

Increased peripheral α -adrenoceptor response in allergic asthmatics

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The peripheral α -adrenoceptor reactivity, measured as dermal blanching response to iontophoretically administered phenylephrine, was studied in 28 allergic asthmatics, 13 patients with allergic rhinoconjunctivitis and 21 healthy controls. The blanching response, which has previously been demonstrated to be mediated via α_1 -adrenoceptors, was found to be significantly increased in allergic asthmatics compared with controls. It is suggested that there is an increased peripheral α -adrenoceptor reactivity in allergic asthma.

Key words: asthma; α -adrenoceptor; peripheral; iontophoresis; skin.

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The significance and function of α -adrenoceptors in asthma is still unclear (1, 12, 13, 14). Increased α_1 -adrenergic sensitivity has previously been demonstrated *in vivo* in atopic asthmatics by recording of topical phenylephrine-induced mydriasis (2, 6) as well as clearance of intradermally injected phenylephrine and Xe¹³³ (6). The latter method however, has been judged inappropriate because of traumatic effects, and the results have thus been questioned (4). We recently demonstrated increased dermal α_1 -adrenoceptor response in subjects with atopic dermatitis by use of the atraumatic iontophoresis technique (9). Therefore, we found it of interest to use iontophoresis to study peripheral α_1 -adrenoceptor reactivity in asthmatics. Iontophoresis is a process in which ionized molecules move from a solution into tissue following the polarity of an electric field and penetrate in proportion to the field strength. It has previously been applied both experimentally and therapeutically with good reproducibility (3, 5, 7, 10). We have used the method to study human adrenoceptor response and have demonstrated that the sympathetic influence on superficial

dermal blood vessels is mediated via α_1 and β_2 -adrenoceptors (8).

Thus, the aim of this study was to investigate whether there is an altered peripheral α_1 -adrenoceptor response in allergic asthma. As an additional allergy group we also studied patients with allergic rhinoconjunctivitis.

SUBJECTS

Age, sex and IgE-values of the 28 patients with allergic asthma, the 13 patients with allergic rhinoconjunctivitis and the 21 healthy controls are shown in Table 1. The diagnosis of allergy was confirmed by a typical case history in combination with positive skin prick test. All 21 healthy controls had a clear non-atopic history confirmed by negative skin prick test and/or RAST (Radio-allergo-sorbent-test).

The 28 allergic asthmatics had mean PEF (Peak Expiratory Flow) 478 l/min, range 300-700 l/min, measured with Wright's Peak Flow Meter. All had a history of mild to moderate asthma that had been stable for at least 1 month prior to iontophoresis. The diagnosis of asthma was based on positive metacholine test, > 20%

reversibility after inhalation of β_2 -agonist or $> 25\%$ diurnal variability of PEF. No one had a history of airway infection during the 6 weeks prior to the metacholine test, which was performed, and considered positive, according to the criteria of Laitinen (11). All 28 patients used β_2 -aerosol. Seven patients used slow-release oral β_2 -agonists as only addition; two used inhaled corticosteroids; eight used oral β_2 -agonists and inhaled corticosteroids. Median dose of inhaled corticosteroids, in patients with this treatment, was 800 μg daily (range 200–1600 μg daily). None of the patients had been treated regularly with oral corticosteroids, and oral short courses of steroids were not allowed at least 6 weeks prior to iontophoresis.

All examinations were performed during November–May. None of the participants had dermatitis, or sun tan or skin redness due to sun exposure. All participants with seasonal allergy were examined off season. No one had a history of smoking. Xantine rich beverages were not allowed 2 h before examination. Informed consent was obtained from the participants, and the study was approved by the Ethics Committee of the University of Umeå.

METHODS

The iontophoresis equipment and technique of examination have been described in detail elsewhere (8, 9). In brief, the anode is a multi-electrode device with 12 chambers. The direct current to each chamber increases in proportional steps, i.e. approximately $\sqrt{2}$ from 39–1261 μA . Three chambers serve as controls, thus receiving no current. The anode was gently

attached to the flexural side of the forearm 10 cm below the antecubital fossa. An aqueous solution of phenylephrine 10 $\mu\text{g}/\text{ml}$ was supplied to the chambers. Current was switched on for 30 s increasing the dermal penetration for the ionized agent proportionally to the current in each chamber. The skin reaction, blanching, under the respective anode was recorded visually after 5 min as an all-or-none response. The recordings were transformed into scores (0–9) expressing the minimal current, i.e. drug dose, which produced an erythematous skin reaction under the anode. A high score thus implies that a low current, i.e. low phenylephrine dose, was sufficient to cause blanching. All recordings were made at room temperature 20–22°C by the same investigator.

Drugs

Phenylephrine-chloride was purchased from Sigma Chemical Corp., St. Louis, Mo., USA. Aqueous solution was prepared and stored at -80°C until used at room temperature.

Statistics

Wilcoxon's rank sum test was used for calculation of differences between groups of subjects.

RESULTS

The 28 allergic asthmatics displayed significantly increased blanching response to phenylephrine compared with controls ($P < 0.05$, Table 2). This was also found for asthmatics without oral β_2 -agonist treatment. However, for

Table 1
Subjects studied with phenylephrine iontophoresis

	Number	Men/Women	Age (years)		Total IgE ¹ (Arbitrary units)	
			range	mean	range	median
Healthy controls	12	9/12	18/59	35	2–148	16
Patients with allergic rhinoconjunctivitis	13	8/5	21–41	31	8–439	24
Allergic asthmatics	28	15/13	18–58	33	7–4010	168

¹Normal range < 150 arbitrary units

asthmatics who were on oral β₂-agonists the blanching responses were somewhat stronger than for healthy controls but the difference was not significant. Patients with allergic rhinoconjunctivitis displayed slightly, but not significantly, stronger responses than controls. Inhaled corticosteroids did not seem to affect phenylephrine responses in asthmatics.

DISCUSSION

To our knowledge this is the first time an increased peripheral α₁-adrenoceptor response has been demonstrated *in vivo* in allergic asthmatics by an atraumatic method. Our results confirm previous studies (2, 6). The results are also in agreement with our recent findings in subjects with atopic dermatitis (9). Allergic asthmatics on oral β₂-agonist medication showed a tendency towards an increased α₁-adrenoceptor response compared with controls, although statistical significance was not reached. Even though the influence of the oral β₂-agonist treatment cannot be excluded we do not find this likely. The response of patients with allergic rhinoconjunctivitis did not differ significantly from controls, which may be due to the local character of this type of allergy.

It is concluded that the α₁-adrenoceptor response in superficial dermal blood vessels was found to be significantly increased in atopic asthmatics, similar to that in atopic dermatitis. Further studies are required to evaluate the significance of these findings and whether it is a primary or secondary phenomenon.

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Table 2
Blanching response to iontophoretically administered phenylephrine

	Phenylephrine reaction (blanching score)	
Healthy controls	1.94 ± 0.45	(17)
Patients with allergic rhinoconjunctivitis	2.15 ± 0.42	(13)
Allergic asthmatics	3.50 ± 0.47*	(28)
Allergic asthmatics on oral β ₂ -agonists	3.20 ± 0.59	(15)
Allergic asthmatics without oral β ₂ -agonists	3.84 ± 0.77*	(13)

* P < 0.05. Significant difference compared to healthy controls.
Responses expressed as scores 0-9 (mean ± SEM).
0 = no blanching by the highest current (drug dose), i.e. low response.
9 = blanching produced by the lowest current (drug dose), i.e. high response. Number of subjects in parantheses.

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