Agents and Actions, vol. 18, 5/6 (1986)

0065-4299/86/060504-04$2.30

Histamine-induced microvascular permeability increases in hamster skin: a response predominantly mediated by H_2-receptors

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Abstract

The pharmacology of histamine-induced increases in cutaneous microvascular permeability was investigated in the hamster by (a) examining the effects of cimetidine and pyrilamine on the increase in microvascular permeability evoked by graded doses of intradermally-injected histamine, and (b) comparing the cutaneous microvascular permeability responses to graded doses of impromidine (0.1–100 μg), dimaprit (1–100 μg) and β-histine (0.1–100 μg). Pretreatment with pyrilamine (0.1 mg/kg i.v. bolus injection) did not reduce the increase in microvascular permeability produced by any dose of histamine. In contrast, cimetidine (0.5 mg/kg/min i.v. infusion) significantly inhibited the microvascular permeability responses to 10 and 100 μg histamine. Although neither cimetidine nor pyrilamine significantly altered the microvascular permeability response to 0.1 and 1 μg histamine, inhibition was afforded by a cimetidine-pyrilamine combination. These results suggest a predominantly H_2-receptor mediated phenomenon with a minor H_1-receptor mediated component. Studies with the H_2-receptor agonists impromidine and dimaprit and the H_1-receptor agonist β-histine provide further support for this contention. Dimaprit and impromidine caused a dose-dependent increase in cutaneous microvascular permeability, but betahistine produced only a relatively modest response. In other laboratory species, increased cutaneous microvascular permeability appears to be mediated solely by H_1-receptors. Therefore, the hamster skin appears unique with respect to the pronounced H_2-receptor involvement in histamine-induced microvascular permeability changes.

Introduction

It has long been recognized that histamine causes cutaneous inflammation [1], and the function of H_1- and H_2-receptor subtypes in mediating the effects of histamine on the cutaneous microvasculature has been extensively studied. In both guinea pigs [2, 3] and man [4–6], the cutaneous vasodilator response to histamine involves both H_1- and H_2-receptor stimulation. However, a divergence between laboratory animal species and man appears to exist with respect to increases in microvascular permeability. Although H_2-receptor involvement in histamine-induced wheal formation in man has been suggested [6], the increase in cutaneous microvascular permeability produced by histamine in guinea pigs [2, 3] and murine species [7, 8] appears to be entirely mediated by H_1-receptors. Thus, a convenient animal model has not been available for studying H_2-receptors associated with microvascular permeability increases in the skin. The studies reported herein describe a distinct species difference where the microvascular permeability response to histamine in hamster skin appears to be predominantly mediated by H_2-receptors.

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Methods and materials

Methods

Syrian hamsters of either sex and weighing 100–200 g were anaesthetized with sodium pentobarbital (60 mg/kg i.p.). A jugular vein was cannulated to permit intravenous administration of drug solutions and radioisotopes for quantitative measurement of cutaneous microvascular permeability. ^{125}I-bovine serum albumin (10 μCi/ml × 0.1 ml), ^{51}Cr-erythrocytes [2] (50 μCi/ml × 0.2 ml) and Evans blue (2.5% w:v × 0.1 ml) were administered intravenously 15 min before intradermal injection of histamine or histamine-like agonists. Histaminergic solutions were injected into the left ear in a 2 μl volume, the right ear received 2 μl saline as a control. The animals were sacrificed 15 min later by intravenous sodium pentobarbital overdose. The ears were then surgically excised and counted together with the appropriate 0.2 ml blood sample in a γ counter (Beckman 8500). Tissue and blood samples were then dried to constant weight at

55–60° C and extravascular albumin content was calculated according to a previously described method [2]. Extravascular albumin content (ml/g dry weight of tissue) was finally expressed as the difference between test and control skin samples.

Cimetidine (5 mg/ml) was administered by continuous intravenous infusion at 100 μl/kg/min (Harvard compact infusion pump). Pyrilamine (0.1 mg/kg) and the radioisotopes were administered as bolus injections immediately before connection of the jugular cannula to the infusion pump. Thus, pyrilamine was injected and cimetidine infusion was commenced at approximately 15 min before intradermal histamine injection.

Materials

Histamine dihydrochloride (Sigma), dimaprit dihydrochloride (SK&F), impromidine trihydrochloride (SK&F) and betahistine dihydrochloride (SK&F) were dissolved in saline and the pH of the solutions was adjusted to 7.0. Pyrilamine maleate (Hexagon) was also dissolved in saline. Cimetidine base (SK&F) was dissolved in 0.1 N HCl and the pH of the solution was adjusted to 6.5. A solution of saline at pH 6.5 was prepared as a vehicle control for cimetidine infusion.

^{125}I-bovine serum albumin and $Na_2\ ^{51}CrO_4$ were purchased from New England Nuclear. Sodium pentobarbital was purchased from Carter-Glogau.

Statistical analysis

Statistical analysis was by analysis of variance at each histamine dose. A p value of 0.05 or less was considered statistically significant.

Results

Histamine produced a dose-dependent increase in cutaneous microvascular permeability in the hamster ear (Fig. 1). Pretreatment with i.v. pyrilamine (0.1 mg/kg) did not reduce the increase in microvascular permeability produced by any dose of histamine over the 0.1–100 μg range. In contrast, cimetidine (0.5 mg/kg/min) significantly inhibited the microvascular permeability responses to 10 and 100 μg histamine (Table I), but the addition of pyrilamine did not provide any further reduction. The profile of antagonist activity, however, differed with the 0.1 and 1 μg doses of histamine. The cimetidine-pyrilamine combination appeared to be the only effective pretreatment and this was reflected as a significant reduction in the cutaneous microvascular permeability response to 1 μg histamine. No other significant reductions were obtained.

The effect of histamine H_2-receptor agonists on cutaneous microvascular permeability in the hamster is depicted in Fig. 2. A dose-dependent microvascular permeability response was produced by both dimaprit (Fig. 2a) and impromidine (Fig. 2b). In contrast, the relatively selective H_1-receptor agonist betahistine produced only a very modest increase in cutaneous microvascular permeability at all doses employed (Fig. 3).

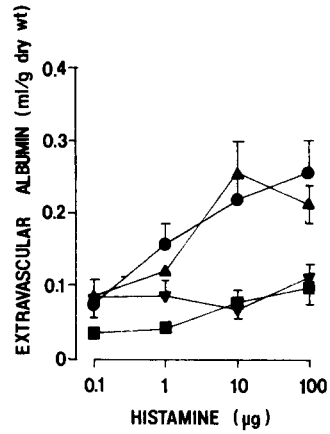

Figure 1
Effect of cimetidine (0.5 mg/kg/min) (▼), pyrilamine (0.1 mg/kg) (▲) and a cimetidine-pyrilamine combination (■) on the increase in cutaneous microvascular permeability evoked by graded doses of histamine. The group that received saline i.v. injection and infusion as a control is represented by (●). Points are mean ± S.E.M. Statistical analyses are given in Table 1. The number of animals in each treatment group was as follows: saline, n = 16; cimetidine, n = 16; pyrilamine, n = 12; cimetidine-pyrilamine, n = 8.

Table 1
Effect of cimetidine, pyrilamine and a cimetidine-pyrilamine combination on the increase in microvascular permeability produced by intradermal injection of graded doses of histamine into the hamster ear. Saline represents the control group which received i.v. injection and infusion of vehicle solutions. $*p<0.05$, $**p<0.01$, NS is nonsignificant

Treatment comparison	*Histamine (μg)*			
	0.1	*1*	*10*	*100*
Saline vs Pyrilamine	NS	NS	NS	NS
Saline vs Cimetidine	NS	NS	**	**
Saline vs Cimetidine-Pyrilamine	NS	*	**	**
Pyrilamine vs Cimetidine	NS	NS	**	**
Pyrilamine vs Cimetidine-Pyrilamine	NS	NS	*	**
Cimetidine vs Cimetidine-Pyrilamine	NS	NS	NS	NS

Discussion

Histamine-induced increases in cutaneous microvascular permeability in the hamster appear to be mediated predominantly by H_2-

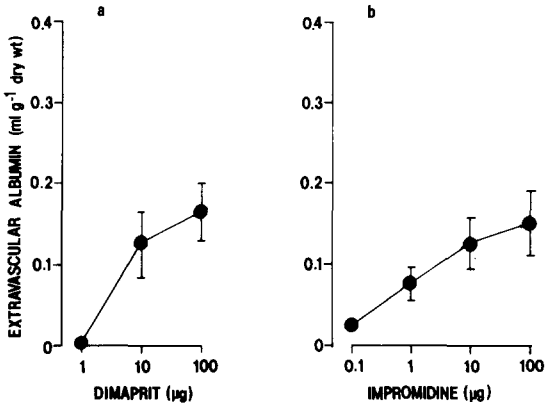

Figure 2
Effect of graded doses of (a) dimaprit and (b) impromidine on cutaneous microvascular permeability. Points are mean ± S.E.M.; n = 8.

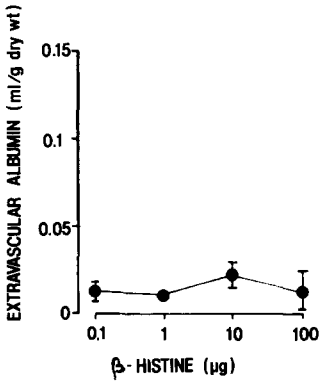

Figure 3
Effect of graded doses of betahistine on cutaneous microvascular permeability. Points are mean ± S.E.M.; n = 8.

receptors, according to the following evidence:

(1) Cimetidine reduced the microvascular permeability response to histamine, whereas pyrilamine was ineffective.
(2) The highly selective H_2-receptor agonists dimaprit and impromidine [9] caused a dose-dependent increase in cutaneous microvascular permeability, whereas the relatively selective H_1-receptor agonist betahistine [9] had only a very modest effect.

The results of these studies in the hamster are distinctly different from those obtained in other species. Cimetidine does not reduce the increase in cutaneous microvascular permeability produced by histamine in the guinea pig [2, 3], the rat [7] or the mouse [8]. However, a continuous infusion of cimetidine, at a dose that would specifically block H_2-receptors [10], antagonized histamine-induced changes in microvascular permeability in hamster skin. In contrast, pyrilamine, at a dose that would abolish the cutaneous microvascular permeability response to histamine in the guinea pig [11], was inactive in the hamster. H_1-receptor blockade also reduces increased microvascular permeability elicited by histamine in rat [7] and mouse skin [8]. Dimaprit does not alter cutaneous microvascular permeability in the guinea pig [3], which provides additional evidence for an exclusive H_1-receptor mediated response in this species. In the rat, dimaprit does increase microvascular permeability, but the response has proved to be independent of H_2-receptors and appears consistent with an indirect action caused by cutaneous mast cell degranulation [7]. The absence of an H_2-receptor mediated vasopermeability response in rat skin was confirmed by the inactivity of impromidine [7]. In view of the nonspecific cutaneous effects of dimaprit that seem to occur in some species, both dimaprit and impromidine were examined for the hamster studies. Since dimaprit and impromidine caused a dose-dependent increase in cutaneous microvascular permeability in the hamster, supportive evidence for H_2-receptor involvement was provided. The relatively selective H_1-receptor agonist betahistine produced a minimal effect in hamster skin, which further indicates only very modest H_1-receptor involvement. No apparent dose-response relationship for betahistine occurred. In view of the residual partial agonist activity of betahistine at H_2-receptors reported in other tissues [9], a microvascular permeability response might be expected at the highest doses. It seems that perhaps greater selectivity for H_1-receptors is achieved in the hamster cutaneous microvasculature.

Although the evidence indicates that increased cutaneous microvascular permeability in the hamster is predominantly mediated by H_2-receptors, H_1-receptors may also participate to a lesser extent. In addition to the small effect of betahistine, a further suggestion of H_1-receptor involvement was afforded by the profile of antagonism for cimetidine and pyrilamine vs the lower doses of histamine, which was characteristic of a single response being mediated by both H_1- and H_2-receptors. Thus, cimetidine and pyrilamine alone had little or no effect and the

greatest inhibition was achieved with the cimetidine-pyrilamine combination. It has been similarly demonstrated that substantial blockade of histamine-induced decreases in systemic blood pressure [12] and cutaneous vasodilatation [2] requires a combination of H_1- and H_2-receptor antagonists.

Since the exudative response occurred within 15 min, the increase in cutaneous microvascular permeability elicited by histamine in the hamster is likely to result from a direct myotropic action involving the post-capillary venules. In the hamster cheek pouch preparation, the plasma leakage evoked by histamine and peptidoleukotrienes exhibits a similar early onset and is independent of polymorphonuclear leukocyte involvement [13]. The hypothesis that histamine and peptidoleukotrienes increase microvascular permeability by a common pathway involving the endothelial cell whereas the response to LTB_4 is relatively delayed and leukocyte-dependent [13] is also indirectly supported by studies comparing the effect of peptidoleukotrienes and LTB_4 on conjunctival microvascular permeability in the hamster [14].

In summary, the microvascular permeability response in hamster skin seems unique in that it appears to be mediated predominantly by H_2-receptors. This provides the basis of an animal model for evaluating the potential utility of therapeutic approaches for blocking the putative H_2-receptor component of histamine-induced cutaneous eodema in man [6].

Acknowledgment

The authors wish to express their gratitude to D. McDonald for preparing the manuscript and figures.

Received 1 October 1985; accepted 21 February 1986

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