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Characterization of contractile adrenoceptors in the human umbilical artery

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Abstract

Adrenoceptors mediating contraction in ring segments of human umbilical arteries from normal term pregnancies were investigated in vitro. Contraction was elicited by (order of potency indicated): noradrenaline = the α_2-adrenoceptor agonist oxymetazoline ≫ the α_1-adrenoceptor agonist phenylephrine. The α_1-adrenoceptor antagonist prazosin antagonized the contraction elicited by noradrenaline and phenylephrine. The α_2-adrenoceptor antagonist rauwolscine antagonized the contraction elicited by noradrenaline and oxymetazoline. Oxymetazoline had an efficacy 5 times higher than that of noradrenaline and the 5-hydroxytryptamine receptor antagonist methysergide antagonized the contraction elicited by oxymetazoline. It is suggested that the contractile adrenoceptors in the human umbilical artery consist of both α_1 and α_2 subtypes. Furthermore, the contractile effect of oxymetazoline seems to be mediated via both α_2-adrenoceptors and 5-hydroxytryptamine receptors.

Keywords: Adrenoceptor; Noradrenaline; Umbilical artery, human; Smooth muscle, vascular

1. Introduction

The umbilico-placental circulation is unique in that it is without innervation. This allows for investigation of the direct action of drugs on endothelial and smooth muscle cells. The human umbilical artery is known to contract in response to stimulation by noradrenaline, though in a weak and inconsistent manner (Gokhale et al., 1966; Altura et al., 1972; White, 1989), which contrasts with the more powerful effect of noradrenaline in other human reproductive vascular preparations like the uterine artery (Stjernquist and Owman, 1990; Ekesbo et al., 1991) and intramyometrial arteries (Maigaard et al., 1986). One explanation for the variation in response to noradrenaline could be that the contractile effect of noradrenaline in the human umbilical artery is dependent on the oxygen tension. Thus, noradrenaline produces a functionally non-significant response at low oxygen tensions ($pO_2 \approx 2.6$ kPa, McGrath et al., 1985), while the response to adrenoceptor stimulation is more marked at higher oxygen tensions (McGrath et al., 1988).

We have found an attenuated contractile effect of noradrenaline in human umbilical artery segments from women with preeclampsia and/or intrauterine growth retardation and abnormal umbilical artery flow velocity waveforms, as measured by Doppler ultrasound in vivo (Bodelsson et al., 1995), suggesting a role for adrenergic mechanisms in the pathogenesis of reduced umbilical blood flow associated with preeclampsia and intrauterine growth retardation.

Based on functional, radioligand and molecular cloning studies, the adrenoceptors have been found to consist of at least nine different subtypes. These can be assigned to three major receptor categories recognised as the classical α_1-, α_2- and β-adrenoceptors (Bylund, 1992). The aim of the present study was to characterize the adrenoceptors mediating contraction at high oxygen tensions in human umbilical arteries obtained from women with normal pregnancies.

2. Material and methods

2.1. Material

Segments of human umbilical artery were obtained from 31 umbilical cords from women with normal,

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full-term pregnancies. Immediately after delivery, a 7–8 cm long segment of the umbilical cord within the 15 cm closest to the child was removed and placed in cold (4°C) Krebs-Ringer solution (composition, see below). The arteries were dissected free of surrounding tissue within 1 h and kept in cold Krebs-Ringer solution until the experiments were carried out 0.5–24 h after specimen collection.

2.2. In vitro recording

The arteries were cut into 2–4 mm long ring segments which were placed in organ baths (volume 4 ml). The segments were each slid on to two L-shaped metal hooks through the lumen of the vessels for recording of circular motor activity. One of the hooks was attached to a Grass FTO3C force-displacement transducer and one could be moved in order to adjust the smooth muscle tension. The isometric mechanical activity was recorded on a Grass model 7D polygraph.

The organ baths contained a modified Krebs-Ringer solution of the following composition (in mM): NaCl 118, KCl 4.7, $CaCl_2 \cdot 2H_2O$ 2.0, $MgSO_4 \cdot 7H_2O$ 1.2, $NaHCO_3$ 24.8, KH_2PO_4 1.2 and glucose 5.6. It was continuously aerated by a gas mixture containing 88.5% O_2 and 11.5% CO_2 at a rate giving a pH of 7.35–7.45, $pO_2 \approx 45$ kPa and $pCO_2 \approx 5.0$ kPa. The temperature was thermostatically maintained at 37°C.

The initial smooth muscle tension was set at 80 mN (Bodelsson and Stjernquist, 1994) and after an equilibration period of 1 h the segments were contracted by exchanging the 118 mM NaCl in the bathing fluid for 126 mM KCl. The magnitude of the resulting contraction was used as an internal standard for each segment and the contractile response developed in subsequent experiments was expressed as a percentage of the KCl-induced response. After the segments were washed, the experiments were carried out as specified below.

In a first series of experiments, the contractile effect of noradrenaline (10^{-9} to 10^{-4} M) was tested in the presence or absence of the neuronal uptake blocker cocaine (10^{-6} M), the extra-neuronal uptake blocker normetanephrine (10^{-6} M) or the β-adrenoceptor antagonist propranolol (10^{-6} M).

In a second series of experiments, the contractile effect of noradrenaline, the α_1-adrenoceptor agonist phenylephrine and the α_2-adrenoceptor agonist oxymetazoline (all at 10^{-9} to 10^{-4} M) was tested in the presence or absence of the α_1-adrenoceptor antagonist prazosin (10^{-10} to 10^{-9} M) or the α_2-adrenoceptor antagonist rauwolscine (10^{-7} to 10^{-5} M).

In a third series of experiments, the contractile effect of oxymetazoline was recorded (10^{-9} to 10^{-4} M) in the presence or absence of the selective 5-hydroxytryptamine (5-HT) receptor antagonist methysergide (10^{-7} M).

The antagonists were added 20 min prior to the agonists. The agonists were added by cumulative administration in 0.5 $_{10}$log units. When the effects of agonists versus antagonists were studied, preparations from the same patient were compared in each individual experiment, with one or two segments serving as controls. Only one cumulative concentration-response experiment was performed with each individual preparation.

2.3. Drugs

The following compounds were used: methysergide (Sandoz, Basel, Switzerland), L-arterenol hydrochloride, oxymetazoline hydrochloride, L-phenylephrine hydrochloride, prazosin hydrochloride, DL-propranolol hydrochloride (Sigma, St. Louis, MO, USA), rauwolscine hydrochloride (Roth, Germany). All substances were dissolved in 0.9% NaCl. After preparation, the stock solutions of the substances were immediately frozen and stored at a temperature below −20°C in order to prevent oxidation. After thawing and use, the remaining stock solution was discarded. The concentrations are given as final molar concentrations in the organ bath.

2.4. Analysis of data

The maximum contractile response (E_{max}) and the negative logarithm of the concentration required to induce half the E_{max} (pEC_{50}) were calculated for the agonists. In the experiments with agonists/antagonists, the interaction between the antagonist and its receptors was analyzed according to Arunlakshana and Schild (1959), provided that the antagonist caused a parallel shift of the concentration-response curve (Tallarida et al., 1979). The dose ratios (DR) were calculated and log (DR − 1) was plotted as a function of the negative logarithm of the antagonist concentration (B). The equation of the line that fitted the coordinates best was calculated using linear regression and the method of least squares. The significance of linear regression and possible regression due to higher polynomials was tested using factorial ANOVA (analysis of variance), and the correlation coefficient was calculated. The regression coefficient and its standard error were computed and compared with the one expected for competitive antagonism (i.e. −1) in a Student's t-test. The antagonism was interpreted as competitive if the plot fitted a straight line with a slope coefficient not different from −1. If these requirements were fulfilled, the pA_2 value (the negative logarithm of the antagonist concentration giving a DR of 2) could be calculated. Values are given as means ± S.E. The num-

ber of observations is given as n; each observation was for preparations from a different individual. In some cases the same experiment was performed on several segments from the same individual and the mean of these results was calculated for presentation and statistical analysis. Student's t-test was used to calculate any significant difference between the means. The P value, indicating statistical significance, was set at 0.05.

3. Results

3.1. Effects of cocaine, normetanephrine and propranolol on the contractile response induced by noradrenaline

Noradrenaline induced concentration-dependent contractions in segments of human umbilical artery (Fig. 1, Table 1). Neither the neuronal uptake blocker cocaine (10^{-6} M), the extra-neuronal uptake blocker normetanephrine (10^{-6} M) nor the β-adrenoceptor antagonist propranolol (10^{-6} M) affected the concentration-response curve for noradrenaline. Neither cocaine, normetanephrine nor propranolol affected the baseline tension in unstimulated segments.

3.2. Contractile response to adrenoceptor agonists

Noradrenaline, the α_1-adrenoceptor agonist, phenylephrine, and the α_2-adrenoceptor agonist, oxymetazoline, all induced concentration-dependent contractions in segments of human umbilical artery (Fig. 1). The E_{max} and pEC_{50} values are presented in Table 1. The oxymetazoline-induced maximum contraction was 5 times higher than that induced by noradrenaline. The pEC_{50} values yielded a similar potency for noradrenaline and oxymetazoline, while the potency for phenylephrine seemed to be markedly lower. However, a reliable pEC_{50} value for phenylephrine could not be calculated since it was not evident that E_{max} was reached at the highest concentration used (10^{-4} M).

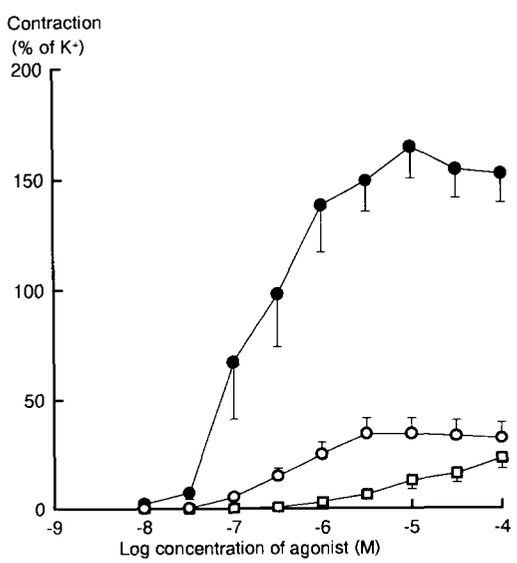


Fig. 1. Contractile response to noradrenaline (○, $n = 25$), oxymetazoline (●, $n = 12$) and phenylephrine (□, $n = 11$) in the human umbilical artery. All agonists induced a concentration-dependent contraction. Means ± S.E.

Table 1
Maximum contractile response (E_{max}) and potency (pEC_{50}; the negative $_{10}$logarithm of the concentration required to induce half E_{max}) of noradrenaline, phenylephrine and oxymetazoline in segments of human umbilical artery

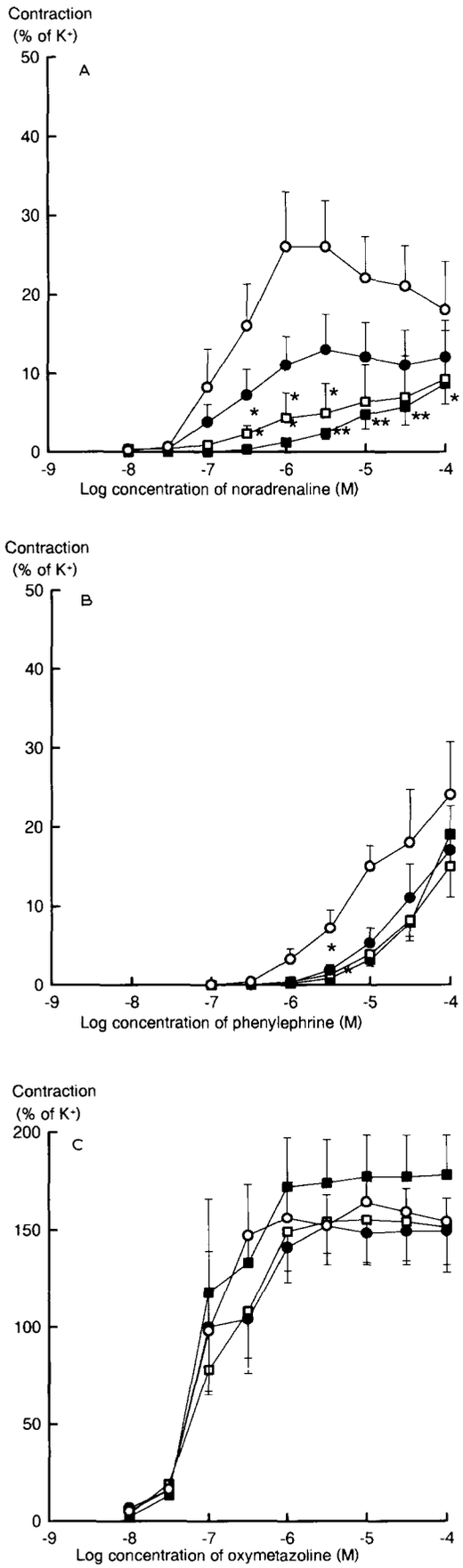
Agonist	E_{max}	pEC_{50}	n
Noradrenaline	36 ± 7.2	6.30 ± 0.08	25
Phenylephrine	≥ 23 ± 4.8[a]	≤ 4.99 ± 0.12 [a]	11
Oxymetazoline	178 ± 11	6.52 ± 0.17	12

Means ± S.E. [a] It was not evident that E_{max} for phenylephrine was reached at the highest concentration used (10^{-4} M) and thus reliable E_{max} and pEC_{50} values could not be calculated.

3.3. Effects of adrenoceptor antagonists

The α_1-adrenoceptor antagonist prazosin (10^{-10} to 10^{-9} M) caused a concentration-dependent reduction of the contractile response to noradrenaline (Fig. 2A) and antagonized the contraction induced by phenylephrine (Fig. 2B), while the contraction to oxymetazoline was unaffected (Fig. 2C). Since no parallel shift of the concentration-response curves of the agonists was obtained, Schild analyses for prazosin could not be performed.

The α_2-adrenoceptor antagonist rauwolscine (10^{-7} to 10^{-5} M) shifted the concentration-response curves induced by noradrenaline and oxymetazoline to the right (Fig. 3A and C, Table 2). The results from calculations of Schild equations for the interaction between noradrenaline/rauwolscine and oxymetazoline/rauwolscine are presented in Table 3. In both cases the regression coefficient differed significantly from unity. The interaction between oxymetazoline and rauwolscine yielded a significantly linear regression with a marked correlation. When interpreting the results from the interaction between noradrenaline and rauwolscine the linear regression as well as the correlation was found to be non-significant. Quadratic regression was however found to be significant. Hence, the Schild plot for the interaction between noradrenaline and rauwolscine might be better represented by a parabola of the second degree, and thus cannot be considered to be linear. Consequently, none of the attempts to calculate Schild plot equations made it possible to compute pA_2 values. The concentration-response curve for phenylephrine remained unaffected by rauwolscine (Fig. 3B).



3.4. Effects of methysergide

The selective 5-HT receptor antagonist methysergide (10^{-7} M) reduced the E_{max} and the pEC_{50} values for the contraction induced by oxymetazoline compared to control ($E_{max} = 130 \pm 20$ versus $183 \pm 27\%$, $pEC_{50} = 6.00 \pm 0.37$ versus 6.91 ± 0.32; Fig. 4).

4. Discussion

Noradrenaline, oxymetazoline and phenylephrine all elicited a concentration-dependent contraction with an agonist order of potency: noradrenaline = oxymetazoline ≫ phenylephrine, which is consistent with an interaction with α_2-adrenoceptors (Starke, 1981). The finding that both the noradrenaline and oxymetazoline concentration-response curves were shifted to the right by the α_2-adrenoceptor antagonist, rauwolscine, confirmed the presence of contractile α_2-adrenoceptors. However, Schild plot equations for the interaction between rauwolscine and both noradrenaline and oxymetazoline yielded slope coefficients that differed significantly from unity. Moreover, the interaction between noradrenaline and rauwolscine turned out to be better represented by an equation of the second degree than by an equation for a straight line. Hence, neither of these two interactions can be explained by a competitive antagonism at a single receptor site. A plausible explanation is the existence of a heterogeneous receptor population. The assumption is supported by the concentration-dependent antagonistic effect of the α_1-adrenoceptor antagonist prazosin on the contraction elicited by noradrenaline, indicating that the response to noradrenaline was also mediated via α_1-adrenoceptors. Consequently, the contraction induced by the α_1-adrenoceptor agonist phenylephrine was antagonized by prazosin. Rauwolscine did not affect the contraction evoked by phenylephrine, supporting the selectivity of phenylephrine for the α_1-adrenoceptor. Experiments in which both prazosin and rauwolscine were present were not conducted in the present study but might further confirm the existence of both α_1-and α_2-adrenoceptors. It should be noted that the antagonistic action of prazosin on the contraction induced by phenylephrine was concentration-depen-

Fig. 2. Influence of the α_1-adrenoceptor antagonist prazosin (control (○), 10^{-10} M (●), 3×10^{-10} M (□), 10^{-9} M (■)) on the contractile response to (A) noradrenaline ($n = 6$), (B) phenylephrine ($n = 6$) and (C) oxymetazoline ($n = 5$) in the human umbilical artery. Prazosin caused a concentration-dependent reduction of the contractile response induced by noradrenaline and phenylephrine. The contraction induced by oxymetazoline remained unaffected by prazosin. Means ± S.E. * Significantly different from control, $P < 0.05$, ** $P < 0.01$.

Table 2
Maximum contractile effect (E_{max}) and potency (pEC_{50}; the negative $_{10}$logarithm of the concentration required to induce half E_{max}) of noradrenaline and oxymetazoline in the presence or absence of rauwolscine (10^{-7} to 10^{-5} M)

Concentration of rauwolscine (M)	E_{max} (%)	Significance level	pEC_{50} (M)	Significance level	n
Noradrenaline					
Controls	34 ± 10	–	5.87 ± 0.12	–	6
10^{-7}	28 ± 13	0.23	5.27 ± 0.21 [a]	0.023	5
10^{-6}	20 ± 4.8	0.55	5.55 ± 0.13	0.15	5
10^{-5}	21 ± 6.0	0.23	4.91 ± 0.13 [a]	0.013	5
Oxymetazoline					
Controls	185 ± 17	–	6.20 ± 0.23	–	7
10^{-7}	143 ± 26	0.12	5.83 ± 0.37 [a]	0.031	6
10^{-6}	149 ± 31	0.19	5.67 ± 0.20	0.059	7
10^{-5}	127 ± 27 [a]	0.023	4.69 ± 0.23 [a]	< 0.001	6

The E_{max} is expressed as a percentage of the potassium-induced contraction. Values are means ± S.E. [a] Significantly different from control.

dent only to a limited extent. This might indicate that phenylephrine is not acting solely at α_1-adrenoceptors. However, this non-selective behaviour of phenylephrine was only evident at concentrations above 10 μM, when the selectivity of phenylephrine for the α_1-adrenoceptor might be questioned.

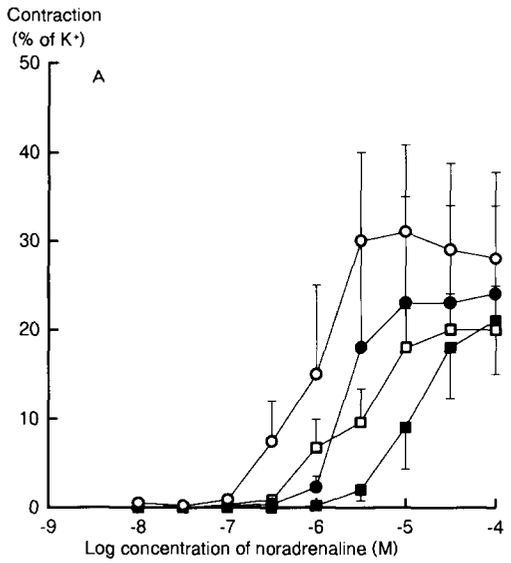
The contraction induced by noradrenaline is weak in the human umbilical artery compared to several other human vascular preparations, with an E_{max} amounting to only 30% of contraction elicited by potassium (Steen et al., 1984; Arner and Högestätt, 1986; Stjernquist and Owman, 1990). The weak contractile response to noradrenaline could not be explained by dilator β-adrenoceptors counteracting the contraction induced by this non-selective adrenoceptor agonist, because the β-adrenoceptor blocker propranolol did not alter the concentration-response curve for noradrenaline. This finding is consistent with early studies which have failed to demonstrate functional β-adrenoceptors in this vessel (Somlyo et al., 1965; Clyman et al., 1975). Furthermore, it seems unlikely that the weak contractile response to noradrenaline was due to its removal by uptake since neither the neuronal uptake blocker cocaine, nor the extra-neuronal uptake blocker normetanephrine affected the concentration-response curve for noradrenaline. This is further sustained by the fact that the human umbilical artery is a non-innervated vessel. We believe that the weak contraction elicited by noradrenaline could be explained by a low α-adrenoceptor density in the human umbilical artery and/or an inefficient coupling between the adrenoceptors and the contractile machinery, although this remains to be determined.

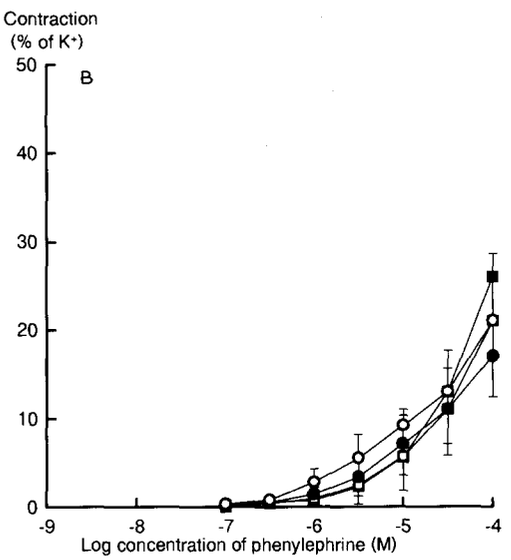
Oxymetazoline displayed an E_{max} 5 times higher than that of noradrenaline. This could be explained by an agonistic effect of oxymetazoline on other receptors in addition to α_2-adrenoceptors. An effect on α_1-adrenoceptors is an unlikely explanation since prazosin did not affect the concentration-response curve for oxymetazoline. However, it has recently been demonstrated that oxymetazoline is a potent agonist at several receptors of the 5-HT_1 receptor family (Schoeffter and Hoyer, 1991). The human umbilical artery contracts in response to 5-HT and this effect is, at least partly, mediated via a 5-HT_1-like receptor (MacLennan et al., 1989). The selective 5-HT receptor antagonist methysergide is an antagonist of 5-HT-induced contraction in the human umbilical artery (pA_2 8.52; MacLennan et al., 1989). In the present study, methysergide, at a concentration well exceeding the pA_2 value, potently antagonised the contraction elicited by oxymetazoline, indicating that part of the contraction was mediated via

Table 3
Statistical variables obtained from Schild plot analysis for the interactions between noradrenaline/rauwolscine and oxymetazoline/rauwolscine

Interaction	Noradrenaline/rauwolscine	Oxymetazoline/rauwolscine
Regression coefficient; b	−0.26 ± 0.14	−0.44 ± 0.11
Significance of $b \neq -1$	$P < 0.001$ [a]	$P < 0.001$ [a]
y-Intercept; a	2.26 ± 0.72	3.60 ± 0.60
Correlation coefficient; r	−0.52 ± 0.27	−0.69 ± 0.18
Significance of r	$P > 0.05$	$P < 0.01$ [a]
Significance of linear regression	$P > 0.05$	$P < 0.01$ [a]
Significance of quadratic regression	$P < 0.01$ [a]	$P > 0.05$
Number of data points	12	18

Equation of line: $y = bx + a$. Values are given ± S.E. [a] Significant.





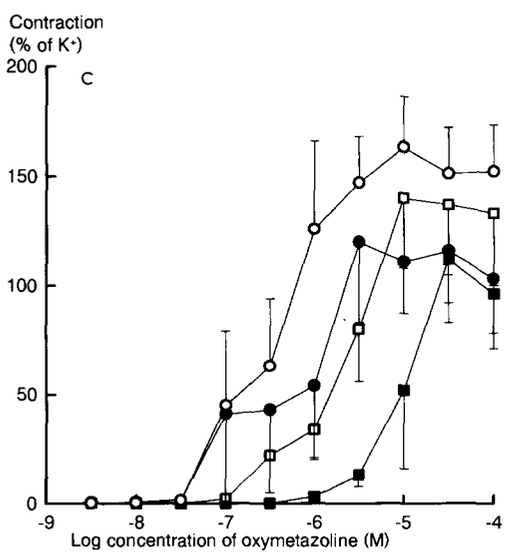


Fig. 3. Influence of the α_2-adrenoceptor antagonist rauwolscine (control (○), 10^{-7} M (●), 10^{-6} M (□), 10^{-5} M (■)) on the contractile response to (A) noradrenaline ($n = 6$), (B) phenylephrine ($n = 5$) and (C) oxymetazoline ($n = 6$–7) in the human umbilical artery. Rauwolscine shifted the concentration-response curves for noradrenaline and oxymetazoline to the right and reduced the maximum contractile response induced by oxymetazoline. The contraction induced by phenylephrine remained unaffected by rauwolscine. Means ± S.E.

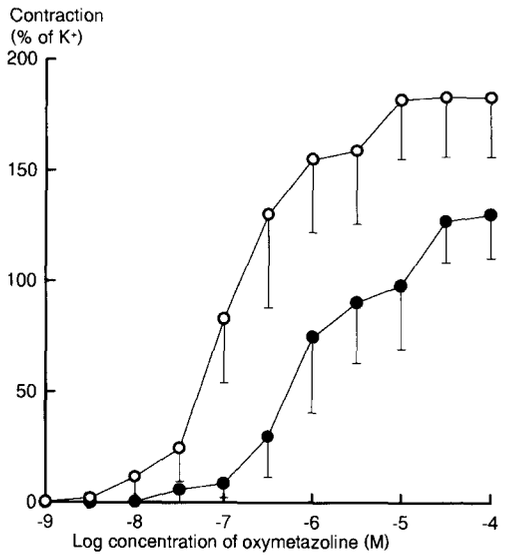


Fig. 4. Influence of the selective 5-hydroxytryptamine receptor antagonist methysergide (control (○), 10^{-7} M (●)) on the contractile response to oxymetazoline. Methysergide shifted the concentration-response curve for oxymetazoline to the right and reduced the maximum contractile response. Means ± S.E. $n = 5$.

5-HT receptors. This nonselective agonist nature of oxymetazoline could explain the high efficacy compared to that of noradrenaline.

Considering the dual effect on both α_2-adrenoceptors and 5-HT receptors of oxymetazoline it is notable that the slope of the concentration-response curves of oxymetazoline was not reduced in the presence of rauwolscine or methysergide. This would be expected for the interaction between a non-selective agonist and a selective antagonist (cf. the interaction between noradrenaline and prazosin or rauwolscine in the present study). Several studies have demonstrated that the effect of simultaneous stimulation of α-adrenoceptors and 5-HT receptors is not merely additive but results in potentiation (see Van Nueten et al., 1985). Thus, antagonism of the α_2-adrenoceptor-mediated response induced by oxymetazoline would also negatively affect the contraction elicited by the 5-HT receptor agonist component of oxymetazoline and vice versa. Such a mechanism could explain the illusory parallel shift in Fig. 3C.

In conclusion, the contractile adrenoceptors in the human umbilical artery, at high oxygen tension, com-

prise both α_1 and α_2 subtypes. Due to its agonistic action at 5-HT receptors, oxymetazoline should be used with caution as a pharmacological tool in the classification of adrenoceptors in preparations with 5-HT receptors mediating similar functional responses as those mediated by adrenoceptors.

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