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Histamine$_1$–histamine$_2$ antagonism: Effect of combined clemastine and cimetidine pretreatment on allergen and histamine-induced reactions of the guinea pig lung *in vivo* and *in vitro*

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Abstract

In a preliminary study high doses of the H_1-antagonist clemastine (clem) and the H_2-antagonist cimetidine (cim) were used in order to detect the side effects of both drugs on allergic reactions. After pretreatment with clem or clem/cim different guinea pigs were challenged with either OA or histamine. Bronchial obstruction was measured by body plethysmography using a new parameter ('compressed air'). Pretreatment with clem/cim in high doses protected guinea pigs against OA-induced bronchial obstruction much more effectively than H_1-receptor antagonism alone; lower cim doses produced insignificant effects. In histamine-challenged animals cim showed no protective effects. *In vitro* clem/cim caused a marked reduction of histamine release measured in perfused lungs from 16.9 ± 4.2 ng/ml (eight control cases) to 2.8 ± 1.7 ng/ml ($n = 8$).

Our preliminary data suggest that high doses of clem/cim can protect sensitized guinea pigs against allergen-induced bronchial obstruction by inhibiting histamine release.

Introduction

Data on the various pharmacological properties of histamine receptor antagonists [1–12] as well as some surprising observations [13] suggest that clemastine combined with cimetidine may have an effect on allergic reactions other than by H_1–H_2-receptor antagonism. In order to detect these side effects, experiments were performed on guinea pigs *in vivo* and *in vitro* using high (non-therapeutic) doses of clemastine and cimetidine.

Materials and methods

Animals

41 male Perlbright white guinea pigs weighing 200–250 g were obtained from Ivanovas (D 7967 Kißlegg/FRG) and sensitized by intraperitoneal and intramuscular injection of ovalbumin (Sigma, grade III). Allergen and histamine challenges were performed 4 and 5 weeks after immunization.

Inhalative challenge

Lung function tests were performed, as previously described [14], on intact spontaneously breathing animals which were not treated with any tranquilizing or anaesthetizing drug. 1 ml of the test solution (5% ovalbumin or 0.5% histamine-dihydrochloride in saline) was aerosolized using an ultrasonic nebulizer (Heyer, USE 77, Bad Ems, FRG) in a 10 l air-containing box. The tested animal was allowed to breathe in this inhalation box for a definite time according to the experimental protocol.

Experimental design

According to a randomized crossover protocol eight Perlbright white guinea pigs were pretreated with either clemastine (0.12 mg/kg body weight) or clemastine and cimetidine (0.12 and 30 mg/kg respectively) intraperitoneally. Ten min later the animals were challenged with ovalbumin in two steps. At first for 150 seconds, 10 minutes later for another 210 seconds (see Fig. 1). Three days later

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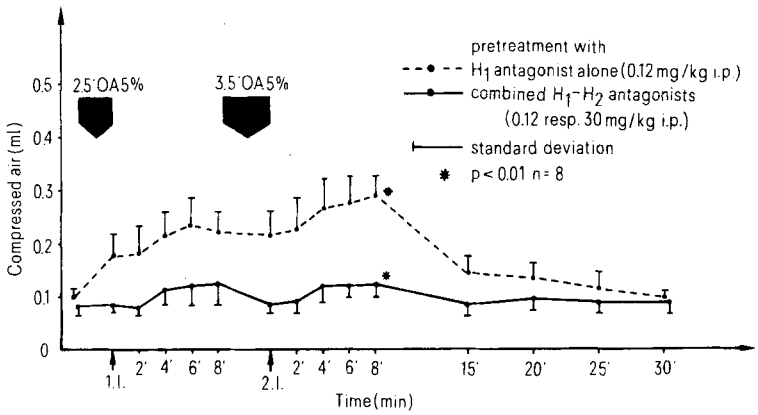

Figure 1
Ovalbumin (OA)-induced bronchial obstruction measured as compressed air (ml) in eight sensitized guinea pigs pretreated either with clemastine or clemastine and cimetidine (high dose).

the experiments were repeated on the same animals by changing the mode of pretreatment (animals which had first been pretreated with clemastine received clemastine/cimetidine and vice versa).

Six other guinea pigs pretreated with clemastine (0.12 mg/kg) or clemastine combined with cimetidine (0.12 and 3 mg/kg respectively) were challenged with allergen in the same manner. Seven animals were challenged by histamine inhalation after pretreatment with either clemastine (0.12 mg/kg) or clemastine combined with cimetidine (0·12 and 10 mg/kg respectively) in a similar crossover protocol. The histamine challenges were performed in three steps: 30 seconds at time 0, 10 and 20 minutes (see Fig. 2).

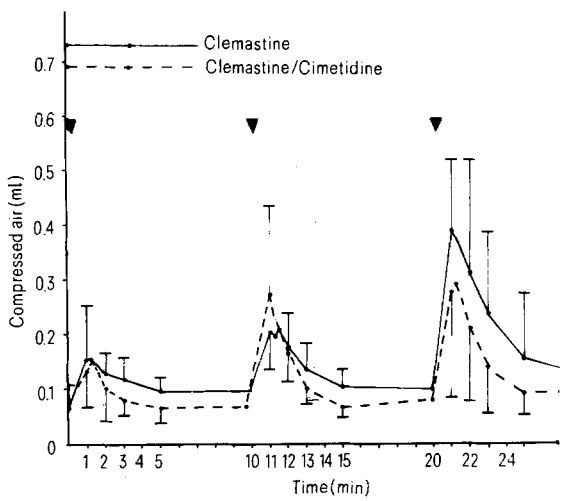

Figure 2
Histamine-induced bronchial obstruction in seven guinea pigs pretreated either with clemastine or clemastine and cimetidine.

In situ lung perfusion

After a lethal dose of ether the thoraces of sixteen guinea pigs were opened and their lungs perfused *in situ* with oxygenated (95% O_2, 5% CO_2) Tyrode solution via the right and left heart ventricles at a flow rate of 5 ml/min. The perfusates were sampled in fractions of 10 ml (=2 min) and assayed spectrofluorometrically for histamine content as described previously [15]. Allergen challenge was performed with 10 mg ovalbumin given once in 0.1 ml saline into the perfusion medium. In eight cases Tyrode solution contained clemastine and cimetidine in high concentrations (10 μg/ml and 1000 μg/ml respectively).

For control purposes – possible interference of clemastine and cimetidine with the histamine assay – the lungs of four animals were perfused with Tyrode solution containing histamine (20 ng/ml) and human albumin (2 mg/ml). Clemastine and cimetidine were added at varying doses and histamine and albumin concentrations of the lung perfusates were measured.

Drugs

Ovalbumin (grade III for immunization and inhalation, grade II for *in vitro* histamine release), as well as histamine dihydrochloride, were purchased from Sigma (FRG), commercial clemastine preparation from Sandoz, and commercial cimetidine preparation from Smith & Kline (both FRG).

Statistics

All figures and tables show means and standard deviations; the significance of differences between means were estimated using Student's *t*-test.

Results
In vivo

Pretreatment with clemastine and cimetidine in high doses (0.12 and 30 mg/kg body weight respectively) protected eight sensitized guinea pigs against allergen-induced bronchial obstruction much more effectively than histamine receptor antagonism alone (Fig. 1). A lower etidine dose (3 mg/kg) produced insignificant effects in six allergen-challenged guinea pigs (Table 1).

Table 1
Inhalative challenge of sensitized guinea pigs pretreated either with clemastine (0.12 mg/kg i.p.) or with clemastine combined with cimetidine (0.12 and 3 mg/kg i.p. respectively). The differences between means of compressed air are below 0.05 ml and are not significant. The experimental protocol was identical to that shown in Figure 1.

Pretreatment		Compressed air (0.01 ml) (time = minutes)												
		0	1	2	4	6	8	0	1	2	4	6	8	15
Clemastine ($n = 6$)	$\bar{x}$	9	15	17	14	13	10	13	20	18	15	13	12	7
	SD	3	14	12	7	8	5	10	12	14	11	8	6	2
Clemastine/cimetidine	$\bar{x}$	10	18	19	19	17	14	13	19	19	19	16	13	8
($n = 6$)	SD	2	11	10	7	5	3	2	10	9	8	7	6	2
	$\Delta\bar{x}$	−1	−3	−2	−5	−4	−4	0	1	−1	−4	−3	−1	−1

Significant differences between H_1- and combined H_1–H_2-receptor antagonism in seven histamine-challenged guinea pigs were not observed (Fig. 2). As demonstrated by the large standard deviations in the figure the animals had a large variance in their asthmatic responses to histamine.

In vitro

High doses of clemastine combined with cimetidine (10 and 1000 µg/ml respectively) caused a marked reduction in histamine release from the allergen-challenged guinea pig lung perfused *in situ* (Fig. 3). The peak histamine concentration of eight clemastine/cimetidine-treated lungs had a mean value of 2.8 (±1.7) ng/ml, whereas in eight control experiments a mean value of 16.9 (±4.2) was measured. The difference between both means was significant ($p < 0.01$).

Four lungs were perfused with Tyrode solution containing 20 ng of histamine per millilitre (Fig. 4). A rapid decrease of histamine concentration was observed after passing through the lung; in other words, histamine given to the lung as a constant infusion rapidly disappears from the circulation. This effect was antagonized in a dose-dependent manner by combined H_1-/H_2-receptor antagonists.

The plasma exudate was estimated in the same experiments by adding human albumin (20 mg/ml) to the perfusion medium and measuring its concentration in the perfusates after passing through the lung. The combined H_1–H_2-receptor antagonists inhibited plasma exudation similarly to histamine disappearance in a dose-dependent manner (Table 2).

Discussion

High doses of clemastine combined with cimetidine protected sensitized guinea pigs against allergen-induced bronchial obstruction much more effectively than histamine$_1$ (H_1)-receptor–antagonism alone. This effect seems to be caused at least in part by inhibition of mediator release, as demonstrated in our *in vitro* experiments. Clemastine and cimetidine in high doses markedly depressed the allergen-induced histamine release of allergen-tested guinea pig lungs (Fig. 2). In a dose-dependent manner this treatment inhibited the disappearance of exogenous histamine from the circulation (Fig. 3). Because of this well-known phenomenon [19] a possible methodological error caused by the interference of clemastine and cimetidine with the assay of

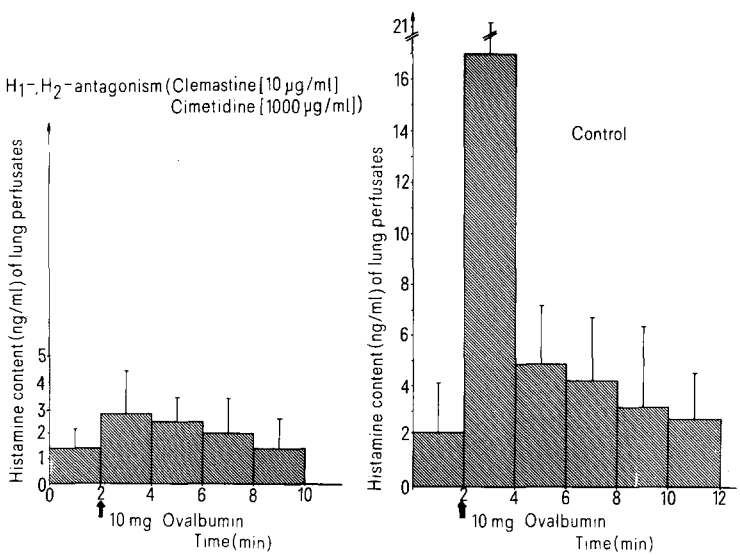

Figure 3
Effect of clemastine and cimetidine on allergen-induced histamine release from perfused guinea pig lungs.

Table 2
Dose-dependent inhibition of histamine-induced plasma exudation by clemastine and cimetidine. The lungs of four guinea pigs were perfused with Tyrode solution containing 20 ng histamine hydrochloride and 20 mg human albumin per ml. Whole protein content of lung perfusates was measured using the Biuret method. Clemastine and cimetidine were added to the perfusion medium in three doses: (a) 0.1 and 10 μg/ml respectively, (b) 1 and 100 μg/ml respectively, (c) 10 and 1000 μg/ml respectively. Note that all drugs exert their effects with a time delay of 2 minutes.

	Time										
	2	6	8	10	12	14	16	18	20	22	24
Clemastine/cimetidine dose			a	a		b	b		c	c	
Protein content (g/l)	19.5	18.0	15.8	17.5	16.8	13.4	17.5	17.0	16.2	17.8	18.0

histamine in the perfusates can be discounted. The prolonged persistence may be caused by an inhibition of histaminase (see Ref. [3]) and/or inhibition of plasma exudation (Table 2).

We were unable to demonstrate different effects between H_1 and H_1–H_2-receptor antagonism in seven histamine-challenged animals. This was due to the great variability in the animals' response to histamine. This well-known biological phenomenon [16, 17] seems to be the result of different histamine receptor densities in the lungs of different animals of the same species. We observed, however, a tendency towards a larger effect of combined H_1–H_2 antagonism, but further research is necessary.

Our findings are not consistent with the classical view on the pharmacological properties of H_1- and H_2-receptors. The actions of histamine on both receptor types in different tissues and species are well documented [18, 19], the negative feedback mechanism by which histamine depresses further histamine release from human basophils is mediated by H_2-receptors [20]. In the guinea pig lung the *in vitro* stimulation of H_1- and H_2-receptors produces opposite effects. Stimulation of H_1-receptors results in increased cGMP and prostaglandin $F_{2\alpha}$ synthesis, whereas prostaglandin E and cAMP synthesis increases after H_2-stimulation ([8], see also [2]). *In vitro* experiments on human lung fragments revealed similar results [7]. H_2-receptor antagonism with cimetidine increases the histamine release from allergen-challenged guinea pig lungs 116]. This observation, however, is in contrast to those of other investigators who were unable to influence mediator release from human lungs by cimetidine [7].

Similar opposite *in vivo* effects of H_1- and H_2-receptor stimulation or antagonism have been observed in guinea pigs, dogs and man.

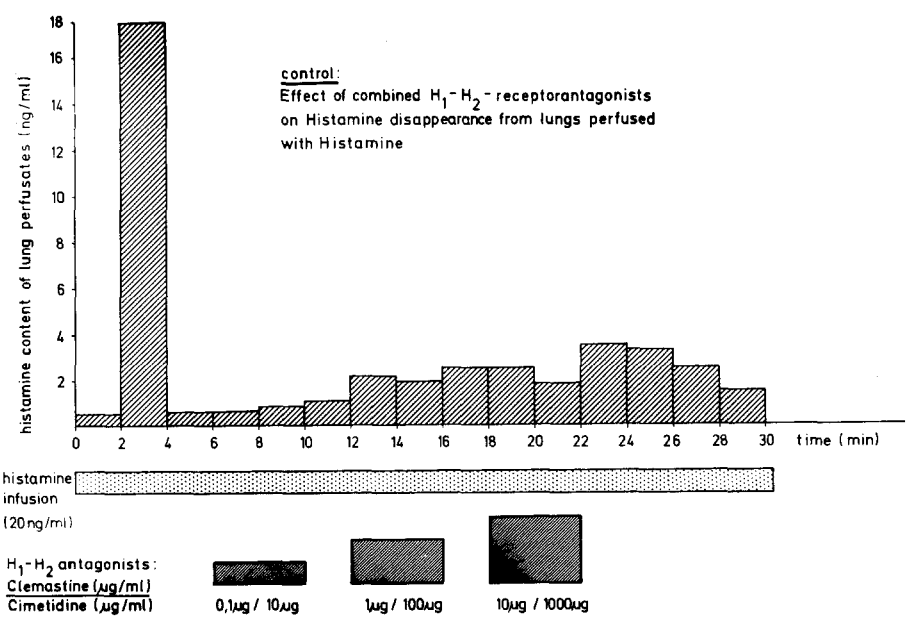

Figure 4
Effect of clemastine and cimetidine on histamine disappearance from the circulation of guinea pig lungs perfused with histamine. Note that all drugs exert their pharmacological effects 2 minutes after they have been added to the perfusion medium!

In guinea pigs, cimetidine in a similar dose to that which we used in our experiments (28.8 mg/kg i.v.) increased antigen- and histamine-induced bronchial obstruction [6]. Similarly both H_2-receptor antagonists metiamide and burimamide increased the severity of systemic anaphylaxis in guinea pigs [4]. Cimetidine, however, produced no such effects [4].

In dogs, H_2 blockade by cimetidine significantly potentiated the animals' pulmonary response to aerosol histamine [21].

Finally, in man, an augmentation of histamine-induced bronchial obstruction was observed after pretreatment with cimetidine in therapeutic doses in some cases; in most cases, however, this treatment was ineffective [10, 22, 24]. Allergen-induced bronchial obstruction was not influenced by cimetidine [10]. Compared to such data, our findings seem to be paradoxical.

There are, however, some pharmacological differences between the three known H_2-receptor antagonists: burimamide, e.g., depressed thromboxane B_2 synthesis in human platelet microsomes, whereas metiamide and cimetidine did not [1]. As mentioned above, cimetidine did not alter the pulmonary response to allergen – examined *post mortem* as 'relaxation volume' – whereas metiamide and burimamide markedly increased these reactions [4].

There are also reports on *supra-additive* effects of *combined* H_1–H_2-receptor antagonism, e.g. during infusion of histamine to normal and allergic asthmatics [23] or during skin testing of atopics with either allergen or histamine [13].

Histamine infusions to normal and allergic asthmatics caused, dose-dependent increases in pulse rate, pulse pressure, skin temperature and headache which were neither affected by H_1- nor by H_2-receptor antagonism. All symptoms were markedly reduced after combination of an H_1-receptor antagonist (hydroxyzine) with cimetidine in both normal and allergic individuals [23].

H_1 blocker alone significantly decreased histamine and allergen-induced wheal and flare reactions and did not alter delayed cutaneous reactions (the latter being most likely caused by secondary inflammatory events [25]). When cimetidine was combined with H_1 blocker, further reduction of histamine- and allergen-induced immediate reactions occurred. This combination also suppressed delayed cutaneous reactions totally in six out of eight patients. Cimetidine pretreatment alone affected neither allergen-induced immediate and delayed reactions nor histamine-induced skin reactions [13].

These observations could be explained in part by our *in vivo* and *in vitro* experiments – despite species and organ differences.

Perhaps allergic diseases may be effectively treated with combined H_1–H_2-receptor antagonists after further research [13]. In pseudo-allergic reactions during anaesthesia this treatment has been well established [26, 27]. Therapeutic doses of combined H_1–H_2-receptor antagonists, however, did not inhibit histamine release induced, e.g. by haemaccel [27].

Acknowledgments

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Role of histamine in the spasmogenic effect of the complement peptides C3a and C5a-desArg (classical anaphylatoxin)

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Abstract

The role of endogenous histamine in the spasmogenic effect of the complement-derived peptides C3a and C5a-desArg (isolated from yeast-activated hog serum) was studied in strips of terminal guinea-pig ileum. The effect of C3a is apparently histamine-independent; it neither induces histamine release from the test organ nor is its spasmogenic action inhibited by the H_1-antihistaminics pheniramine and triprolidine, used in concentrations effective against histamine. However, endogenous histamine may be involved in the spasmogenic effect of C5a-desArg; when applied repeatedly C5a-desArg induces histamine release during its first and second application. Furthermore, both H_1-antihistaminics inhibited C5a-desArg-induced contractions considerably, though less efficiently than those of added histamine.

Introduction

The complement-derived peptides C3a and C5a-desArg, the latter being identical with classical anaphylatoxin [1, 2], are either generated locally where they act as phlogistic mediators (for review see [3]), or they are formed systemically in the course of gross intravascular complement activation. In the latter case, they can induce circulatory and respiratory disturbances by increasing adhesion of leukocytes to vessel walls, by causing leukocyte aggregation and by exerting spasmogenic actions. Spasmogenicity is usually measured by bioassay on pieces of isolated guinea-pig ileum. This effect has been assumed to be mediated by endogenous histamine liberated by the complement peptides. The assumption was based on two observations, namely that the peptides induce histamine release from mast cells and basophils [4–7] and that the spasmogenic effect of classical anaphylatoxin was blocked by H_1-antihistaminics [8–11] (for older literature see [12]). On the other hand, histamine-independent effects of classical anaphylatoxin were suggested since it also contracted histamine-insensitive organs such as rat duodenum, ileum, colon, uterus or strips of pulmonary artery and that neither these effects nor that on guinea-pig uterus were inhibited by H_1-antihistaminics [13–15]. Furthermore, in guinea-pig ileum the histamine-releasing effect of this peptide decreased much earlier than its spasmogenic effect after repeated applications [16].

In this study we have re-evaluated the participation of histamine in the spasmogenic action of C5a-desArg and compared it with C3a. Because in most former studies anti-