ethnic groups or to males. We do, however, feel that these findings are important as regards the training of doctors and pharmacists and the provision of health services and health education. The wide contact with and belief in traditional medicines certainly influence the attitude of these people to Western medicine.

A developing community is certainly at risk of exploitation in terms of advertising in the mass media and via mail-order systems, and it would certainly be to their benefit if the major source of medicines for self-medication could be responsible, informed professional people in pharmacies, clinics and hospitals, provided that the cost remained realistic.

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Comparison of the metabolic responses to alpha-adrenergic stimulation in asthmatics and non-asthmatics after clonidine

J. M. KALLENBACH, B. I. JOFFE, H. C. SEFTEL, S. ZWI

Summary

The role of the α-adrenergic system in the pathogenesis of asthma is investigated. We administered 150 μg oral clonidine to a group of patients with relatively mild asthma and a group of non-asthmatic subjects, and compared their responses by measuring plasma levels of growth hormone (GH), immunoreactive insulin, potassium and glucose. There was no significant difference between the groups in respect of any of these variables, nor was there a significant difference in the blood pressure responses. However, 3 of the asthmatic subjects demonstrated marked hyper-responsiveness of the plasma GH levels after clonidine. It is possible that increased α-adrenergic responses may be more frequently demonstrable in a group of severe asthmatics or by means of an α-agonist which is more potent and less selective than clonidine. Alternatively, the 3 hyper-responsive individuals may represent a subgroup of asthmatics in whom α-adrenergic overactivity is an important pathogenetic mechanism.

Bronchial asthma is characterized by hyper-reactivity of the airways to various physical, chemical and pharmacological stimuli. Mechanisms that could account for this include increased responsiveness of the bronchial muscle, abnormality of airway epithelium allowing increased accessibility of stimuli to irritant receptors, and a number of different types of imbalance in the autonomic control of airway calibre.

Szentivanyi originally suggested that asthma is caused by an abnormality of β-adrenergic receptors resulting in bronchoconstriction. A number of subsequent studies reported diminished adrenergic responses to various stimuli in asthmatics compared with those in non-asthmatics. We were unable, however, to demonstrate any differences between atopic asthmatics and non-asthmatic atopic individuals in the haemodynamic and metabolic responses to selective β-adrenergic stimulation after salbutamol.

The fact that the α-adrenergic system may play a role in bronchial hyper-reactivity was suggested by the finding that α-blockade prevents the bronchoconstriction induced by histamine and exercise. Subsequently Henderson er al. showed that asthmatics have increased pupillary and cutaneous reactions to locally administered phenylephrine. This α-adrenergic hyper-responsiveness, in contrast to other reported autonomic abnormalities, appears to be a feature of asthma itself rather than of the atopic state. The object of this study, therefore, was to compare the metabolic responses to α-adrenergic stimulation in asthmatics and non-asthmatics.

Clonidine is a selective α2-adrenergic agonist. It has a potent antihypertensive action, the mechanism of which is complex and controversial, and may be related to stimulation of either central inhibitory α-adrenergic receptors or peripheral α2-receptors. Clonidine has been shown to cause a rise in plasma GH levels by stimulation of central α-receptors. Clonidine also causes a rise in plasma potassium levels by inhibiting renin secretion, an...
effect which also appears to be mediated by α-adrenergic pathways, as well as causing a rise in plasma glucose which is probably related to the secretion of GH.

It was decided to use clonidine for this study because this was the only pure α-adrenergic agonist available to us which has been used extensively orally. It has also been shown to be effective in raising plasma GH levels after oral administration. We were reluctant to use any intravenous α-stimulant because we were concerned about possible serious haemodynamic side-effects.

Subjects and methods

Nineteen non-obese subjects were studied after having given informed consent for the study which was approved by the University Committee for Research on Human Subjects. Pulmonary function testing and an exercise test on a treadmill were performed on each individual prior to inclusion in the study. Lung volumes and airway resistance were measured using a Jaeger plethysmograph, and flow volume curves were obtained with a Pulmolab 5300 (Cardiopulmonary Instruments, Houston, Texas).

The subjects were divided into two groups. Group I consisted of 9 patients with a history and the clinical features of bronchial asthma as defined by the American Thoracic Society. All were being treated with bronchodilators and some with disodium cromoglycate and/or beclomethasone dipropionate in addition. None had ever required systemic corticosteroid therapy. All the asthmatics were in a stable condition at the time of the metabolic phase of the study. Disodium cromoglycate and/or beclomethasone dipropionate in standard dosages were continued or introduced as required. All the asthmatics were in a stable condition at the time of the metabolic phase of the study.

Group II consisted of 10 subjects with no history and no clinical features of bronchial asthma as defined by the American Thoracic Society. Five of them had hay fever and the other 5 were normal. We had initially intended to compare the α-adrenergic responses of asthmatics, normal subjects and those with hay fever. However, on finding no difference between the responses of the normal subjects and those with hay fever we pooled their data when comparing them with those of the asthmatic group. Each subject in group II had completely normal pulmonary function and a normal response in the peak expiratory flow rate to exercise (i.e. a fall of less than 10% of the resting value).

None of the subjects in either group had been using vasoconstrictor nose-drops.

With the subjects at rest after an overnight fast, blood was sampled 10 and 20 minutes after an intravenous saline infusion had been started in an arm vein. Clonidine hydrochloride 150 µg was administered orally and blood was sampled at half-hourly intervals for 3 hours. Blood pressure readings were taken simultaneously. Aliquots of each blood sample were used for determination of the plasma levels of GH, immunoreactive insulin, potassium (IL 543 flame photometer) and glucose (Beckman Glucose I analyser).

The mean responses to clonidine were assessed for each variable by pooling the results of all 19 subjects. Values at 30-minute intervals after the administration of clonidine were compared with the basal value which was the average of the two results obtained before its administration. The paired t test was used for the statistical analyses. Data from the asthmatic and non-asthmatic groups were compared by means of the unpaired t test.

Results

Sex distribution, age and the physical characteristics of groups I and II are shown in Table I. There were no significant differences. Variables of pulmonary function and the response to exercise in terms of peak flow rate are shown in Table II. The residual volume and the airway resistance were significantly higher, and the forced expiratory volume in 1 second significantly lower, in group I (asthmatics). The fall in expiratory peak flow rate on exercise was significantly greater in this group.

The mean responses of all 19 subjects to the administration of clonidine are shown in Table III. Systolic and diastolic blood pressures fell significantly and plasma potassium and glucose levels rose significantly. The plasma GH level did not rise significantly at any time after the administration of clonidine, but this was partly due to the differences in the time of the peak response in individual subjects. The mean peak GH level was,
TABLE III. METABOLIC AND BLOOD PRESSURE RESPONSES TO CLONIDINE IN 19 SUBJECTS (MEAN ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Basal</th>
<th>30 min</th>
<th>60 min</th>
<th>90 min</th>
<th>120 min</th>
<th>150 min</th>
<th>180 min</th>
<th>Peak</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma GH (µg/l)</td>
<td>3.2 ± 1.0</td>
<td>2.8 ± 1.6</td>
<td>2.2 ± 0.9</td>
<td>5.5 ± 1.6</td>
<td>5.6 ± 1.4</td>
<td>3.8 ± 1.4</td>
<td>2.9 ± 1.6</td>
<td>9.1 ± 2.2**</td>
</tr>
<tr>
<td>Plasma insulin (mU/l)</td>
<td>13.5 ± 0.9</td>
<td>13.2 ± 0.9</td>
<td>13.7 ± 1.1</td>
<td>13.4 ± 1.0</td>
<td>13.0 ± 1.0</td>
<td>12.5 ± 1.2</td>
<td>12.4 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>4.8 ± 0.1</td>
<td>4.9 ± 0.1</td>
<td>5.1 ± 0.2*</td>
<td>5.0 ± 0.2</td>
<td>4.8 ± 0.1</td>
<td>4.7 ± 0.1</td>
<td>4.8 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Plasma potassium (mmol/l)</td>
<td>3.6 ± 0</td>
<td>3.7 ± 0.1*</td>
<td>3.8 ± 0.1*</td>
<td>3.8 ± 0.1***</td>
<td>3.8 ± 0.1</td>
<td>3.9 ± 0.1*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>114 ± 2.0</td>
<td>108 ± 3.0'</td>
<td>104 ± 3.0''</td>
<td>98 ± 2.0''</td>
<td>97 ± 2.0''</td>
<td>98 ± 3.0''</td>
<td>100 ± 2.0''</td>
<td></td>
</tr>
<tr>
<td>Diastolic</td>
<td>72 ± 2.0</td>
<td>69 ± 2.0</td>
<td>65 ± 2.0''</td>
<td>65 ± 3.0''</td>
<td>65 ± 2.0''</td>
<td>65 ± 2.0''</td>
<td>64 ± 2.0''</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05; **P < 0.025; ***P < 0.01; 'P < 0.005; "P < 0.0005 (compared with basal level).

however, significantly higher than the mean basal level. Plasma insulin levels did not change significantly.
There were no significant differences between the asthmatic and non-asthmatic groups as regards any of these variables at any time after the administration of clonidine. The asthmatic group had a higher basal plasma GH level and higher levels following administration of clonidine, but these differences never achieved statistical significance (Fig. 1). The higher GH levels after clonidine in the asthmatic group appeared to be mainly due to 3 subjects who demonstrated marked hyper-responsiveness compared with the other 6 asthmatics (Fig. 2) and with the non-asthmatic subjects. Details of these 3 individuals are given in Table IV; although none of them differed significantly from the rest of the subjects with regard to age, physical characteristics or the other responses to clonidine, 2 of them (subjects LL and RL) appeared to have the most severe derangements in pulmonary function of the asthmatic group.

The only side-effect of clonidine which we observed was drowsiness, which affected most of the subjects, none of whom reported any change in pulmonary symptoms. We did not attempt to confirm this objectively, however, since we were concerned that changes in GH levels might be induced by the stress and physical activity involved in the performance of respiratory testing manoeuvres.20

Table IV. Anthropometric data and pulmonary function variables of 3 asthmatic subjects with GH hyper-responsiveness

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Residual volume (%) predicted value</th>
<th>FEV₁ (% predicted value)</th>
<th>% fall in PEF rate with exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL</td>
<td>19</td>
<td>F</td>
<td>160</td>
<td>62</td>
<td>274</td>
<td>41</td>
<td>65</td>
</tr>
<tr>
<td>RL</td>
<td>26</td>
<td>M</td>
<td>187</td>
<td>71</td>
<td>199</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>LD</td>
<td>17</td>
<td>M</td>
<td>173</td>
<td>55</td>
<td>97</td>
<td>74</td>
<td>46</td>
</tr>
</tbody>
</table>
Discussion

The metabolic responses to clonidine observed in our study have all been described previously.13-16 With the exception of the rise in plasma glucose levels they appear to be directly related to α-adrenergic stimulation. The well-known hypotensive effect is similarly mediated. We have not been able to demonstrate any significant differences between groups of asthmatic and non-asthmatic individuals in these α-adrenergic responses. We consider it noteworthy, however, that 3 of our asthmatic subjects demonstrated marked hyper-responsiveness of the plasma GH levels to clonidine administration. Allowing for differences in radio-immunoassay methods, these responses were also markedly in excess of those of normal subjects to 150 μg intravenous clonidine reported by Lal et al.14

A cautionary note regarding the interpretation of the results of GH stimulation tests has been sounded by Spitz et al.,21 who found significant rises in serum GH levels in simulated tests. They attributed this 'agnogenic' release of GH, which occurred either early (within 1 hour of needle placement) or late (3 hours or more after needle placement) in the course of the tests, to stress associated with needle placement. In our study it is conceivable that the high basal level and relatively early rise in GH in subject LD were related to this phenomenon, but the GH responses of subjects LL and RL took place between 1 and 3 hours after needle placement (i.e. during the 'critical zone' suggested by the authors to constitute the optimal time for true assessment of stimuli).

The asthmatics in our study all had relatively mild disease. None had ever required therapy with systemic corticosteroids, and each patient was able to discontinue all bronchodilators for 1 week without difficulty. It is possible that increased α-adrenergic responses may be more frequently demonstrable in severe asthmatics, or by means of an α-adrenergic stimulant which also exists that the hyper-responsive subjects represent a particular subgroup of asthmatic patients in whom α-adrenergic overactivity is an important pathogenetic factor.

The complexity of autonomic interactions in the lung and elsewhere is considerable and abnormalities of one component of the autonomic nervous system may lead to secondary changes in another.22 Our knowledge of the autonomic nervous system and its effects on the lungs, particularly in disease, remains elementary.23 Clearly, the fundamental concept underlying this study and many others which attempt to implicate the autonomic nervous system in the pathogenesis of asthma, namely that autonomic events in the airways are mirrored by those at distant sites, may be a misleading one.

The results of our study therefore allow for no conclusions regarding the pathogenesis of bronchial hyper-reactivity in asthma. We feel, however, that they indicate the need for further investigation of the role of the α-adrenergic system, and in particular of its α₁-component. In addition we suggest that a search for subgroups of asthmatics, each characterized by different abnormalities predisposing to bronchial hyper-reactivity, may be more fruitful than attempts to identify a single underlying pathogenetic mechanism applicable to all patients with the disease.

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