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BRONCHIAL REACTIVITY TO INHALED
HISTAMINE IN ASTHMATIC PATIENTS,
BEFORE AND AFTER ADMINISTRATION OF
ATROPINE, PHENTOLAMINE OR
DISODIUM CROMOGLYCAT

By

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The normal bronchial muscle tonus is chiefly the result of an interaction between parasympathetic, mainly bronchoconstrictive, activity and sympathetic dilating influences. Mechanical or chemical stimulation of the irritant receptors in the bronchial tree can cause vagally mediated reflex bronchoconstriction. The sympathetic and catecholamine induced bronchodilatation is mediated via beta-receptors in the bronchial wall. In addition to the vagally mediated reflex, bronchoconstriction can also arise from vagus independent direct influence on the smooth muscle of mechanical and chemical stimuli or of pharmacologic mediators liberated in connection with allergic reactions. Stimulation of the alpha-receptors in the bronchial wall results in a weak bronchoconstriction. Bronchodilatation which chiefly arises through stimulation of the beta-receptors, can also be aroused by repression of the vagus from stretch- or inflation-receptors in the lungs (25, 33).

Bronchial hyperreactivity to mechanical and chemical stimuli is a characteristic feature of both extrinsic and intrinsic asthma as well as of many cases of chronic bronchitis (5, 24, 28, 31). The degree of such unspecific hyperactivity can be

determined by measuring the sensitivity to inhaled solutions of histamine or acetylcholine. It is not fully clear if this increased reactivity of the bronchial tree in asthmatics is caused only by sensitized irritant receptors or if other mechanisms regulating the bronchial muscle tonus are also engaged; such as, for example, a functional imbalance between the adrenergic receptors in the airways.

Atropine more or less blocks the effect of inhaled acetylcholine (9). In many cases of asthma, on the other hand, the effect of inhaled histamine is not modified by atropine (10). In other cases again there is a partial blockade (23). The bronchoconstriction due to inhaled histamine thus seems to be only partly mediated via the cholinergic pathway.

Szentivanyi (27) has presented a theory that the cause of bronchial hyperreactivity is a partial blockade of the beta-receptors depending on an inborn or acquired defect in the adenylcyclase—cyclic AMP system.

In studies on human bronchial muscle *in vitro* Simonsson et al. have shown (25) that if the beta-receptors are blocked, a stimulation of the alpha-receptors gives rise to bronchoconstriction, which can be completely repressed by an alpha-receptor blocker. The same investigators, as well as de Kock (12) and later Orehek (20) and Patel & Kerr (21) have, in human *in vivo* studies, confirmed the bronchoconstrictive effect of alpha-receptor stimulation after beta-receptor blockade. Kerr et al. (11) have demonstrated that bronchoconstriction provoked by intravenous histamine infusion in asthmatics fails to appear if the patients are pretreated with an alpha-receptor blocking agent, or disodium cromoglycate. Similarly Gaddie et al. (8) have shown that bronchoconstriction induced by inhaled histamine was significantly reduced by an alpha-receptor blocking drug.

The aim of the present investigation was to study to what extent the bronchial reactivity to inhaled histamine chloride solution in a number of patients with asthma could be modified by pretreatment with atropine, phentolamine or disodium cromoglycate.

PATIENTS

In 19 patients (6 women and 13 men, age 18-52 years), with extrinsic (8) and intrinsic (11) asthma of intermittent type, the degree of bronchial reactivity was determined by inhalation of a histamine aerosol in rising concentrations up to the maximum tolerance threshold. All patients were subjectively free from asthma at the time of study. None were taking corticosteroids. Neither was any bronchodilating agent taken during the last 6 hours before the study which, in the majority of the cases, took place at 9.30 a.m.

METHODS

Airway resistance and simultaneous lung volume were measured in a whole body pletysmograph before and within the 2 minutes after each provocation. The airway conductance i.e. the inverted value from airway resistance is expressed as airway conductance/thoracic gas volume (G_A/TGV) to correct for small variations in lung volume during testing (2). The mean of 2-3 readings of G_A and TGV was calculated. The conductance per liters BTPS thoracic gas volume was $0.31 \pm 0.05 \text{ l} \times \text{cm H}_2\text{O}^{-1} \times \text{sec}^{-1}$ (mean $\pm$ S.E. of mean) in 10 healthy controls. Directly after plethysmographic measuring the peak expiratory flow (PEF) was determined by means of a Wright's peak flow meter. The best of 2-3 exhalations was taken as the patient's PEF value. The lowest concentration that produced a 50 per cent or greater reduction of G_A , and a 10 per cent or greater reduction of PEF was regarded as the patient's histamine threshold.

A stock solution of 64 mg histamine chloride per ml saline was diluted in isotonic NaCl in such way that each concentration contained half the quantity of histamine chloride of the previous one, down to 0.063 mg/ml.

The histamine aerosol was inhaled for 30 seconds (with ten breaths on average) by means of a de Vilbiss spray no. 40, operated with compressed air at a flow rate of 6 liters per minute. The patients inhaled normal tidal volumes from the nebulizer. After registration of the resting values of G_A and PEF, the test was started with inhalation of saline and, if no reduction of G_A or PEF was recorded, the challenge began with the lowest concentration of histamine chloride (0.063 mg/ml). If still no change in the lung function values could be established, the inhalation was continued with the next highest concentration of histamine chloride and so on up to the tolerance limit (Fig. 1). The threshold value for healthy subjects is, when using this technique, $\geq 32 \text{ mg histamine chloride per ml}$ (31). The histamine threshold was recorded under the same conditions, at the same time of day, a week later (32). On this second occasion, atropine, phentolamine or disodium cromoglycate were administered before the histamine inhalation as follows:

CASE NO. 3

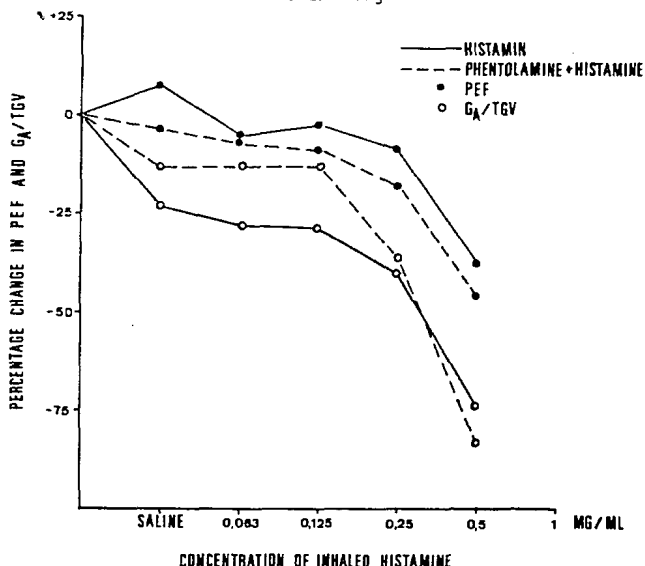


Fig. 1.

Provocation tests with histamine inhalation in one asthmatic subject before and after injection of phentolamine. Change in peak expiratory flow (PEF) and airway conductance/thoracic gas volume (G_A/TGV) as percentage of initial values.

Test No. 1

In 6 cases atropine sulphate (0.5 mg/ml) was inhaled for 30 seconds before each 30 seconds of histamine inhalation. Approximately 0.05 mg atropine sulphate was inhaled each time.

Test No. 2

In 6 cases 5 mg phentolamine (Regitin® 10 mg/ml) was slowly given intravenously, immediately prior to the histamine inhalation.

Test No. 3

In 5 cases, 3 of which were also included in test No. 1, phentolamine (Regitin® 10 mg/ml) was given by inhalation with a de Vilbiss spray for 30 seconds prior to every 30 seconds of histamine inhalation. Approximately 1 mg phentolamine was inhaled each time.

Test No. 4

One patient from the second test group (No. 3) was also challenged on another occasion with an intravenous infusion of 75 μ g of histamine chloride in 100 ml of normal saline over a period of 6 minutes. Registration of G_A and PEF was made before and within 2 minutes of the infusion being finished. The same trial was repeated one week later under the same conditions, but 5 mg phentolamine (Regitin® 10 mg/ml) was this time given intracutaneously before the histamine infusion. The infusions were started with normal saline and, after checking that the lung function values did not change, were switched over to histamine solution.

Test No. 5

In 6 cases, 1 of which was also included in tests No. 1 and 3, one capsule of disodium cromoglycate (Lomudal®) was given for inhalation 20 minutes before the histamine inhalation.

The nature of the tests was explained to the patients and all gave their consent.

RESULTS

Test No. 1

In 1 case previous atropine inhalation did not cause any change in histamine reactivity; in 4 cases the threshold values were raised two concentration steps, and in 1 case four steps (Table 1). No side effects were noted.

Test No. 2

In 3 cases there was no difference in histamine reactivity after the injection of phentolamine. In 1 case the threshold value was lowered one step, and in 2 cases the threshold values were raised one step which is within the limits of normal variations with this technique (Table 2). No side effects, apart from a moderate increase in heart rate and a slight decrease in blood pressure, were registered in 2 cases.

Test No. 3

In 3 cases the histamine reactivity was unchanged after preceding phentolamine inhalation. In 1 case the threshold value was lowered one step, while it was raised one step in another

TABLE 1
Effect of Inhaled Histamine (Hi) on Airway Conductance/Thoracic Gas Volume (G_A/TGV) and Peak Expiratory Flow (PEF) before and after Atropine (Atr) Inhalation in 6 Asthmatic Subjects.

Pat. No.	Age	Sex	Inhaled substance	Initial values		Histamine threshold values		Changes in % of initial values		Histamine threshold
				G_A/TGV	PEF	G_A/TGV	PEF	G_A/TGV	PEF	
7	40	M	Hi	0.165	540	0.034	460	-79	-15	0.5
			Atr + Hi	0.153	520	0.018	340	-88	-35	0.5
8	28	M	Hi	0.154	560	0.024	420	-84	-25	1
			Atr + Hi	0.0148	570	0.032	500	-78	-12	4
10	25	M	Hi	0.169	570	0.034	420	-80	-26	1
			Atr + Hi	0.118	580	0.010	420	-85	-28	4
11	43	F	Hi	0.155	410	0.078	370	-50	-10	0.5
			Atr + Hi	0.305	420	0.090	380	-70	-10	8
12	30	F	Hi	0.145	450	0.066	300	-54	-33	1
			Atr + Hi	0.190	440	0.085	320	-55	-27	4
13	40	M	Hi	-	460	-	310	-	-33	1
			Atr + Hi	0.071	440	0.032	360	-56	-18	4

TABLE 2

Effect of Inhaled Histamine (Hi) on Airway Conductance/Thoracic Gas Volume (G_A/TGV) and Peak Expiratory Flow (PEF) before and after Injection of Phenolamine (Phe) in 6 Asthmatic Subjects.

Pat. No.	Age	Sex	Inhaled or injected substance	Initial values		Histamine threshold values		Changes in % of initial values		Histamine threshold
				G_A/TGV	PEF	G_A/TGV	PEF	G_A/TGV	PEF	
1	18	M	Hi	0.171	530	0.047	460	-72	-13	2
			Phe + Hi	0.120	555	0.024	380	-80	-31	4
2	27	M	Hi	0.204	515	0.016	305	-92	-41	0.25
			Phe + Hi	0.112	480	0.033	350	-70	-27	0.125
3	30	M	Hi	0.128	465	0.034	295	-75	-37	0.5
			Phe + Hi	0.150	535	0.026	290	-83	-46	0.5
4	18	M	Hi	0.171	565	0.056	450	-67	-21	0.5
			Phe + Hi	0.137	550	0.026	490	-80	-11	0.5
5	27	F	Hi	0.417	470	0.032	310	-92	-34	8
			Phe + Hi	0.204	485	0.036	380	-82	-22	8
19	19	F	Hi	0.103	365	0.043	270	-58	-26	0.5
			Phe + Hi	0.077	350	0.030	250	-61	-29	1.0

TABLE 3
Effect of Inhaled Histamine (Hi) on Airway Conductance/Thoracic Gas Volume (G_A/TGV) and Peak Expiratory Flow (PEF) before and after Inhalation of Phentolamine (Phe) in 5 Asthmatic Subjects.

Pat. No.	Age	Sex	Inhaled substance	Initial values		Histamine threshold values		Changes in % of initial values		Histamine threshold
				G_A/TGV	PEF	G_A/TGV	PEF	G_A/TGV	PEF	
6	32	M	Hi	-	250	-	180	-	-28	0.25
			Phe + Hi	-	240	-	160	-	-33	0.25
7	40	M	Hi	0.165	540	0.034	460	-79	-15	0.5
			Phe + Hi	0.111	520	0.015	370	-86	-29	0.5
8	28	M	Hi	0.154	560	0.024	420	-84	-25	1
			Phe + Hi	0.186	570	0.038	500	-80	-12	1
9	23	M	Hi	0.291	510	0.077	385	-74	-25	2
			Phe + Hi	0.223	510	0.050	440	-78	-14	1
10	25	M	Hi	0.138	550	0.032	375	-77	-32	1
			Phe + Hi	0.136	515	0.061	460	-55	-11	2

TABLE 4
Effect of Inhaled Histamine (Hi) on Airway Conductance/Thoracic Gas Volume (G_A/TGV) and Peak Expiratory Flow (PEF) before and after Inhalation of Disodium Cromoglycate (DSCG) in 6 Asthmatic Subjects.

Pat. No.	Age	Sex	Inhaled substance	Initial values		Histamine threshold values		Changes in % of initial values		Histamine threshold
				G_A/TGV	PEF	G_A/TGV	PEF	G_A/TGV	PEF	
10	25	M	Hi	0.138	550	0.032	375	-77	-32	1
			DSCG + Hi	0.148	575	0.035	480	-76	-16	1
14	27	F	Hi	0.076	180	0.037	150	-53	-17	0.063
			DSCG + Hi	0.084	240	0.027	165	-68	-31	0.063
15	27	M	Hi	0.243	465	0.024	385	-90	-17	0.25
			DSCG + Hi	0.236	520	0.018	415	-92	-20	0.25
16	37	M	Hi	0.197	520	0.052	315	-73	-39	0.125
			DSCG + Hi	0.117	520	0.025	295	-79	-43	1
17	47	F	Hi	0.202	305	0.028	170	-86	-44	1
			DSCG + Hi	0.239	320	0.033	185	-86	-12	1
18	52	M	Hi	0.155	425	0.071	330	-54	-22	4
			DSCG + Hi	0.309	370	0.066	170	-79	-54	4

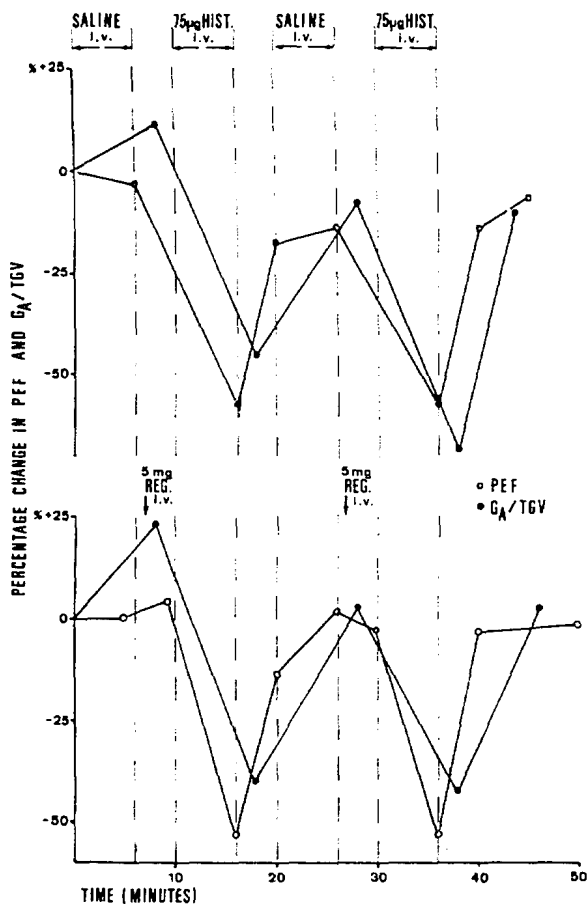


Fig. 2.

Provocation tests with histamine (Hist) infusion in one asthmatic subject before and after injection of phentolamine (REG). Change in peak expiratory flow (PEF) and airway conductance/thoracic gas volume (G_A/TGV) as percentage of initial values.

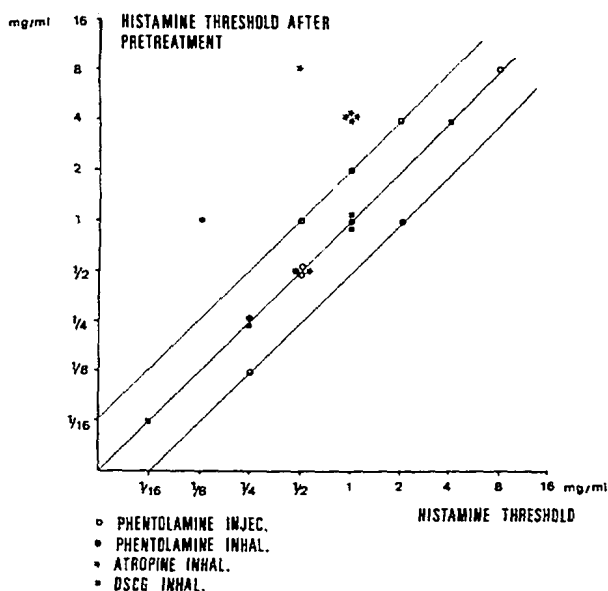


Fig. 3.

Correlation between histamine threshold before and after pretreatment with phentolamine, atropine or disodium cromoglycate. Symbols on the lines are, for the method used, within the limits for normal variations of histamine threshold on different days, provided that the provocations are made at the same time of day and with equal base line values for pulmonary function.

case. Thus phentolamine, in the dose used here, did not cause any significant changes in the histamine reactivity (Table 3). No side effects were registered.

Test No. 4

The bronchial obstruction after intravenous histamine infusion was of very short duration. After 4 minutes it could no longer be objectively registered. No effect on the histamine reactivity could be demonstrated with previous intravenous injection of phentolamine. The histamine challenge was re-

peated after 15 minutes, preceded by a new dose of phentolamine, with identical results (Fig. 2).

Test No. 5

In 5 of the 6 cases, previous DSCG inhalation did not change the histamine threshold value. In 1 case, however, it was raised three concentration steps. Control inhalations in this case gave the same results (Table 4).

In Fig. 3 the results of Tests No. 1, 2, 3 and 5 are brought together.

DISCUSSION

The etiology of the bronchial hyperreactivity in asthmatics to histamine, acetylcholine and a number of chemical and physical factors (such as coal dust, sulphur dioxide, cold air and fog) is not fully understood. Several theories explaining this excessive irritability of the bronchial tree have been given and some of them will be discussed here in relation to the results of the present study.

Increased Sensitivity of the Irritant Receptors in the Bronchial Tree

This results in bronchoconstriction via vagal reflex from weaker stimuli than normal.

There is rather a good correlation between the bronchial sensitivity to inhaled acetylcholine and histamine in bronchial asthma. In a study on 27 patients Makino found a correlation which was statistically significant at 0.05 per cent level. This explains at least some common effects on the bronchial tree of the two substances (13). But there are also differences in the reaction mechanisms. Duron & Humbert, in a study of 26 asthma cases, found a reduction of the acetylcholine sensitivity in all cases when 0.5 mg atropine was given intramuscularly before the inhalation. The histamine response, on the other hand, was not modified at all by atropine in 7 out of 26 cases (7). Itkin & Anand, in 1 out of 19 asthma patients, could

block the histamine reactivity by atropine inhalation, while the acetylcholine effect was totally blocked by atropine in all 26 cases studied (10).

In the present study, the threshold value for histamine was not modified by atropine inhalation in 1 out of 6 cases. In 5 cases the tolerance increased 4-16 times, but normalization of the histamine reactivity did not occur in any case. The conclusion must be that histamine-induced bronchoconstriction as distinguished from acetylcholine is only partly mediated via cholinergic pathways.

Disturbed Functional Balance between the Alpha- and Beta-adrenergic Receptors in the Bronchial Tree

This could be the result of an increased sensitivity of the alpha-receptors or of a partial blockade of the beta-receptors, or both. It has been shown by Simonsson et al. in *in vitro* studies on bronchial muscle preparations that coli endotoxine potentiates the bronchoconstrictive effect of the alpha-receptor stimulant metaoxedrine. This is the case in the bronchial muscle from non-obstructive patients, but the potentiation is much more obvious in the bronchial muscle from patients with chronic obstructive bronchitis (26). It is a common clinical observation that asthma bronchiale often begins or exacerbates after respiratory infections caused by virus or bacteria. Therefore it is possible that bronchial hyperreactivity might be the result of endotoxine effects on the bronchial smooth muscle i.e., for example, alpha-receptor sensitization.

If a partial blockade of the beta-receptors is also present (which Szentivanyi (27) has suggested is a fundamental feature of asthma), then a disturbed relationship between the adrenergic receptor systems in the bronchial tree is further accentuated, and the bronchoconstrictive effect of alpha-receptor stimulation should be much more potent than normally.

In that case a blocking of the alpha-receptors might diminish the functional imbalance between the alpha- and beta-receptors and thereby possibly also raise the challenge thresh-

old for histamine by restoration of the normal homeostatic defence against bronchoconstrictive stimuli.

The study by Kerr et al. on 10 asthmatic patients (11) supports this hypothesis. Bronchoconstriction provoked by intravenous histamine infusion did not occur if phentolamine was given intravenously before the histamine. Gaddie et al. have also shown (8), in a study on 6 asthmatics that another alpha-receptor blocking drug, thymoxamine, significantly ($P < 0.05$) reduced the mean fall in FEV₁, when given intravenously before inhaled histamine.

These results have not been confirmed in the present study. Neither intravenously administered nor inhaled phentolamine has significantly modified the bronchial reactivity to inhaled histamine solution. What then is the reason for this discrepancy in results? Is there an essential difference in the reaction mechanisms when histamine is given intravenously or when inhaled?

Histamine given intravenously causes a bronchoconstriction which passes very rapidly (1-4 minutes), while inhalation causes a reaction that remains usually for 5-20 minutes. It might depend on different reaction sites. It is conceivable that histamine infused via the pulmonary circulation mainly causes a reaction in the most peripheral airways (the so-called "silent zone"), while the reaction on inhaled histamine, with the method used here, takes place in the upper airways (12). Intravenously administered phentolamine should then also give a poorer blocking effect if histamine is inhaled instead of infused. But in the present study inhaled phentolamine had no influence on the histamine reactivity either.

In one of the cases an attempt was made to confirm Kerr's findings on the blocking effect of phentolamine on the reaction after histamine infusion, but without success.

Consequently this study does not support the theory that a functional imbalance between the alpha- and beta-adrenergic receptors is a contributive cause to the bronchial hyperreactivity to histamine in these cases of initially asymptomatic asthma.

The hypothesis of Szentivanyi that a blockade of the beta-

adrenergic receptors is a defect which all asthmatics have in common, has certainly been brought into question. Beta-receptor stimulants like isoprotrenol have, as a rule, a good effect in asthma, and the sensitivity of the receptors is the same as in normal individuals (30). Further, no increased sensitivity to histamine has been demonstrated in healthy persons after beta-adrenergic blockade (14, 34). Finally corticosteroids do not affect the bronchial reactivity to histamine or acetylcholine but block the bronchoconstriction provoked by antigen aerosol (3, 6, 29).

Mathé et al. (17) have not been able to modify the bronchoconstrictive effect of acetylcholine and histamine with alpha-adrenergic blockade on bronchial muscle preparations in *in vitro* studies. On the other hand, the constriction produced by these agonists could readily be abolished by atropine or an antihistamine.

A study by Marcelle (15), however, favours the belief that a functional imbalance between the alpha- and beta-receptors in the bronchial tree could under certain circumstances be present in asthmatics. Six patients with prolonged status asthmaticus, which was refractory to adrenergic drugs and theophylline, produced bronchodilatation after inhalation of phentolamine. This alpha-receptor blocker also restored the normal bronchodilator response to sympatomimetics. This result offers indirect evidence of beta-adrenergic blockade with the unmasking of a constricting alpha-adrenergic response in severe asthma (22).

Deficiency of Circulating Epinephrine

An alternative hypothesis produced by Mathé (18) postulates deficiency of circulating epinephrine as one of the basic defects in bronchial asthma. Such a condition, like beta-receptor blockade, should impair the normal homeostatic defence against bronchoconstrictive stimuli. Alpha-receptor blockade might therefore, if the hypothesis were true, possibly restore this defence and diminish the bronchial hyperreactivity.

The present study does not give support to such a presumption, as alpha-receptor blockade was without effect in all the cases studied. Mathé & Knapp have reported decreased urinary excretion of epinephrine in 6 asthmatic subjects, both at rest and after physical stress (16). So far, however, this observation has not been confirmed.

Sensitization of the Bronchial Smooth Muscles to Direct, Not Reflexly Mediated, Nonallergic Stimuli

A direct, non vagus dependent effect of histamine on the bronchial smooth muscle certainly exists. Probably there are specific histamine receptors in smooth muscles whose constrictive effects on stimulation are mediated via the adenylyl cyclase-cyclic AMP system. In *in vitro* studies on smooth muscles Andersson (1) has shown that histamine decreases the cyclic AMP content in the muscle for 10–15 seconds before the contraction develops. The same pattern was found when carbacholine or phenylephrine (alpha-receptor stimulator) were administered. The reduction of cyclic AMP can be due to either reduced synthesis through inhibition of adenylyl cyclase activity or increased break-down through stimulation of the phosphodiesterase enzyme. It has previously been shown that beta-receptor stimulation is associated with an increase in cyclic AMP by means of activation of adenylyl cyclase. Cyclic AMP thus seems to be a regulator substance for the relaxation as well as for the contraction of smooth muscles.

It has also been shown by the same authors that cyclic AMP works by changing the relationship between free and bound calcium ions. An increase of the tissue level of cyclic AMP stimulates a Ca^{++} binding mechanism, which in turn leads to a decreased concentration of myoplasmic Ca^{++} , and subsequent relaxation of the muscle. A reduction of the cyclic AMP level caused by contracting agents probably leads to a release of bound Ca^{++} , which activates the contractive proteins. The Ca^{++} ion transport thus seems to play a major role in the relaxation-contraction cycle of smooth muscles with cyclic AMP as a regulator substance.

It has been suggested by Kerr et al. (11) that disodium cromoglycate (DSCG) has an influence upon this calcium ion transport. DSCG is supposed to exert its effects in allergic asthma by stabilizing the mast cell membrane and thereby inhibiting the amine release after antigen-antibody reactions (4). If DSCG also stabilizes other cell membranes it might alter the calcium ion transport and prevent the release of bound Ca^{++} ; in that way it might inhibit smooth muscle contraction following bronchoconstrictive stimuli. This would explain why DSCG has protective effects not only in allergic asthma but also in many cases of exercise and intrinsic asthma.

As mentioned before, Kerr et al. (11) showed in ten asthmatic subjects that DSCG completely inhibited the fall of VC and FEV_1 provoked by histamine infusion. On the other hand Cade & Pain (3) could not demonstrate any protective effects of DSCG against inhaled metacholine in two asthmatic subjects.

In the present study the results of pretreatment with DSCG on the bronchial reactivity to inhaled histamine are somewhat divergent. In 1 out of 6 cases there was a clear protective effect of DSCG which was confirmed in repeated trials, while in the rest no influence at all was traced. Consequently it remains to explain why DSCG has a modifying effect on bronchial hyperreactivity in some cases and not in other. Further studies are needed to clarify the mechanism of action of this drug.

SUMMARY

The degree of bronchial reactivity to inhaled histamine was determined in 19 asthmatic patients. Trials were made to modify the histamine reactivity by means of pretreatment with atropine, phentolamine and disodium cromoglycate. In 5 out of 6 cases, atropine significantly raised the histamine threshold. One case did not show any change. Phentolamine did not modify the histamine reactivity significantly in any of 11 cases studied. DSCG raised the threshold value significantly in only 1 out of 6 cases.

The main theories about the etiology of bronchial hyper-reactivity are discussed in relation to these results. The conclusion is that bronchial hyperreactivity to histamine is due in part to an increased sensitivity of the irritant receptors in the bronchial tree. Possibly it is also partly due to a sensitization of the bronchial smooth muscles to direct, non-vagus-dependent stimuli, as a full normalization of the threshold value does not occur after pretreatment with atropine. This study does not support the theory that bronchial hyperreactivity is the result of a functional imbalance between the alpha- and beta-adrenergic receptors in the bronchi.

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