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Characterization of histamine receptors in isolated human cerebral arteries

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1 The subtypes of histamine-receptors which mediate dilatation of small human cerebral arteries have been characterized *in vitro* using 'selective' agonists and antagonists.

2 Dilator responses were studied after preconstriction with prostaglandin $F_{2\alpha}$, since contraction was not seen with histamine concentrations up to 10^{-4} M. Histamine caused a concentration-related relaxation of cerebral vessels with an IC_{50} value of $5.2 \pm 1.6 \times 10^{-8}$ M.

3 Mepyramine caused a parallel shift to the right of the histamine concentration-response curve whereas cimetidine was without observable effect. This suggests the presence of histamine H_1-receptors only. However, combined treatment with mepyramine and cimetidine caused a more marked displacement of the concentration-response curve to the right. Schild analysis indicated that in situations of near complete blockade of either of the histamine receptor subtypes, simple competitive antagonism both at H_1- and H_2-receptors can be revealed with a pA_2 value of 8.64 for mepyramine and a pA_2 value of 6.52 for cimetidine.

4 The 'selective' H_1-receptor agonists pyridylethylamine, 2-methylhistamine (2-Me-histamine) and thiazolylethylamine, and the H_2-receptor agonists dimaprit, impromidine and 4-methylhistamine (4-Me-histamine) all mimicked the histamine response, but were less potent than histamine. The order of potency was thiazolylethylamine > dimaprit > impromidine > 2-Me-histamine > pyridylethylamine > 4-Me-histamine.

5 These results indicate that the histamine-induced dilatation in small human cerebral arteries is mediated by both H_1- and H_2-receptors and that the former subtype of histamine receptor predominates.

Introduction

The potential importance of histamine in the physiological control of the cerebral circulation or in its involvement in the mediation of cerebrovascular events in various pathological states, such as vascular headache or migraneous neuralgia, has been indicated in previous studies (Diamond *et al.*, 1976; Hardebo *et al.*, 1980; Gross 1982). This is further supported by the presence of mast cells adjacent to cerebral vessels (Edvinsson *et al.*, 1977), the non-mast cell pool of histamine in cerebrovascular smooth muscle (El-Ackad & Brody, 1974) and the occurrence of histamine binding sites in cerebral microvessels (Peroutka *et al.*, 1980).

The cerebrovascular reactions to histamine have been studied in animals both *in vitro* and *in situ*. In the rabbit and guinea-pig histamine was found to be a strong vasoconstrictor agent (Hamel *et al.*, 1985), whereas it caused dilatation in the cat (Edvinsson & Owman, 1975; Wahl & Kuschinsky 1979; Gross *et al.*, 1981b; Edvinsson *et al.*, 1983), monkey (Duckworth *et al.*, 1976) and rat (Gross *et al.*, 1981a; Dacey & Bassett 1987). This vasodilatation seems to be mediated mainly via histamine H_2-receptors (see Gross, 1984). However, it is not known if these results are applicable to human cerebral arteries, since there might be differences in the type of receptor stimulated and in the relative amount of receptor subtypes in different vessels.

Data on human cerebral vessels are indeed sparse in the literature. Histamine has been demonstrated to produce a dilatation of precontracted cerebral

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arteries *in vitro*, whereas contraction appears only to be weak and occasional (Edvinsson *et al.*, 1976; Toda, 1977). Effective tools are now available which may assist in clarifying the role of histamine in the cerebrovascular bed by the use of selective H_1- and H_2-receptor agonists and antagonists (Owen 1977; Owen *et al.*, 1979). The present study was performed in order to characterize in detail the histamine receptors mediating the dilator effects in human cerebral arteries.

Methods

Material was obtained from 8 patients (5 males and 3 females aged 32–58 years) who were undergoing surgery for brain tumours. None of the patients had received an H_1-antagonist as a pre-medication. Small pial arteries overlying macroscopically intact brain tissue were immediately dissected out and placed in ice-cold Krebs-Ringer solution and kept at 4°C during transporatation to the laboratory (about 2 h). Vessels with a diameter of 0.3–0.6 mm were cut into ring segments (approximately 2–4 mm in length) and mounted between two L-shaped metal prongs in temperature-controlled (37°C) 2.5 ml tissue baths. The baths contained an aerated (95% O_2 plus 5% CO_2) buffer solution of the following composition (mM): NaCl 119, KCl 4.6, $CaCl_2$ 1.5, $MgCl_2$ 1.2, NaH_2PO_4 1.2, $NaHCO_3$ 15 and glucose 11; pH was kept at 7.4.

The metal prongs were attached to Grass FT-03C transducers and a Grass polygraph for measurement and recording of circular vasomotor effects following exposure to various agents (Högestätt *et al.*, 1983). After mounting the vessels were subjected to a passive load of 4 mN and allowed to stabilize at this tension for 90 min. Concentration-response data were derived by cumulative addition of histamine or other agonists to the tissue bath. Full concentration-response curves were run for all agents tested. Dilator effects were studied after the arteries had been precontracted by addition of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) 3×10^{-6} M; this concentration yielded a stable level of contraction of long enough duration to allow for analysis of relaxant responses (i.e. up to 30 min). Antagonists were given into the baths 20 min before the responses to histamine were tested. The values for relaxation are expressed as percentage of the level of contraction induced by 3×10^{-6} M $PGF_{2\alpha}$. The responses were characterized in terms of I_{max} (maximum effects of the drugs) and IC_{50} (concentration eliciting half maximum response) values. Vessel reactivity was tested with a modified buffer solution containing 124 mM potassium which was achieved by equimolar substitution of NaCl for KCl. At the end of each experiment a potassium-induced contraction was used as an indicator of the reactivity of the vessel. When appropriate mean values ± s.e. mean are given. The *n* values (the number of vessel segments) cited in Figures 1–5 never include more than two vessel segments from the same patient.

Quantitation of antagonism

Concentration-response curves to histamine were obtained in the absence and presence of various concentrations of either cimetidine or mepyramine, or both. The IC_{50} values for histamine were calculated as well as the concentration-ratios (IC_{50} after antagonist/IC_{50} before antagonist). The dextral displacements of the concentration-response curves were utilized in an analysis according to the Gaddum–Schild equation: log(concentration-ratio − 1) = log B − log K_B, where B is the concentration of the antagonist and K_B is the apparent dissociation constant for the receptor antagonist complex. For each experiment with antagonist the pA_2 value was determined according to: $pA_2 = -\log K_B$. Data are presented as calculated mean pA_2 ± s.e. mean. The slope of the Schild plot is an indication of the nature of the antagonism. The slope should ideally be 1 if the response involves a simple competitive antagonism at one type of receptor only. When the slope departs significantly from 1 other mechanisms are probably involved.

Drugs

Histamine dihydrochloride (Sigma Chemical Co, St Louis, MO, U.S.A.), mepyramine maleate (May and Baker Ltd, Dagenham, U.K.), cimetidine, 2-pyridylethylamine (PEA), 2-methylhistamine, 2-thiazolylethylamine (TEA), tele-methyl-histamine, impromidine, dimaprit and 4-methylhistamine (kind gifts from the Smith, Kline & French Laboratories, Welwyn Garden City, U.K.). The drugs were dissolved in 0.9% w/v NaCl solution (saline). All concentrations are expressed as the final molar concentration in the bath.

Results

Application of the 124 mM potassium-containing buffer invariably resulted in a strong and stable contraction amounting to 9.7 ± 1.3 mN (mean ± s.e. mean) which rapidly disappeared on washout. Cumulative application of histamine did not induce any constriction in the majority of vessels, but in a few there was a weak constriction at concentrations of and above 10^{-4} M. Neither of the antagonists in the concentrations used had any direct effect on the

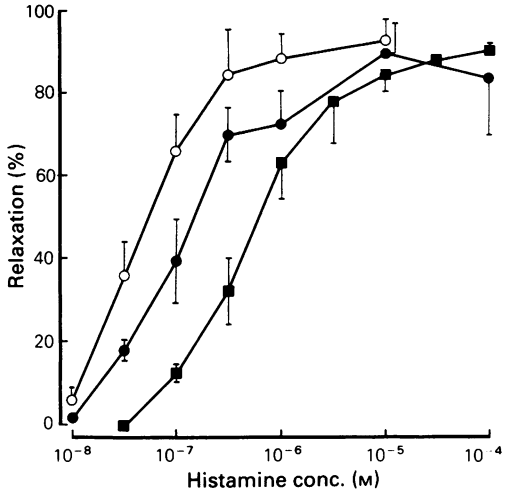

Figure 1 Relaxant effect of increasing concentrations of histamine on small human cerebral arteries precontracted with prostaglandin $F_{2\alpha}$. Studies were performed without mepyramine (○) and in the presence of mepyramine in concentrations of 1×10^{-7} M (●) and 1×10^{-6} M (■). Mean values are shown, $n = 10$; vertical lines indicate s.e. mean.

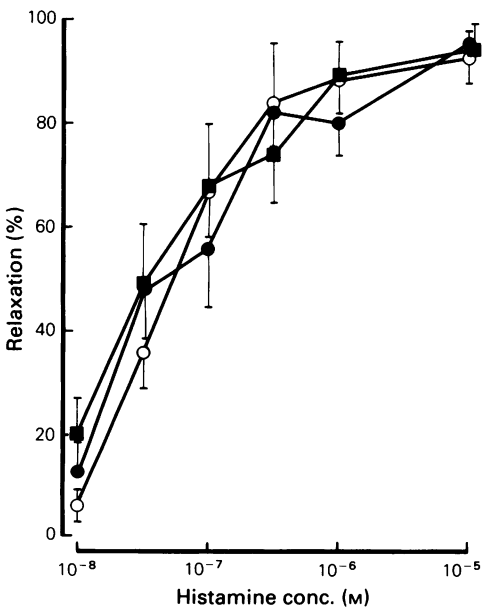

Figure 2 Relaxant effect of increasing concentrations of histamine on small human cerebral arteries precontracted with prostaglandin $F_{2\alpha}$. Responses to histamine before treatment with antagonist are indicated by (○). The concentration-response curves were unaltered by cimetidine 1×10^{-6} M (●) and 1×10^{-5} M (■). Mean values are shown, $n = 8$; vertical lines indicate s.e. mean.

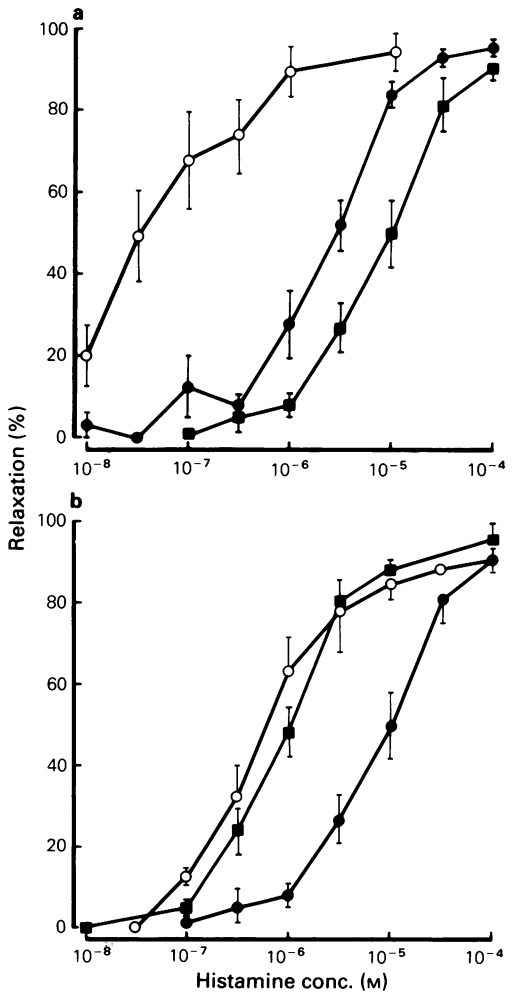

Figure 3 Relaxant effect of increasing concentrations of histamine on small human cerebral arteries precontracted with prostaglandin $F_{2\alpha}$. (a) Responses to histamine in the presence of cimetidine 1×10^{-5} M are indicated by (○). Mepyramine 1×10^{-7} M (●) and mepyramine 1×10^{-6} M (■), both in the presence of cimetidine 1×10^{-5} M, caused a further dextral displacement of the histamine concentration-response curve as compared to mepyramine alone. (b) Responses to histamine in the presence of mepyramine 1×10^{-6} M are indicated by (○). Cimetidine 1×10^{-6} M (■) and cimetidine 1×10^{-5} M (●), both in the presence of mepyramine 1×10^{-6} M, caused a dextral displacement of the histamine-induced concentration-response curve. In (a) and (b) mean values are shown, $n = 10$; vertical lines indicate s.e. mean.

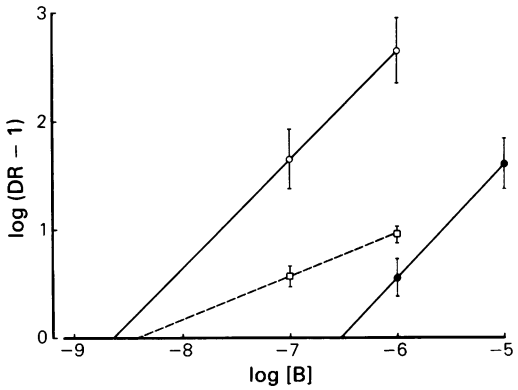

Figure 4 Schild plots for: mepyramine in the presence of cimetidine 1×10^{-5} M (○) ($y = 8.73 + 1.01x$); mepyramine without simultaneous H_2-receptor blockade (□) ($y = 3.37 + 0.40x$) and cimetidine in the presence of mepyramine 1×10^{-6} M (●) ($y = 6.92 + 1.06x$). [B] is the antagonist concentration and CR is the concentration-ratio.

vessel segments. Dilator responses were studied in vessel segments in which a preconstriction had been produced by 3×10^{-6} M $PGF_{2\alpha}$. The mean effect of $PGF_{2\alpha}$ was calculated from 21 vessel segments (3 segments from 5 patients and 2 segments from 3 patients) and amounted to 5.4 ± 0.7 mN. In these precontracted arterial segments, histamine invariably produced concentration-related relaxations with an I_{max} of 5.0 ± 0.2 mN or $93 \pm 5\%$ inhibition of the $PGF_{2\alpha}$-induced level of precontraction. The IC_{50} for histamine was $5.2 \pm 1.6 \times 10^{-8}$ M.

The histamine-induced response was shifted in parallel to the right by mepyramine in concentrations between 1×10^{-7} M and 1×10^{-6} M, without any reduction in the maximum response (Figure 1). Administration of cimetidine up to a concentration of 1×10^{-5} M did not significantly alter the histamine-induced concentration-response curve (Figure 2). Combined treatment with mepyramine and cimetidine caused a more marked displacement of the histamine-induced concentration-response curve to the right than that achieved by H_1-receptor blockade alone. In the presence of cimetidine 1×10^{-5} M a mepyramine concentration of 1×10^{-7} M caused a dextral shift with a concentration-ratio of 61.4 ± 8.2, and mepyramine 1×10^{-6} M caused a further parallel shift to the right with a concentration-ratio of 295.5 ± 38.2 (Figure 3a). The concentration-ratio was only 8.8 ± 1.3 for mepyramine (10^{-6} M) alone (Figure 1).

Administration of cimetidine in the presence of mepyramine 1×10^{-6} M now caused a parallel shift to the right with a concentration-ratio of 2.8 ± 0.5 at a cimetidine concentration of 1×10^{-6} M and

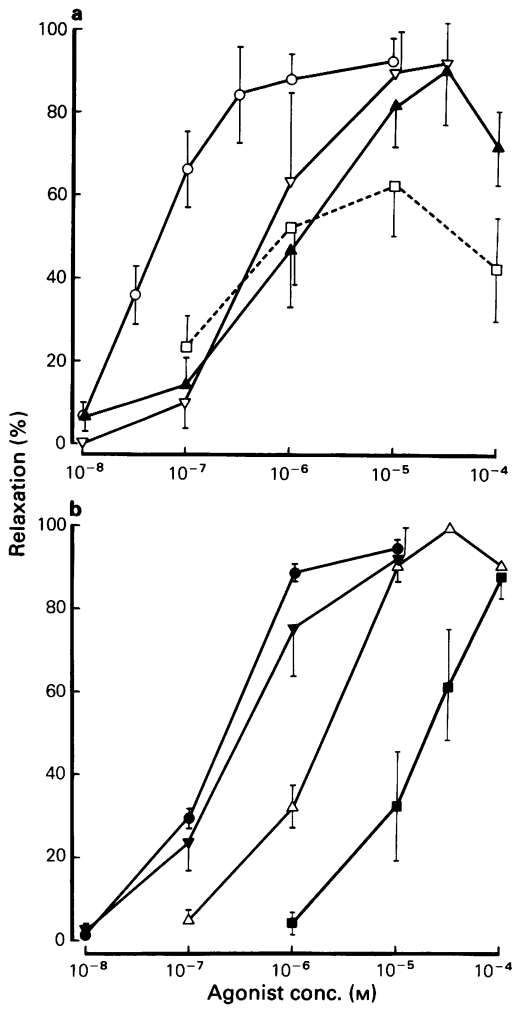

Figure 5 Relaxant effects of increasing concentrations of (a) histamine (○) and the histamine agonists 2-methyl-histamine (▽) ($n = 4$), pyridylethylamine (▲) ($n = 5$) and impromidine (□) ($n = 4$), and (b) the histamine agonists (2-thiazolylethylamine (●) ($n = 4$), dimaprit (▼) ($n = 6$), 4-methyl-histamine (△) ($n = 5$) and tele-methyl-histamine (■) ($n = 5$) in small human cerebral arteries precontracted with prostaglandin $F_{2\alpha}$. Mean values are shown with vertical lines indicating s.e. mean.

28.3 ± 3.2 at a cimetidine concentration 1×10^{-5} M (Figure 3b).

Schild analysis using the concentration-ratios for mepyramine alone yielded a line with a slope of 0.40 indicating that there was not a simple competitive antagonism for the agonist at only one receptor subtype (Figure 4). When using the concentration-ratios for mepyramine in the presence of 1×10^{-5} M cimetidine, Schild analysis yielded a line with a slope

Table 1 Concentrations of histamine agonists eliciting half maximum relaxation (IC_{50}), maximum effects of the agonists (I_{max}) and agonist potency relative to that of histamine

Agonists	IC_{50}	I_{max} (mN)	*Relative potency* (histamine = 100) *Human cerebral artery*	*Guinea-pig ileum** (H_1)	*Guinea-pig atrium** (H_2)
Histamine	$5.2 \pm 1.6 \times 10^{-8}$	5.0 ± 0.2	100	100	100
TEA	$2.7 \pm 0.6 \times 10^{-7}$	5.0 ± 0.1	19.3	26	2.2
2-Me-Histamine	$6.5 \pm 4.0 \times 10^{-7}$	5.0 ± 0.3	8.0	16.5	4.4
PEA	$1.1 \pm 0.6 \times 10^{-6}$	4.9 ± 0.4	4.7	5.6	2.5
Tele-Me-Histamine	$2.5 \pm 0.9 \times 10^{-5}$	5.1 ± 0.1	0.2	0.4	<0.1
Dimaprit	$3.4 \pm 1.4 \times 10^{-7}$	4.9 ± 0.6	15.3	$<10^{-4}$	71
Impromidine	$3.8 \pm 2.4 \times 10^{-7}$	3.5 ± 0.6	13.7	$<10^{-3}$	4810
4-Me-Histamine	$3.0 \pm 0.8 \times 10^{-6}$	5.3 ± 0.1	1.7	0.2	43

Data are given as mean ± s.e. mean, $n = 4$–6.
* Adapted from Ganellin (1982). TEA = 2-thiazolylethylamine, PEA = 2-pyridylethylamine and 2-Me-histamine = 2-methylhistamine.

of 1.01. This suggests simple competitive antagonism at a histamine H_1-receptor site. The resulting pA_2 value for mepyramine was 8.64 ± 0.23. Similarly, Schild analysis using the concentration-ratios for cimetidine in the presence of mepyramine 1×10^{-6} M yielded a line with a slope of 1.06 and a pA_2 value of 6.52 ± 0.20 (Figure 4).

The relatively selective H_1-receptor agonists TEA, 2-Me-histamine, PEA and tele-Me-histamine and the relatively selective H_2-receptor agonists dimaprit, impromidine and 4-Me-histamine all relaxed $PGF_{2\alpha}$ precontracted arterial segments in a concentration-dependent manner (Figure 5a and b). Maximum effects of both H_1- and H_2-receptor agonists were equal to that of histamine, with the exception of impromidine which showed an I_{max} of $68 \pm 9\%$ of the histamine-induced relaxation. The potency of all agonists tested was considerably lower than that of histamine itself; the most potent being TEA, followed by dimaprit, impromidine and 2-Me-histamine (Table 1).

Discussion

The administration of histamine to human pial arteries pre-contracted with $PGF_{2\alpha}$ resulted in dilatation of the vessels. In most other species investigated (Edvinsson & Owman, 1975; Wahl & Kuschinsky, 1979; Brody, 1980; Gross *et al.*, 1981a,b; Edvinsson *et al.*, 1983, Dacey & Bassett, 1987), there is a predominance of H_2-receptor participation in the vasodilator responses to histamine in cerebral arteries. However, in human cerebral arteries this response seemed mainly to be mediated via H_1-receptors. Thus, H_1-receptor blockade with mepyramine caused a parallel displacement to the right of the histamine concentration-response curve, whereas H_2-receptor blockade with cimetidine was without effect. Combined treatment with both H_1- and H_2-receptor antagonists resulted in further dextral displacement of the histamine-induced concentration-response curve. This indicates that the H_1-receptor predominates in mediating dilatation in this vascular region. With increasing H_1-receptor blockade the H_2-receptor mediated dilatation can be unmasked, as shown by the additional dextral displacement of the histamine-induced concentration-response curve by mepyramine in the presence of cimetidine. This also explains why no simple competitive antagonism at one receptor type by Schild analysis was seen with H_1-receptor blockade alone (Figure 4), because the dilator response here was influenced by the effect of histamine on the H_2-receptor population. On the other hand, in the presence of effective H_2-receptor blockade (cimetidine 1×10^{-5} M) the experiments revealed a simple competitive antagonism at the H_1-receptor site. Effective H_1-receptor blockade (mepyramine 1×10^{-6} M) in the same way indicated simple competitive antagonism at the H_2-receptor.

For mepyramine, pA_2 values of 8.0–9.3 have been obtained in different test preparations (9.0—human brain tissue, Chang *et al.*, 1979; 9.07—cat extracranial arteries, Edvinsson & Owman, 1975; 9.3—guinea-pig ileum, Arunlakshana & Schild 1959; 8.2—guinea-pig brain tissue, Palacios *et al.*, 1978; 9.3—rabbit detrusor muscle, Fredericks, 1975; 8.01—mouse brain tissue, Quach *et al.*, 1980; 8.7—mouse neuroblastoma cells, Richelson, 1978). For cimetidine, pA_2 values of 6.1–7.0 have been obtained in different test preparations (7.03—cat cerebral arteries, Edvinsson *et al.*, 1983; 6.55—guinea-pig atrium, Bradshaw *et al.*, 1979; 6.10—guinea-pig atrium, Angus *et al.*, 1978; 6.40—guinea-pig papillary muscle, Bertaccini & Coruzzi, 1981; 6.2—guinea-pig ventricle muscle preparation, Johnson

1977; 6.25—rat peripheral vascular resistance, Owen *et al.*, 1981; 6.68—rabbit atrium, Polanin *et al.*, 1980). Thus, the pA_2 values found in the present study (mepyramine 8.64 and cimetidine 6.52) are well in accordance with those found in histamine receptor subtype characterizations carried out by others.

The dextral displacement of the histamine concentration-response curve by H_1-receptor blockade, the lack of effect of H_2-receptor blockade alone and the pronounced dextral displacements obtained with combined H_1- and H_2-receptor blockade have been observed in previous experimental models. Such effects with histamine agonists and antagonists have been seen following examination of systemic blood pressure in the cat and dog (Black *et al.*, 1975), and in peripheral resistance vessels of the hind-limb, mesentery and stomach of the cat (Flynn & Owen, 1975). There are, however, exceptions such as pial arteries of the cat, where Wahl & Kuschinsky (1979) obtained no additional dextral displacement upon combined H_1- and H_2-receptor blockade. Here the histamine receptors have been shown to be of the H_2-subtype, and there is no indication of the presence of H_1-receptors (Edvinsson *et al.*, 1983).

The present result is an example of a drug receptor interaction where a single agonist (histamine) interacts with two independent receptor subtypes (H_1 and H_2) to produce a common physiological effect (dilatation). In their theoretical consideration of such concentration-receptor interactions, Ariëns *et al.* (1959) suggested that the slope of the concentration-response curve is determined primarily by the interaction of the agonist (histamine) with the receptor to which it binds with greater affinity (H_1). The interaction with the other receptor (H_2) would be concealed until unmasked by a competitive antagonist (mepyramine) for the interaction of the agonist with the first receptor. According to this, the receptor having the lower dissociation constant determines the shape of the concentration-response curve, which is well in accordance with our findings for the H_1-receptor. However, the dominance of a given receptor will not only depend on the relative dissociation constants of histamine for H_1- and H_2-receptors but will also depend on the spare receptor reserve for each response.

Further support for the involvement of both H_1- and H_2-receptors in the vasodilator response of human pial arteries to histamine was obtained by using relatively selective receptor agonists. All agonists, both H_1- and H_2-receptor agonists, mimicked the histamine-induced response and all, except impromidine, equalled the I_{max} of histamine. The potency of the agonists was assayed and the values for the relatively selective H_1-receptor agonists in pial arteries are similar to the values obtained for H_1-receptors on guinea-pig ileum (Table 1). The potencies of the selective H_2-receptor agonists dimaprit and impromidine were only slightly lower than that of the most potent H_1-receptor agonist TEA. This may be taken as a further indication for the presence of H_2-receptors in human pial arteries.

In conclusion, the effects of relatively selective H_1- and H_2-receptor agonists and antagonists revealed that histamine-induced dilatation of human pial arteries is mediated by both H_1- and H_2-receptors, but the H_1-receptor mediated relaxation is predominant.

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References

ANGUS, J.A., BLACK, J.W. & STONE, M. (1978). Comparative assays of histamine H_2-receptor antagonists using isolated mouse stomach. *Br. J. Pharmacol.*, **62**, 445–446.

ARUNLAKSHANA, O. & SCHILD, H.O. (1959). Some quantiative uses of drug antagonists. *Br. J. Pharmacol.*, **14**, 48–58.

ARIËNS, E.J., VAN ROSSUM, J.M. & SIMONIS, A.M. (1959). A theoretical basis of molecular pharmacology. *Arzneim. Forsch.*, **6**, 737–746.

BERTACCINI, G. & CORUZZI, G. (1981). Effect of impromidine on the isolated papillary muscle of the guinea-pig. *Br. J. Pharmacol.*, **72**, 197–199.

BLACK, J.W., OWEN, D.A.A. & PARSONS, M.E. (1975). An analysis of the depressor responses to histamine in the cat and dog: Involvement of both H_1- and H_2-receptors. *Br. J. Pharmacol.*, **54**, 319–324.

BRADSHAW, J., BRITTAIN, R.T., CLITHEROW, J.W., DALY, M.J., JACK, D., PRICE, B.J. & STABLES, R. (1979). Ranitidine (AH 19065): a new potent, selective histamine H_2-receptor antagonist. *Br. J. Pharmacol.*, **66**, 464P.

BRODY, M.J. (1980). Histamine and vascular smooth muscle. In *Vascular Neuroeffector Mechanisms.* ed. Bevan, J., Godfraind, T., Maxwell, R. & Vanhoutte, P. pp. 81–87. New York: Raven Press.

CHANG, R.S., TRAN, V.T. & SNYDER, S.H. (1979). Heterogeneity of histamine H_1-receptors: Species variations in [^{3}H]mepyramine binding of brain membranes. *J. Neurochem.*, **32**, 1653–1663.

DACEY, R.G. & BASSETT, J.E. (1987). Histaminergic vasodilation of intracerebral arterioles in the rat. *J. Cereb. Blood Flow Metab.*, **7**, 327–331.

DIAMOND, S., DALESSIO, D.J., GRAHAM, J.R. & MEDINA, J.L. (eds) (1976). Vasoactive Substances Relevant to Nigraine. Springfield: Thomas.

DUCKWORTH, J.W., LANCE, J.W., LORD, G.D.A. & MYLECHARANE, E.J. (1976). Histamine receptors in the

cranial circulation of the monkey. *Br. J. Pharmacol.*, **58**, 444–444P.

EDVINSSON, L. & OWMAN, CH. (1975). A pharmacologic comparison of histamine receptors in isolated extracranial and intracranial arteries in vitro. *Neurology*, **25**, 271–276.

EDVINSSON, L., OWMAN, C. & SJÖBERG, N.-O. (1976). Autonomic nerves, mast cells, and amine receptors in human brain vessels. A histochemical and pharmacological study. *Brain Res.*, **115**, 377–393.

EDVINSSON, L., CERVOS-NAVARRO, J., LARSSON, L.-I., OWMAN, C. & RÖNNBERG, A.-L. (1977). Regional distribution of mast cells containing histamine, dopamine or 5-hydroxytryptamine in the mammalian brain. *Neurology*, **27**, 878–883.

EDVINSSON, L., GROSS, P.M. & MOHAMED, A. (1983). Characterization of histamine receptors in cat cerebral arteries in vitro and in situ. *J. Pharmacol. Exp. Ther.*, **225**, 168–175.

EL-ACKAD, T.M. & BRODY, M.J. (1974). Fluorescence histochemical localization of non-mast cell histamine. In *Neuropsychopharmacology*, Series 359, pp. 551–559. Amsterdam: Excerpta Medica.

FLYNN, S.B. & OWEN, D.A.A. (1975). Histamine receptors in peripheral vascular beds in the cat. *Br. J. Pharmacol.*, **55**, 181–188.

FREDERICKS, C.M. (1975). Characterization of the rabbit detrusor response to histamine through pharmacologic antagonism. *Pharmacology*, **13**, 5–11.

GANELLIN, C.R. (1982). Chemistry and structure-activity relationships of drugs acting at histamine receptors. In *Pharmacology of Histamine Receptors*. ed. Ganellin, C.R. & Parsons, M.E. pp. 10–102. Bristol: John Wright & Sons Ltd.

GROSS, P. M. (1982). Cerebral histamine: Indications for neuronal and vascular regulation. *J. Cereb. Blood Flow Metabol.*, **2**, 3–23.

GROSS, P.M. (1984). Histaminergic dilatation of resistance vessels in the brain. *Biblthca Cardiol.*, **38**, 138–147.

GROSS, P.M., HARPER, A.M. & TEASDALE, G.M. (1981a). Cerebral circulation and histamine: 1. Participation of vascular H_1- and H_2-receptors in vasodilatory responses to carotid arterial infusion. *J. Cereb. Blood Flow Metabol.*, **1**, 97–108.

GROSS, P.M., HARPER, A.M. & TEASDALE, G.M. (1981b). Cerebral circulation and histamine. 2. Responses of pial veins and arterioles to receptor agonists. *J. Cereb. Blood Flow Metab.*, **1**, 219–225.

HAMEL, E., EDVINSSON, L. & MACKENZIE, E.T. (1985). Reactivity of various cerebral arteries to vasoactive substances in different mammalian species. *J. Cerebr. Blood Flow Metabol.*, **5**, (suppl. 1), 553–554.

HARDEBO, J.E., KRABBE, A.A. & GJERRIS, F. (1980). Enhanced dilatory response to histamine in large extracranial vessels in chronic cluster headache. *Headache*, **20**, 316–320.

HÖGESTÄTT, E.D., ANDERSSON, K.-E. & EDVINSSON, L. (1983). Mechanical properties of rat cerebral arteries as studied by a sensitive device for recording of mechanical activity in isolated small blood vessels. *Acta Physiol. Scand.*, **117**, 49–61.

JOHNSON, C.L. (1977). The action of histamine, dimaprit and related compounds on H_2-receptor linked adenylate cyclase in heart, brain and stomach. *Fed. Proc.*, **36**, 1022.

OWEN, D.A.A. (1977). Histamine receptors in the cardiovascular system. *Gen. Pharmacol.*, **8**, 141–156.

OWEN, D.A.A., HARVEY, C.A. & GRISTWOOD, R.W. (1979). Cardiovascular studies with impromidine (SK&F 92676), a new very potent and specific histamine H_2-receptor agonist. *J. Pharm. Pharmacol.*, **31**, 577–582.

OWEN, D.A.A., HARVEY, C.A. & QUINN, E.H. (1981). Vascular studies with histamine in vitro. *Agents & Actions*, **11**, 116–118.

PALACIOS, J.M., GARBARG, M., BARBIN, G. & SCHWARTZ, J.C. (1978). Pharmacological characterization of histamine receptors mediating the stimulation of cAMP accumulation in slices from guinea-pig hippocampus. *Mol. Pharmacol.*, **14**, 971–982.

PEROUTKA, S.J., MOSCOWITZ, M.A., REINHARD, J.R. & SNYDER, S.H. (1980). Neurotransmitter receptor binding in bovine cerebral microvessels. *Science*, **208**, 610–612.

POLANIN, A., LONGHURST, P.A. & MCNEILL, J.H. (1980). Comparison of histamine receptors in left and right rabbit atria. *Proc. West. Pharmacol. Soc.*, **23**, 49–52.

QUACH, T.T., DUCHEMIN, A.M., ROSE, C. & SCHWARTZ, J.C. (1980). [^{3}H] Glycogen hydrolysis elicited by histamine in brain slices: selective involvement of H_1-receptors. *Mol. Pharmacol.*, **17**, 301–308.

RICHELSON, E. (1978). Tricyclic antidepressants block histamine H_1-receptors of mouse neuroblastoma cells. *Nature*, **274**, 176–177.

TODA, N. (1977). Responses of isolated cerebral and peripheral arteries to vasoconstricting agents. In *Neurogenic Control of Brain Circulation*. ed. Owman, C. & Edvinsson, L. pp. 207–217. Oxford: Pergamon Press.

WAHL, M. & KUSCHINSKY, W. (1979). The dilating effect of histamine on pial arteries of cats and its mediation by H_2 receptors. *Circ. Res.*, **44**, 161–165.

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