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NATURE OF HISTAMINE RECEPTORS CONCERNED IN CAPILLARY PERMEABILITY

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1 Histamine and 2-methyl-histamine (H_1-receptor agonist) caused dose-dependent increases in capillary permeability in albino mice, but 4-methyl-histamine (H_2-receptor agonist) caused no significant increase.

2 Mepyramine (H_1-receptor antagonist) blocked the histamine-induced increase in capillary permeability whereas burimamide (H_2-receptor antagonist) produced no significant blockade of the histamine-response.

3 Combined mepyramine and burimamide pretreatment did not give any significantly greater protection than mepyramine alone.

4 The results indicate involvement of the H_1-receptors in histamine-induced increase in capillary permeability.

Introduction

Increase in capillary permeability observed during the acute inflammatory process has been ascribed to the liberation of chemical mediators. The role of histamine in increasing capillary permeability was first described by Eppinger (1913) and was subsequently confirmed by Sollmann & Pilcher (1917) and Dale & Richards (1918). Lewis's (1927) classical 'triple response' induced by pricking histamine into human skin has been shown to be similar to the response evoked by thermal, chemical, mechanical and electrical injury (Dekanski, 1947; Sevitt, 1957). Histamine has also been reported by Gaddum (1948) to produce leakage of circulating proteins and protein-bound dye into the tissues in many species including man. Since then, several investigators have confirmed the role of histamine in the vasodilatation and increase in capillary permeability effects characteristic of acute inflammation (Wilhelm, 1962; Lichtenstein, Plaut, Henney & Gillespie, 1973; Maling, Webster, Williams, Saul & Anderson, 1974). However, the nature of the receptors involved in the capillary permeability effects of histamine are not known. With the delineation of H_1- and H_2-receptors for the action of histamine, it is now possible to determine the nature of the receptor type involved in the effect of histamine on capillary permeability.

The present investigation was undertaken to study the effects of H_1- and H_2-receptor agonists and antagonists on capillary permeability by the dye diffusion technique.

Method

The present study was carried out in albino mice using the method of Whittle (1964) as modified by Macaraeg, Bianchine & Lazagna (1968). Healthy albino mice of either sex, weighing 20–25 g, were divided into groups of six animals. One group served as control and was injected with dye alone and other groups were injected with the dye, followed 5 min later by graded doses of histamine. Each animal was injected with 0.1 ml of 2% Evan's blue in the lateral tail vein and histamine was given intraperitoneally in graded doses of 0.75, 1.25, 2.5 and 5 μg as base. After half an hour of dye injection, the mice were killed by cervical dislocation and viscera were irrigated with 4–6 ml of distilled water over a clean petri-dish.

The irrigated fluid was filtered through glass wool and made up to 10 ml with distilled water and 0.1 ml of 0.1 N NaOH was added to clear the turbidity. The optical density of the fluid was determined at 590 nm with a spectrophotometer. The amount of dye which diffused out was calculated as μg/mouse and expressed as the increase times that in control animals. Similar studies were done with 2-methyl histamine (H_1-receptor agonist) and 4-methyl-histamine (H_2-receptor agonist).

The PD_{50} for mepyramine (the dose causing 50% reduction in the amount of dye diffusion produced by 2.5 μg histamine/mouse) was calculated and the effect of this dose (PD_{50}) was seen on dye diffusion induced by graded doses of histamine and 2-methyl histamine. Similarly, the effect of burimamide (in a dose equal to

the PD_{50} dose of mepyramine) alone and together with mepyramine was studied on histamine-induced dye diffusion. The antagonists were given orally, 30 min before the test.

Drugs employed were histamine dihydrochloride (Ward Blenkinsop Co.), mepyramine maleate (May and Baker, Bombay), burimamide, 2-methyl histamine hydrochloride and 4-methyl histamine (SKF). The doses of histamine and 2-methyl histamine refer to the base and those of other drugs to their salts.

Results

Effects of histamine, 2-methyl histamine and 4-methyl histamine on capillary permeability

Intraperitoneal administration of graded doses of histamine (0.75, 1.25, 2.5 and 5 μg/mouse) caused dose-dependent increases in dye-diffusion into the peritoneal cavity (Table 1). 2-Methyl histamine in graded doses (0.75–5 μg/mouse) also increased permeability but it was less potent than histamine (Table 2). On the other hand, graded doses of 4-methyl histamine (0.75–15 μg/mouse) caused very little increase in dye diffusion.

Role of histamine receptor antagonists on histamine induced dye diffusion

The PD_{50} of the H_1-receptor antagonist, mepyramine, was calculated from the dose-response curve as 13.18 mg/kg. This dose also significantly ($P<0.01$) decreased the amount of dye which diffused into the peritoneal cavity after other doses of histamine although the effect decreased with high doses of histamine (Table 1). In contrast, the H_2-receptor antagonist, burimamide, at the same concentration (13.18 mg/kg) afforded no significant protection against dye diffusion induced by the standard graded doses of histamine. Combined mepyramine and burimamide pretreatment produced greater protection than mepyramine alone but the difference was not significant.

Effect of mepyramine on 2-methyl histamine-induced dye diffusion

Mepyramine (13.18 mg/kg) pretreatment greatly reduced the amount of dye which diffused into the peritoneal cavity after the standard graded doses of 2-methyl histamine (Table 2). Results were highly significant ($P<0.01$).

Table 1 Effect of H_1- and H_2-receptor antagonists on dye diffusion induced by histamine

Histamine (μg)	*Dye diffusion values (× control) ± s.e.*			
	No pretreatment	*After mepyramine (M)*	*After burimamide (B)*	*After M and B*
0.75	1.7 ± 0.13	1.1 ± 0.03*	1.6 ± 0.06	1.0 ± 0.04*†
1.25	2.8 ± 0.34	1.6 ± 0.03*	2.6 ± 0.12	1.5 ± 0.14*†
2.50	4.8 ± 0.11	2.9 ± 0.06*	4.6 ± 0.18	2.5 ± 0.36*†
5.00	8.9 ± 0.22	7.5 ± 0.57*	8.7 ± 0.17	6.9 ± 0.48*†

Mepyramine and burimamide were given orally in doses of 13.2 mg/kg 30 min before histamine.
* Significant difference compared with histamine alone ($P<0.01$); † Difference not significant when compared with mepyramine pretreatment ($P>0.05$).

Table 2 Effect of mepyramine on dye diffusion induced by 2-methyl histamine

2-Methyl histamine (μg)	*Dye diffusion values (× control) ± s.e.*	
	No pretreatment	*After mepyramine*
0.75	1.6 ± 0.28	1.1 ± 0.10*
1.25	2.2 ± 0.10	1.3 ± 0.07*
2.50	3.0 ± 0.12	1.9 ± 0.13*
5.00	4.4 ± 0.22	3.2 ± 0.11*

Mepyramine was given orally in doses of 13.2 mg/kg 30 min before 2-methyl histamine.
* Significant difference compared with 2-methyl histamine alone ($P<0.01$).

Discussion

Although it has been proposed that histamine receptors in blood vessels may fully account for the capillary permeability induced by intraperitoneal administration of histamine (Dale & Richards, 1918; Lewis, 1927), the nature of these receptors is not known. A duality of cardiovascular histamine receptors was suggested by the work of Folkow, Haeger & Kahlson (1948). These investigators showed that the histamine-induced decrease of blood pressure in cats was only partially attenuated by large doses of mepyramine. Later on, with the discovery of specific H_2-antagonists, Black, Duncan, Durant, Ganellin & Parsons (1972) showed that the depressor effect of histamine can be blocked completely by a combination of mepyramine and burimamide. Similarly, Parsons & Owen (1973) demonstrated the role of both H_1- and H_2-receptors in the cardiovascular system of dog, cat and rabbit.

In the present work we have studied the nature of the receptors involved in the histamine-induced increase in capillary permeability of peritoneal blood vessels in albino mice. When histamine, and 2-methyl histamine (H_1-agonist) were injected (i.p.) in graded doses they produced increases in dye diffusion while 4-methyl histamine (H_2-agonist) had little effect. Therefore, the unavoidable inference is that H_2-receptors are not concerned in the increase of capillary permeability.

In another set of experiments, the effect of H_1- and H_2-receptor antagonists was studied on the capillary permeability induced by histamine and 2-methyl histamine. It is evident from Tables 1 and 2 that pretreatment with mepyramine afforded highly significant protection against increases in the capillary permeability induced by histamine and 2-methyl histamine. On the other hand, burimamide pretreatment (in doses equivalent to mepyramine) afforded no significant protection. Moreover, burimamide combined with mepyramine pretreatment also did not show any significantly greater protection than mepyramine alone against histamine-induced increase in capillary permeability. These experiments give further support to the suggestion that in the histamine-induced increase in capillary permeability, H_1-receptors play a major role and H_2-receptors have an insignificant role.

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References

BLACK, J.W., DUNCAN, W.A.M., DURANT, G.J., GANELLIN, C.R. & PARSONS, M.E. (1972). Definition and antagonism of histamine H_2-receptors. *Nature, Lond.*, **236**, 385–390.

DALE, H.H. & RICHARDS, A.N. (1918–19). The vasodilator action of histamine and of some other substances. *J. Physiol., Lond.*, **52**, 110–165.

DEKANSKI, J. (1947). The effect of severe burns and some protein precipitants on skin histamine in cats. *J. Physiol., Lond.*, **106**, 33–41.

EPPINGER, H. (1913). Über eine eigentumliche Hautreaktion, hervorgerufen durch Ergamin. *Wien. med. Wschr.*, **63**, 141.

FOLKOW, B., HAEGER, K. & KAHLSON, G. (1948). Observations on reactive hyperaemia as related to histamine, on drugs antagonising vasodilation induced by histamine and on vasodilator properties of adenosine triphosphate. *Acta physiol. scand.*, **15**, 264–278.

GADDUM, J.H. (1948). Histamine. *Br. med. J.*, **i**, 867–873.

LEWIS, T. (1927). *The Blood Vessels of the Human Skin and Their Responses*. London: Shaw and Son.

LICHTENSTEIN, L.M., PLAUT, M., HENNEY, C. & GILLESPIE, E. (1973). The role of H_2-receptors on the cells involved in hypersensitivity reactions. In *International Symposium on Histamine H_2-receptor Antagonists*. ed. Wood, C.J. & Simkins, M.A. pp. 187–203. Welwyn Garden City: Smith, Kline & French Laboratories Ltd.

MACARAEG, P.V.J. Jr., BIANCHINE, J.R. & LAZAGNA, L. (1968). Tolerance to drug induced writhing in mice. *J. Pharmac. exp. Ther.*, **161**, 130–140.

MALING, H.M., WEBSTER, M.E., WILLIAMS, M.A., SAUL, W. & ANDERSON, W. (1974) Inflammation induced by histamine, serotonin, bradykinin and compound 48/80 in the rat, antagonist and mechanism of action. *J. Pharmac. exp. Ther.*, **191**, 300–310.

PARSONS, M.E. & OWEN, D.A.A. (1973). Receptors involved in the cardiovascular responses to histamine, In *International Symposium on Histamine H_2-receptor Antagonists*. ed. Wood, C.J. & Simkins, M.A. pp. 127–136. Welwyn Garden City: Smith, Kline & French Laboratories Ltd.

SEVITT, S. (1957). *Burns: Pathology and Therapeutic Implications*. London: Butterworth.

SOLLMANN, T. & PILCHER, J.D. (1917). Endermic reactions. *J. Pharmac.*, **9**, 309–340.

WHITTLE, B.A. (1964). The use of changes in capillary permeability in mice to distinguish between narcotic and non-narcotic analgesics. *Br. J. Pharmac. Chemother.*, **22**, 246–253.

WILHELM, D.L. (1962). The mediation of increased vascular permeability in inflammation. *Pharmac. Rev.*, **14**, 251–280.

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