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THE EFFECTS OF HISTAMINE ON RESPONSES OF THE RABBIT EAR ARTERY TO ELECTRICAL STIMULATION AND TO EXOGENOUS NORADRENALINE

A. FOLDES[1] & R.C. HALL

Department of Human Physiology and Pharmacology, University of Adelaide, Adelaide, S.A. 5000, Australia

1 The effects of a subconstrictor dose of histamine (9×10^{-7} mol/l) on the responses of the isolated perfused ear artery of the rabbit to electrical stimulation (E.S.) and to exogenous noradrenaline (NA) were investigated.

2 Both intraluminal (I/L) and extraluminal (E/L) histamine potentiated responses to E.S. and to I/L NA to the same extent.

3 Mepyramine alone (2.5×10^{-6} mol/l) had no effect on the response of the ear artery to either stimulus, but in the presence of this concentration of mepyramine, the potentiation by histamine of the response to I/L NA was significantly decreased and that to E.S. was replaced by inhibition.

4 The H_1-receptor agonist, 2(2-pyridyl) ethylamine, applied I/L potentiated responses to I/L NA at both concentrations used (5.1 and 51×10^{-7} mol/l), but only potentiated the effects of E.S. at the higher concentration.

5 The H_2-receptor antagonist, metiamide (4×10^{-6} mol/l), alone did not alter the extent of potentiation of responses to either E.S. or I/L NA by histamine. This suggests relatively weak H_2-receptor activity in the rabbit ear artery. In the presence, but not the absence of metiamide, the potentiation by histamine of the I/L NA response was reversible, an observation suggesting an interaction between metiamide and the non-reversible component of the potentiating effect of histamine.

6 These results are interpreted in terms of postsynaptic H_1-receptors which potentiate and presynaptic H_2-receptors which inhibit contractile responses in the ear artery.

Introduction

The presence of histamine in blood vessels (Howland & Spector, 1972; Foldes, Head & de la Lande, 1977) and in sympathetic nerves (Ryan & Brody, 1970; Ehinger, 1974) is well documented. Histamine modifies the effects of sympathetic nerve function *in vitro* in cerebral (Bevan, Duckles & Lee, 1975) and other blood vessels (Glover, Carroll & Latt, 1973; McGrath & Shepherd, 1976) and in sympathetic ganglia (Brezenoff & Gertner, 1972). The isolated perfused central ear artery of the rabbit provides a useful model for examining drug interactions at a vascular sympathetic neuroeffector site (de la Lande, Cannell & Waterson, 1966). Since both H_1- and H_2-receptors have been demonstrated in this tissue, (Carroll & Glover, 1977), the present study was designed to examine the effects of histamine on the response of the rabbit ear artery to electrical stimulation and exogenous noradrenaline (NA). In addition, information was sought on the nature and localization of the histamine receptors involved in the modification of noradrenergic function.

[1] Present address: C.S.I.R.O. Div. of Animal Production, P.O. Box 239, Blacktown, N.S.W. 2148, Australia.

Methods

Tissues

Semi-lop-eared rabbits of either sex (1.5 to 2.5 kg in weight) were killed by cervical dislocation. The central ear arteries were dissected free of adhering tissue and artery segments 2 to 3 cm in length were cannulated at each end. The arteries were mounted at approximately 1 g tension in 13 ml organ baths containing gassed (95% O_2 and 5% CO_2) Krebs solution at 37°C. The composition of the Krebs solution in mmol/l was: NaCl. 120, KCl 4.7, $NaHCO_3$ 25, glucose 5.5, $CaCl_2$ 2.5, $MgCl_2$ 1.1 and KH_2PO_4 1.0. Arteries were perfused at a constant rate of 2 ml/min with gassed Krebs solution at 37°C. Responses were recorded as changes in perfusion pressure with a

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Statham pressure transducer (model P23AC) connected to a Rikadenki recorder.

The mean basal perfusion pressure in 73 arteries was 6.6 ± 0.6 mmHg in the absence of drugs. Of this basal pressure, less than 5 mmHg could be attributed to the resistance to flow of the cannula system at the perfusion rate used.

Electrical stimulation

Electrical stimulation (E.S.) of the arteries was performed by means of platinum electrodes introduced into the bath, parallel to and on either side of the artery. Arteries were stimulated by 10 s trains of square wave pulses 1 ms duration and supramaximal voltage in the frequency range 0.1 to 10 Hertz, with an EILCO laboratory stimulator (Type 6418). De la Lande & Rand (1965) have shown pharmacologically that under these conditions the nerves only are being stimulated.

Protocol

In all arteries, the protocol consisted of obtaining initial dose-response curves to NA added cumulatively to the perfusate, and frequency-response curves to E.S., respectively. The stimuli applied were sufficient to cause a rise in perfusion pressure greater than 60 mmHg. Following the recording of control dose and frequency-response curves, drugs were added either intraluminally (I/L) or extraluminally (E/L), and arteries were perfused for 30 min, during which time they were stimulated electrically at 5 min intervals, using a single test frequency of stimulation (in the range 2 to 10 Hz). The dose and frequency-response curves to NA and E.S. were then repeated. A period

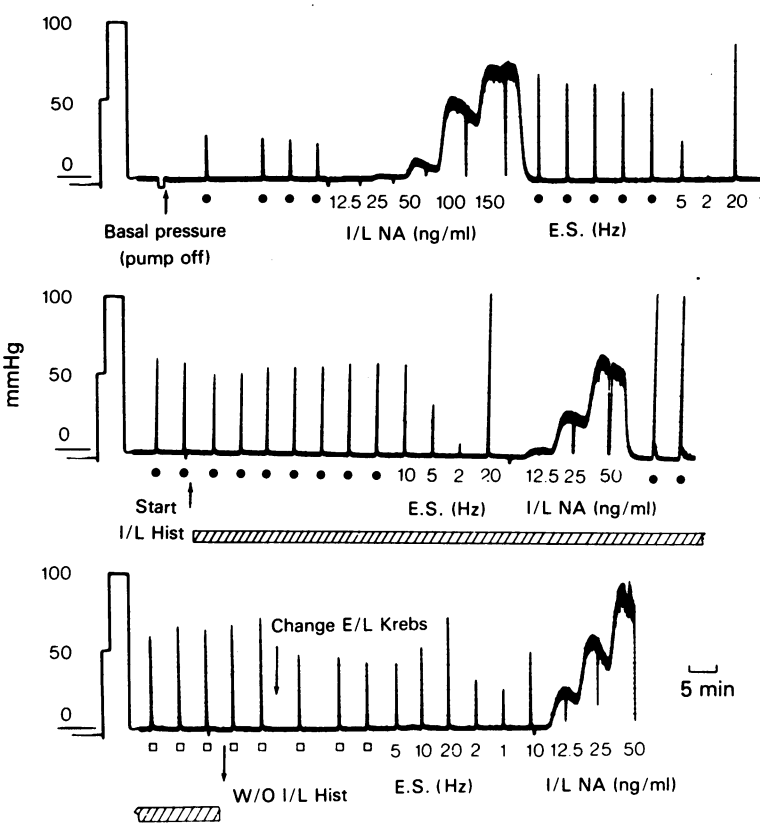

Figure 1 Contractile responses of the rabbit isolated ear artery preparation to electrical stimulation (E.S. 2-20 Hz) and to intraluminal noradrenaline (I/L Na, 6.25 to 150 μg/l) before I/L perfusion of histamine (100 μg/l), in the presence of histamine and following washout (W/O) of the histamine. The hatched bar indicates the duration of I/L histamine (I/L Hist) perfusion. NA was added cumulatively to the perfusion stream. The arteries were stimulated at 5 min intervals. The circles (●) indicate test stimulations at 10 Hz. The squares (□) indicate test stimulations at 5 Hz in the latter part of the experiments where 10 Hz gave a high contractile response due to tachyphylaxis of the tissue.

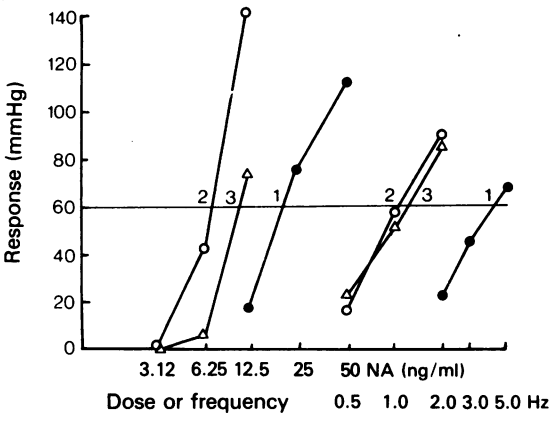

Figure 2 Dose- and frequency-response curves of the rabbit ear artery preparation to intraluminal noradrenaline and to electrical stimulation (E.S.): (1) prior to; (2) during, and (3) after washout of extraluminal histamine (100 μg/l).

of washout from drug-treatment, sufficient to yield reproducible responses to several consecutive stimulations at the test frequency, was then allowed. Finally, the dose and frequency-response curves to these stimuli were repeated once again in the absence of drugs (Figures 1 and 2).

Concentrations of I/L NA in the range 7.4×10^{-8} mol/l to 1.2×10^{-6} mol/l (12.5 to 200 μg/l) were required before, and 1.8×10^{-8} mol/l to 2.9×10^{-7} mol/l (3.1 to 50 μg/l) after exposure to histamine. Similarly, E.S. frequencies in the range 2.0 to 10.0 Hz and 0.5 to 5.0 Hz were used before and after addition of histamine respectively in most experiments.

Presentation of data

Changes in sensitivity of the arteries during and after drug treatments were assessed by determining from the dose-response curves the dose of NA or frequency of E.S. required to produce a rise in perfusion pressure of 60 mmHg. The calculated doses from the second and third dose-response curves were then expressed as a ratio of the dose derived from the first dose-response curve. Geometric means of the dose-ratios and ranges of the geometric means were calculated (Fleming, Westfall, de la Lande & Jellett, 1972). The significance of drug effects within arteries was tested with Student's paired t test while an unpaired t test was used to compare treatments between arteries. An increase over basal perfusion pressure of 60 mmHg was chosen for the calculation of dose-ratios because the rabbit ear artery does not yield reproducible responses over 200 mmHg I/L pressure (Carroll & Glover, 1977), and for most preparations, 60 mmHg approximates the midpoint of the linear portion of the dose-response curve (see e.g. Figure 2).

Materials

Metiamide base (mol.wt. 244.4) and 2(2-pyridyl) ethylamine dihydrochloride (mol.wt. 194) were generous gifts of Dr V. Balmer, Smith, Kline and French Pty Ltd, N.S.W. Mepyramine maleate (mol.wt. 401.4) was obtained from May and Baker Ltd, Footscray, Victoria. Histamine dihydrochloride (Koch-Light Laboratories, Bucks) was stored at 4°C as a 9×10^{-3} mol/l (1 g of histamine base/l) standard solution. Noradrenaline bitartrate (Sigma Chemical Co., St. Louis, Mo., U.S.A.) was prepared as a stock solution of 1.5×10^{-4} mol/l (25 mg of NA base/l) in ascorbic saline at pH 5.6. Final dilutions were made in Krebs solution immediately before use.

Results

Intraluminal histamine

Histamine (9×10^{-7} mol/l, 100 μg/l) added to the perfusion fluid caused no change in perfusion pressure (Figure 1), but this concentration caused a mean potentiation of the response to I/L NA of 3.0, i.e. the mean value of the ratio second dose/first dose was 3.0 (Tables 1 and 2). A similar potentiation of the response to E.S. (Table 2) also occurred. This latter effect was fully reversed following washout of the histamine. However, the potentiation of the response to I/L NA was only partially reversed.

Effects of histamine receptor antagonists

Mepyramine (2.5×10^{-6} mol/l, 1 mg of mepyramine maleate/l) added to the perfusion fluid had no effect on the basal perfusion pressure, or on the response of the artery to either E.S. or I/L NA (Table 2). In the presence of this concentration of mepyramine, while the potentiation by histamine (9×10^{-7} mol/l, I/L) of the response to I/L NA was significantly decreased ($P < 0.02$) compared to the response in the absence of mepyramine, a significant potentiation still occurred ($P < 0.02$). The response to E.S. varied from a significant inhibition ($P < 0.05$, $n = 5$) in five arteries to no change in one artery. The overall effect of histamine in the presence of mepyramine on E.S. was inhibition rather than potentiation, significant at the $P < 0.1$ level ($n = 6$) (Table 2). This inhibition proved reversible on removal of the drugs from the perfusion fluid.

In the presence of metiamide (4×10^{-6} mol/l, 1 mg/l, I/L), but not mepyramine in the perfusion fluid,

Table 1 Geometric means of doses of noradrenaline (NA) and frequencies of stimulation required to yield responses of 60 mmHg intraluminal (I/L) pressure increase

Treatment	n	I/L NA 1	I/L NA 2	I/L NA 3	E.S. 1	E.S. 2	E.S. 3
I/L Histamine 9×10^{-7} mol/l (100 μg/l)	6	54.3 (73.7 / 39.9)	18.1 (27.2 / 12.0)	21.8 (29.4 / 16.1)	5.9 (8.8 / 4.0)	2.8 (3.9 / 2.0)	6.2 (9.0 / 4.3)
I/L Histamine + mepyramine 2.5×10^{-6} mol/l (1 mg/l)	6	66.3 (79.5 / 55.3)	36.9 (43.8 / 31.1)	37.8 (41.1 / 34.7)	7.4 (10.5 / 5.2)	10.9 (15.7 / 7.6)	6.0 (8.9 / 4.0)
I/L Histamine + metiamide 4×10^{-6} mol/l (1 mg/l)	5	54.7 (84.8 / 35.3)	23.1 (32.3 / 16.5)	41.8 (56.6 / 30.8)	5.0 (8.4 / 3.0)	2.2 (3.1 / 1.5)	5.4 (7.8 / 3.8)
2(2-Pyridyl) ethylamine 51×10^{-7} mol/l (1 mg/l)	6	72.5 (98.9 / 53.1)	24.9 (37.6 / 16.5)	26.2 (42.3 / 16.2)	4.2 (4.6 / 3.8)	1.9 (2.4 / 1.5)	3.3 (4.0 / 2.7)
E/L Histamine 9×10^{-7} mol/l (100 μg/l)	6	30.3 (44.6 / 20.5)	12.7 (18.4 / 8.8)	16.1 (23.5 / 11.0)	2.9 (3.9 / 2.2)	1.3 (1.7 / 1.0)	1.1 (1.5 / 0.8)
E/L Histamine + mepyramine 2.5×10^{-6} mol/l (1 mg/l)	7	86.0 (108.0 / 68.5)	34.4 (40.1 / 29.6)	23.5 (27.5 / 20.0)	3.4 (5.4 / 2.1)	3.1 (4.9 / 2.0)	2.6 (3.8 / 1.8)

Geometric means and ranges of the means are shown of stimuli (I/L NA [μg/l] and E.S. [Hz]) required to yield a response of 60 mmHg I/L pressure increase: (1) prior to, (2) in the presence of and (3) following washout of the drugs shown in the first column of the table.

Table 2 Effect of drugs on the potentiation by intraluminal (I/L) and extraluminal (E/L) histamine on the responses of the rabbit ear artery to electrical stimulation (E.S.) and I/L noradrenaline (NA)

(*a*) *Intraluminal histamine*

Treatment	n	E.S. 1/2	P	E.S. 1/3	P	I/L NA 1/2	P	I/L NA 1/3	P
I/L Histamine 9×10^{-7} mol/l	6	3.1 (4.0 / 2.4)	<0.01	1.4 (1.8 / 0.8)	N.S.	3.0 (3.5 / 2.5)	<0.01	2.5 (3.0 / 2.0)	<0.01
I/L Mepyramine 2.5×10^{-6} mol/l	5	1.2 (1.4 / 1.0)	N.S.	0.9 (1.1 / 0.7)	N.S.	1.1 (1.2 / 0.9)	N.S.	1.2 (1.3 / 1.1)	N.S.
I/L Mepyramine + I/L histamine	6	0.7 (0.8 / 0.6)	<0.1	1.1 (1.4 / 0.9)	N.S.	1.7 (2.0 / 1.5)	<0.02	1.7 (2.3 / 1.3)	N.S.
I/L Metiamide 4×10^{-6} ml/l + E/L histamine	5	2.3 (2.9 / 1.8)	<0.05	0.9 (1.2 / 0.7)	N.S.	2.4 (3.0 / 1.8)	<0.05	1.3 (1.7 / 1.0)	N.S.

(*b*) *Extraluminal histamine*

E/L Histamine 9×10^{-7} mol/l	6	2.3 (2.6 / 2.1)	<0.01	2.7 (3.3 / 2.2)	<0.01	2.4 (2.7 / 2.1)	<0.001	1.9 (2.0 / 1.8)	<0.001
Mepyramine 2.5×10^{-6} mol/l + E/L histamine	7	1.1 (1.2 / 1.0)	NS	1.3 (1.6 / 1.0)	NS	2.2 (2.6 / 1.9)	<0.01	2.7 (3.2 / 2.2)	<0.02

Results are expressed as geometric means and range of the means of dose-ratios at the 60 mmHg response level. Significant differences from a dose-ratio of 1 (i.e. no drug effect) were calculated by Student's paired *t* test.

Table 3 Effect of intraluminal (I/L) perfusion of the histamine H_1-receptor agonist, 2(2-pyridyl) ethylamine (2PE) on the response of the rabbit ear artery to electrical stimulation (E.S.) and intraluminal noradrenaline (I/L NA).

		E.S.				*I/L NA*			
Treatment	n	*1/2*	P	*1/3*	P	*1/2*	P	*1/3*	P
2PE 5.1×10^{-7} mol/l	4	1.2 (1.3 – 1.1)	N.S.	1.1 (1.4 – 0.8)	N.S.	2.9 (3.7 – 2.3)	<0.05	3.4 (4.9 – 2.4)	<0.05
2PE 51×10^{-7} mol/l	6	2.2 (2.7 – 1.9)	<0.01	1.3 (1.5 – 1.1)	N.S.	2.9 (3.9 – 2.2)	<0.02	2.8 (3.7 – 2.1)	<0.05

Results are expressed as geometric means and range of the means of dose-ratios at the 60 mmHg response level. Significant differences from a dose-ratio of 1 (i.e. no drug effect) were calculated by Student's paired *t* test.

histamine (9×10^{-7} mol/l, I/L) potentiated the effects of both I/L NA and E.S. (Tables 1 and 2), the magnitude of this potentiation being not significantly different ($P > 0.5$) from that elicited by histamine alone, but this time, the effect was reversible for both E.S. and I/L NA.

Extraluminal histamine

Histamine, added to the bath to give an initial concentration of 9×10^{-7} mol/l, potentiated the responses of the ear artery to both E.S. and I/L NA to comparable extents (Table 2), but the potentiation was less than that elicited by I/L histamine. Furthermore, after washing out the E/L histamine, the response to electrical stimulation was not reversible in contrast to the effect observed following application of I/L histamine.

In the presence of mepyramine (2.5×10^{-6} mol/l, applied both I/L and E/L), the potentiation by E/L histamine of the response to I/L NA remained unchanged, whereas the potentiation of the response to E.S. was abolished (Table 2).

Effect of the selective H_1-receptor agonist, 2(2-pyridyl) ethylamine (2PE)

2PE (150×10^{-7} mol/l, 2.8 mg of 2PE dihydrochloride/l) applied intraluminally invariably constricted the rabbit ear artery; accordingly, two subconstrictor concentrations of this agonist (5.1 and 51×10^{-7} mol/l, 100 μg/l and 1 mg/l, I/L) were used in subsequent experiments. Both concentrations of 2PE significantly potentiated the response of the artery to I/L NA (mean potentiation of 2.9); this potentiation was not reversible (Table 3). The lower concentration of 2PE did not potentiate the effects of E.S., whereas a significant reversible potentiation (of 2.2) of the response to E.S. was obtained in six arteries with the higher concentration.

Histamine assays

Endogenous histamine. After 4 to 5 h perfusion with histamine-free Krebs solution, the apparent endogenous content of histamine was 7.0 ± 0.7 μg/g in nine ear arteries.

Histamine in the perfusate. Thirty minutes after the start of an I/L perfusion of histamine, samples were taken simultaneously for histamine assays from three sites; (a) the perfusion fluid before passing through the artery; (b) the perfusion fluid after passing through the artery; (c) the external bathing medium.

In a total of ten arteries the mean concentration of histamine in the post-artery perfusate was significantly lower ($P < 0.01$, paired *t* test) than that in the pre-artery perfusate. In four arteries perfused with histamine (9×10^{-7} mol/l) the mean difference was $(0.41 \pm 0.15) \times 10^{-7}$ mol/l, while in six arteries perfused with both histamine and mepyramine, the mean difference was $(1.2 \pm 0.41) \times 10^{-7}$ mol/l. This effect of mepyramine was not significant at the $P = 0.05$ level, when compared to the difference due to histamine alone.

The external bath concentration at this time was $(0.60 \pm 0.18) \times 10^{-7}$ mol/l ($n = 4$) when histamine was perfused through the ear artery, and $(0.53 \pm 0.12) \times 10^{-7}$ mol/l ($n = 6$) in the presence of both histamine and mepyramine. This difference due to mepyramine is again non-significant.

Histamine in the external bath. Following the addition of histamine to the external bath, the perfusate was collected continuously in 10 ml aliquots, and aliquots (50 μl) were also taken from the bath at 5 min intervals. While histamine never reached detectable concentrations in the post-artery perfusate

($<1.8 \times 10^{-9}$ mol/l), there was a progressive decline in the bath concentration with time.

Discussion

The results of the present studies clearly demonstrate that a sub-constrictor concentration of histamine (9×10^{-7} mol/l) potentiates the responses of the rabbit ear artery both to exogenous noradrenaline and to substances released during electrical stimulation of the sympathetic nerves. These findings confirm the observations of others in the rabbit cerebral artery (Bevan *et al.*, 1975), dog saphenous vein strips (McGrath & Shepherd, 1976) and the rabbit ear artery (Carroll & Glover, 1977). Responses to both E.S. and I/L NA were potentiated to similar extents. While maximum responses cannot be obtained in the rabbit ear artery, these changes in sensitivity were associated with parallel shifts of the dose-response curve.

Potentiation of the response to E.S. was abolished by mepyramine, showing that this effect of histamine was mediated by H_1-receptors. Further evidence in support of this was provided by the data from arteries treated with the specific H_1-receptor agonist, 2PE (Durant, Gannellin & Parsons, 1975). A postsynaptic localization is suggested for these H_1-receptors since concentrations of 2PE applied intraluminally which did not affect the response to electrical stimulation did cause potentiation of the response to I/L NA. While the potentiation of the response to I/L NA was of the same order of magnitude as that observed with E.S., it is likely that more than one factor is contributing to this effect of histamine. Thus while mepyramine (2.5×10^{-6} mol/l) significantly reduced the potentiating effect of histamine, a significant potentiation still remained. Furthermore, following washout of histamine the potentiation of the response to I/L NA was only partially reversed. This contrasts with the return to the initial sensitivity to E.S. following removal of histamine. There is no clear explanation for these differences between the effects of histamine on electrical stimulation and I/L NA. However, it is possible that the explanation may be in the relative concentration of histamine across the wall of the artery. Our results show that 30 min after the start of perfusion with I/L histamine, the concentration of histamine in the bath was approximately 1/20th that of the perfusate. There is thus a marked concentration gradient across the artery wall. That this may be an important factor is supported by the fact that when the concentration gradient was reversed and histamine was initially applied to the bath, the response to electrical stimulation was now no longer reversible. These results suggest that in higher concentrations, irreversible non-specific binding of histamine to the tissues may contribute to the observed changes in sensitivity.

The nature of the histamine receptors involved was examined in arteries pretreated with mepyramine alone. In these arteries, the potentiation by histamine of the response to I/L NA was reduced after H_1-receptor blockade, but the dose-ratio was still significantly greater than one. In contrast to this observation, the response to E.S. was not only decreased, but in fact an inhibition was observed in five out of six arteries. It is thus apparent that H_2-receptors as well as H_1-receptors are involved in the effects of histamine, and that the former exert a greater inhibitory effect on the response to E.S. than to I/L NA. The precise mechanism of this inhibition cannot be ascertained from the present experiments, but two possibilities seem likely. Firstly, postsynaptic H_2-receptors could exert a vasodilator effect only apparent when the constrictor agent is applied. This possibility is in keeping with the observations of Glover *et al.* (1973). However, while postsynaptic vasodilator receptors could account for a reduced response to both I/L NA and E.S. this possibility is unlikely to explain the very much greater effect on the latter stimulus. This effect could be explained by a second possibility, namely inhibition of the release of NA, mediated by presynaptic H_2-receptors. Such a localization of H_2-receptors is in keeping with the observations of McGrath & Shepherd (1976). Thus, the change in response to E.S. could be accounted for by two effects of H_2-receptor activation, postsynaptic vasodilatation and presynaptic inhibition. Further experiments involving labelled NA and other agonists are required to quantify the significance of these two possible effects of H_2-receptor activation in the rabbit ear artery.

Regarding the relative importance of H_1- and H_2-receptors in the rabbit ear artery, the binding of agonist to these receptors suggests a preponderance of H_1-receptors in this tissue. In this respect it is noteworthy that the efficacy for the H_1-agonist, 2PE, relative to histamine on the guinea-pig ileum is 5.6% (Durant *et al.*, 1975) while in our study the ratio of subconstrictor concentrations of both agonists was in the range 15% to 20% suggesting more marked H_1-receptor activity in the rabbit ear artery. Further evidence for relatively weak H_2 activity is provided from arteries treated with metiamide. In these arteries the potentiation observed to both E.S. and I/L NA was not significantly different from that observed in untreated arteries. In fact, the mean dose-ratio was lower in metiamide-treated arteries. It is also noteworthy that in these arteries the potentiation observed during I/L histamine perfusion was completely reversible suggesting an interaction between metiamide and the non-reversible component of the potentiating effect of histamine.

Further studies are necessary to characterize the distribution and metabolism of histamine across the artery wall in order to clarify the mechanisms behind the effect of histamine in potentiating the response to E.S. and to exogenous NA.

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