade of the α_2-adrenoceptors, activated by endogenously released noradrenaline, enhanced the inhibitory effect of PGE_2 on noradrenaline release. In the model of the rat vena cava, such an interaction does not appear to exist since the effect of PGE_2 was virtually identical in the absence and presence of the α_2-adrenoceptor antagonist, rauwolscine (which was added to the superfusion medium in subsequent experiments in order to increase noradrenaline release). On the other hand, an interaction betwen the presynaptic 5-HT_{1B}- and α_2-receptors has been previously shown for the rat vena cava (Molderings & Göthert, 1990).

In conclusion, the present results suggest that the sympathetic nerve fibres supplying the rat vena cava are endowed with inibitory EP_3-receptors. The latter are not tonically activated by endogenously formed prostanoids. An interaction between the EP_3- and α_2-receptors does not appear to occur.

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