Acute bronchoconstriction is not a stimulus for sympa-tho-adrenal activation in asthmatic or healthy subjects

K. Larsson*, P. Hjemdahl**, E. Theodorsson***

Acute bronchoconstriction is not a stimulus for sympa-tho-adrenal activation in asthmatic or healthy subjects. K. Larsson, P. Hjemdahl, E. Theodorsson.

Abstract: Bronchoconstriction has been found to cause little sympatho-adrenal activation in asthmatic patients. It has been questioned whether this is due to blunted sympatho-adrenal reactivity in asthmatics or if bronchoconstriction is a stimulus for sympa-tho-adrenal activation at all. We therefore compared sympatho-adrenal responses in eight asthmatic patients and 12 healthy subjects by measurements of plasma adrenaline and noradrenaline concentrations before, during and after methacholine-induced bronchoconstriction. Significant bronchoconstriction was obtained in eight of the healthy subjects and in all of the asthmatics. Considerably higher concentrations of methacholine were required to evoke bronchoconstriction in the healthy subjects but the relative magnitudes of bronchoconstriction were similar in the two groups: peak expiratory flow (PEF) decreased by $-24$ and $-28\%$ and specific airway conductance (SGaw) decreased by $-68$ and $-70\%$ in asthmatics and controls, respectively. Methacholine-induced bronchoconstriction did not alter plasma catecholamine levels significantly in either group. In addition, plasma concentrations of catecholamines and neuropeptide Y-like immunoreactivity (NPY-LI) were measured before and during bronchoconstriction induced by histamine or allergen in 8 and 5 asthmatic subjects, respectively. Plasma noradrenaline, adrenaline and NPY-LI remained unchanged up to 30 min after bronchoconstriction induced by histamine or allergen. We, therefore, conclude that bronchoconstriction is not a stimulus for sympatho-adrenal activation and that the lack of an adrenaline response to bronchoconstriction is not likely to be related to NPY release.

It has been debated whether sympatho-adrenal reactivity is altered in bronchial asthma. This is of great interest since counter-regulatory effects of the potent endogenous $\beta$-adrenoceptor agonist adrenaline would be advantageous during bronchoconstriction in asthmatic subjects. An impaired sympatho-adrenal response to moderate exercise in asthmatic patients has been claimed [1, 2], but these findings were not confirmed by us [3]. Since adrenaline secretion is increased by mental stress [4, 5] and many other physiological stimuli [6], it seems reasonable that bronchoconstriction should activate sympatho-adrenal mechanisms, if for no other reason than due to the stress of experiencing breathing difficulties. This has, however, not been found to be the case, since the plasma levels of adrenaline are unaltered when acute bronchoconstriction is induced by hyperventilation [1], inhalation of allergen [7] or histamine [8]. In fact, even asthmatic patients admitted to a casualty department due to acute severe asthma have been found to have low levels of adrenaline in plasma [9].

Noradrenaline is released from sympathetic nerve terminals by several stimuli [6]. However, venous plasma noradrenaline levels also remain unchanged in experimentally induced bronchoconstriction [1, 7, 8] and only slight elevations are seen in acute severe asthma [9]. These findings suggest that sympathetic activation occurs with severe, prolonged symptoms of asthma but not following acute transient bronchoconstriction. The lack of a plasma catecholamine response to induced bronchoconstriction raises the question of whether sympatho-adrenal reactivity is selectively impaired in asthmatic patients or if bronchoconstriction per se is not a stimulus for sympatho-adrenal activation.

Neuropeptide Y (NPY) coexists with noradrenaline in sympathetic post-ganglionic nerve terminals and upon sympathetic stimulation the increase in plasma levels of noradrenaline is associated with increase in plasma levels of neuropeptide Y-like immunoreactivity (NPY-LI) [10, 11]. NPY may also be released from the adrenal medulla [12]. NPY is capable of inhibiting noradrenaline.

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overflow from sympathetic nerve terminals in isolated human blood vessels [13] and experiments in rats suggest that NPY may also inhibit the release of adrenaline from the adrenal medulla [14]. Thus, NPY-LI may be a marker for sympatho-adrenal activation as well as a modulator of the catecholamine response. It has been suggested that the lack of a sympatho-adrenal response to asthma is caused by co-release of NPY, in turn inhibiting noradrenaline and adrenaline release [15].

The aims of the present study were to elucidate these questions by comparing the sympatho-adrenal response (measured by venous plasma catecholamine levels) to acute bronchoconstriction induced by methacholine inhalation in both asthmatic patients and healthy subjects and to study the NPY-LI response to bronchoconstriction induced by inhalation of histamine and allergen in asthmatic subjects.

Material and methods

Subjects

Data for all participating subjects are presented in Table 1.

Bronchial asthma was defined according to the American Thoracic Society [16]. Eight patients (three women), with a mean age of 36 yrs, with bronchial asthma (called the A-M group) and twelve healthy control subjects participated in the first part of the study, i.e. inhalation of methacholine. Four of the controls did not achieve significant bronchoconstriction as evaluated by peak expiratory flow (PEF) readings (the C- group). Results from these subjects are presented separately. The remaining eight healthy subjects, i.e. responders to methacholine (C+ group) and were matched to the asthmatics with regard to sex and age. The asthmatic subjects had provocative concentration producing a 20% fall in forced expiratory volume in one second (FEV1) values for histamine of <3.0 mg/ml, as assessed in a pre-trial bronchial provocation test. All healthy subjects were familiar with lung function testing and five of them had performed bronchial provocations with methacholine inhalations prior to this study.

In the second part of the study bronchial provocations were performed with histamine in eight (A-H group) and allergen in five (A-A group) asthmatic subjects. The mean age of the patients in the A-H group (three women) was 27 yrs and in the A-A group (three women) 28 yrs. All subjects gave their informed consent to participate in the study, which had been approved by the local Ethics Committee.

Procedure

In the control groups (C+ and C) and in the A-M group electrocardiogram (ECG) electrodes were adapted and a venous cannula was inserted in an antecubital vein. After 30 min of rest, blood pressure and heart rate were measured, and blood samples were drawn twice with a 5 min interval. Thereafter, lung function (lung volumes, specific airway conductance and flow-volume loops) was assessed. The bronchial provocation test then commenced with inhalation of the diluent, followed by inhalation of methacholine in increasing concentrations, each increment representing a doubling of the concentration. The provocation was performed by five slow, i.e. not forced, inhalations from functional residual capacity (FRC) to total lung capacity (TLC) at each concentration. The asthmatics started the methacholine inhalations at 0.032–0.125 mg·ml⁻¹ (depending on results from a pre-trial bronchial challenge) and the healthy subjects started at 1.0 mg·ml⁻¹. Measurements of blood pressure, heart rate and lung function were performed three minutes after starting the inhalation at each dose step. The provocation was stopped at a reduction of PEF ≥20% of the pre-challenge value and a blood sample was drawn and blood pressure and heart rate were measured immediately after the lung function measurements, i.e. maximal bronchoconstriction. Blood samples were drawn and blood pressure, heart rate and lung function were measured 5, 10 and 20 min after cessation of the bronchial challenge. The trial was concluded by inhalation of 5 mg salbutamol, and final lung function measurements 10 min thereafter.

The A-H (histamine) and A-A (allergen) groups were also fitted with cannulae into an antecubital vein. After 30 min rest two blood samples for determinations of catecholamines and NPY-LI were collected. In the A-H group histamine provocation was then started at a concentration of 0.032–0.25 mg·ml⁻¹, as guided by a pre-trial challenge. The provocation was performed exactly as the methacholine challenge described above, with the exception that FEV₁ was the only lung function parameter measured. In the A-A group allergen provocations were performed with timothy (n=2), birch, house dust mite (Deratophagoides pteronyssinus) or mugwort (Spectralgen, Pharmacia, Uppsala, Sweden), starting at 1 or 10 BE (Biological Units) after inhalation of the diluent. One ml was inhaled at each concentration and FEV₁ was measured 15 min after starting the inhalation. The provocation was stopped at a decrease of FEV₁, of ≥20% from the pre-challenge value. Following cessation of histamine or allergen provocations blood was collected (for determinations of catecholamines and NPY-LI) at 5, 10, 15 and 30 min after which 5 mg salbutamol was inhaled.

Measurements

Lung function was measured in a volume constant body plethysmograph (PK Morgan Ltd, Chatham, UK). Functional residual capacity (FRC) and specific airway conductance (SGaw) were calculated from mean values of three recordings. Airway resistance was measured at a breathing frequency of 2 Hz and an inspiratory flow rate of 0.5 l·s⁻¹. The body-box was also equipped to record vital capacity and flow-volume loops. Basally, the flow-volume curve with the highest PEF out of three blows was chosen. During the provocation only one
Table 1. - Data for all participating subjects

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<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age yrs</th>
<th>Groups</th>
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<th>PC,PEV, mg·ml⁻¹ BE</th>
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Mean/median

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<td>95.2</td>
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Note: FEV₁: forced expiratory volume in one second; PEF: peak expiratory flow; PCPE₁: provocative concentration producing a 20% fall.

Data of 8 healthy control subjects with significant bronchoconstriction (C+), 4 healthy control subjects with no significant bronchoconstriction (C-) at methacholine provocation and 8 asthmatic subjects (A-M) who underwent bronchial provocation with methacholine, 8 with histamine (A-H) and 5 with allergen (A-A). Mean values for basal lung function and for PCPE₁ are also given.

Flow-volume curve was performed at each dose step unless a significant decrease in PEF was found, in which case the change was confirmed by a second measurement. Mid- and end-expiratory flows at 50 and 25% of forced vital capacity (MEF₅₀, PVc and MEF₂₅, PVc, respectively), were calculated from the flow-volume loop. FEV₁ was measured with a wedge spirometer (Vitalograph).

Methacholine and salbutamol solutions were nebulized in an Aiulos System Inhaler (Karlstad Syrgasfabrik AB, Karlstad, Sweden) which, at a driving pressure of 160 kPa, has an output of 0.626±0.005 ml·min⁻¹ and generates an aerosol with a median diameter (dry particles) of 0.8 µm, in which 80% of the mass represents particles <3.75 µm.

In the A-M and the C groups heart rate was
continuously monitored by telemetry and blood pressure was measured with an aneroid manometer.

Plasma catecholamines were determined by microparticulate cation exchange high-performance liquid chromatography (HPLC) with electrochemical detection [17, 18]. This method has been validated against other methods and has a sensitivity better than 0.05 nM for noradrenaline and adrenaline, as performed in our laboratory. The inter- and intra-assay coefficients of variation are 2–3% at 1–2 nmol·l⁻¹ and 9–13% at 0.1–0.2 nmol·l⁻¹ [18].

Plasma concentrations of NPY-LI were determined using a competitive radioimmunoassay described by Theodorsson-Norrheim and co-workers [19]. The main immunoreactive component in human plasma recognized by this antiserum represents the whole NPY molecule. Plasma samples were assayed with two different sample clean-up and concentrated procedures. Thus, samples were extracted in acid ethanol [19] or on reverse-phase silica cartridges (Bond Elute Cl8, Analytichem International, Harbor City, CA, USA) [20], before analysis as described by Theodorsson-Norrheim and co-workers [19].

Statistical analysis

Data are presented as mean values ±SEM. Statistical analyses were performed by Student’s t-test for paired and unpaired observations, by linear regression and by analysis of variance (ANOVA) and p-values <0.05 were considered significant.

Results

None of the participating subjects had signs or symptoms of respiratory tract infection and all patients were free from asthmatic symptoms at the time of the trial. Basal lung function values in % of predicted values [21, 22] are given in table 1.

Methacholine provocation

There was a significant difference in basal lung function between the A-M and the control group, as assessed by PEF and sGaw (p<0.05), but no difference in FRC. Methacholine inhalation induced significant bronchoconstriction (a reduction in PEF >20% of pre-challenge value) in all asthmatics and in eight of the healthy subjects (C+ group). In 4 of the healthy subjects methacholine inhalation failed to induce significant bronchoconstriction (i.e. a 20% decrease in PEF) despite inhalation of high doses of methacholine (C- group). The data from these 4 subjects are presented separately (table 2) and are thus not used to compare healthy subjects and asthmatic patients, since our aim was to study the effect of bronchoconstriction on sympatho-adrenal reactivity. The very high doses of methacholine given to the C- group may also have produced systemic effects unrelated to the effects of methacholine on the airways.

The magnitude of the bronchoconstriction induced by

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<tr>
<th>Age</th>
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<th>Decrease in PEF</th>
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<td>m</td>
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sGaw: specific airway conductance; PEF: peak expiratory flow.

Fig. 1. Specific airway conductance (sGaw) and peak expiratory flow (PEF) before provocation, at the final methacholine concentration (i.e. at maximal bronchoconstriction), 5, 10 and 20 min after cessation of the bronchial methacholine challenge and 10 min after inhalation of 10 mg salbutamol in eight asthmatic patients (A-M group), eight healthy subjects in whom PEF decreased >20% (C+ group) and in four healthy subjects in whom PEF did not reach 20% decrease (C- group) during the bronchial challenge. Mean±SEM.

methacholine was similar in the A-M and the C+ groups (fig. 1) and the PEF decrease (compared to pre-challenge values) at the final methacholine concentration (i.e. at maximal bronchoconstriction) was ±3.0% in the healthy subjects and 24.0±2.9% in the asthmatics. The corresponding values for decreases in sGaw were 70.2±7.0% (C+ group) and 68.0±3.6% (A-M group).
Sympathoadrenal Responses to Bronchoconstriction

Median provocative concentration producing a 20% fall in peak expiratory flow (PC_{20PFEF}) for methacholine was 3.0 and 0.87 mg·ml^{-1} and median provocative concentration producing a 35% fall in specific airway conductance (PC_{35SGaw}) was 4.3 and 0.33 mg·ml^{-1} in the C+ and the A-M groups, respectively. The post-challenge restitution of lung function was not completed within 20 min, as there was still significant bronchoconstriction at this time when compared to pre-challenge values. For sGaw < 0.05 in the C+ and p < 0.001 in the A-M group; for peak expiratory flow p < 0.01 in the C+ and p < 0.001 in the A-M group). The post-challenge recovery of lung function was slower in the asthmatic patients. However, the difference was not significant when comparing the A-M and C+ groups.

Histamine and allergen provocations

Histamine induced significant bronchoconstriction, i.e., a decrease of >20% of basal pre-challenge FEV_{1} in all 8 asthmatic subjects (the A-A group) and the median value for PC<sub>35</sub>FEV<sub>1</sub> was 0.10 mg·ml<sup>-1</sup>. Inhalation of allergen induced significant bronchoconstriction in all 5 subjects in the A-A group; the median PC<sub>35</sub>FEV<sub>1</sub> was 375 BE. Salbutamol inhalation restored the FEV<sub>1</sub> completely in all subjects. Lung function and PC values are shown in table 1.

Histamine and allergen provocations

Histamine induced significant bronchoconstriction, i.e., a decrease of >20% of basal pre-challenge FEV<sub>1</sub> in all 8 asthmatic subjects (the A-H group) and the median value for PC<sub>35</sub>FEV<sub>1</sub> was 0.10 mg·ml<sup>-1</sup>. Inhalation of allergen induced significant bronchoconstriction in all 5 subjects in the A-A group; the median PC<sub>35</sub>FEV<sub>1</sub> was 375 BE. Salbutamol inhalation restored the FEV<sub>1</sub> completely in all subjects. Lung function and PC values are shown in table 1.

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Sympatho-adrenal responses to bronchoconstriction

The basal prechallenge plasma levels of catecholamines did not differ between the five groups (F=0.49); p=0.74 for noradrenaline and [F=1.18]; p=0.34 for adrenaline.

At the final methacholine concentration level (i.e. at maximal bronchoconstriction) non-significant elevations of venous noradrenaline or adrenaline levels in plasma were observed in the C+ and the A-M groups with no significant differences between the two groups (fig. 3). In the A-M group this slight increase in plasma noradrenaline persisted during 20 min after provocation, while in the C+ group the noradrenaline levels in plasma returned to pre-challenge values. This post-challenge noradrenaline reaction did not, however, differ significantly between the two groups ([F=3.15]; p=0.099). There was no relationship between changes in lung function and plasma levels of catecholamines with the exception of an inverse correlation between the changes in FRC and plasma adrenaline in the asthmatic subjects (r=-0.804, p<0.05).

In the C- group significant decreases in tNAL (i.e. >35%) were observed despite small changes in FRC in two subjects (table 2). The 4 subjects in the C- group showed marked and significant increases in plasma noradrenaline and heart rate (p<0.001), whereas increases in plasma adrenaline were not significant (figs 2 and 3). No major changes in blood pressure were seen. Increases in plasma catecholamine levels and heart rate during the bronchial challenge were related to the dose of methacholine in the C-group. Thus, the two subjects who received the highest methacholine dose also had the greatest increases in plasma noradrenaline and adrenaline and in heart rate. In these two subjects side-effects such as headache, increased salivation and sweating were observed at the time of cessation of the provocation test.

Neither histamine nor allergen induced bronchoconstriction altered venous plasma catecholamine levels during 5–30 min after cessation of the provocations, when compared to pre-challenge levels (fig. 4).

NPY-LI

Fig. 5. - Plasma concentrations of NPY-LI before and 5, 10, 15 and 30 min after bronchial provocations with histamine (A-H group) and allergen (A-A group) in eight and five asthmatics, respectively. NPY-LI was determined after extraction with acid ethanol (○...○) on reversed-phase silica cartridges (•...•). Mean±SEM.

Basal, pre-challenge plasma levels of NPY-LI were 20.2±2.2 pM in the A-H group and 18.8±2.1 pM in the A-A group as assessed by the ethanol extraction method and 18.5±2.8 pM and 12.3±0.8 pM, respectively, as assessed by the reversed phase extraction method. Plasma NPY-LI remained unchanged throughout the whole trial (fig. 5).
Discussion

All patients were free from asthmatic symptoms at the start of the trial and had PEF values ≥65% of the predicted values. All participating subjects were familiar with the hospital environment and lung function testing with the hospital and performed bronchial provocation tests prior to this study. Thus, the basal bronchial state or possible stress effects due to unfamiliarity with the test situation and the induced bronchoconstriction probably did not influence our results. The asthmatics and control subjects were matched with regard to sex and age and the magnitude of the induced bronchoconstriction was similar, which makes comparisons between the groups possible.

The lack of significant increases of plasma catecholamine levels in all three groups of asthmatic patients and in responding non-asthmatic healthy subjects (C-group) following methacholine implies that acute bronchoconstriction evokes no major increase of sympathetic-adrenal activity. Hence, earlier findings of "a blunted sympatho-adrenal response to bronchoconstriction" in asthmatic patients [1, 7, 8] should not be interpreted as evidence for altered sympatho-adrenal responsiveness in asthmatic subjects. Rather, the present findings and that of a previous study of responses to inhaled methacholine [23] indicate that acute bronchoconstriction is not a stimulus for sympatho-adrenal activation.

Since other stimuli such as pain, psychological stress, hypoglycaemia etc increase sympatho-adrenal activity [4-6] it might seem surprising that bronchoconstriction does not. In the study by Samsa et al. [23] the magnitude of induced bronchoconstriction was similar to that seen in the present study. The present and previous findings concerning venous plasma catecholamine levels do not exclude the possibility that some sympatho-adrenal activation can be elicited by acute bronchoconstriction, since regional activation of e.g. the heart is not necessarily reflected in venous plasma noradrenaline levels [24].

It has been proposed that the lack of elevation of plasma adrenaline levels in response to bronchial obstruction in asthmatic subjects might be due to an inhibitory effect of NPY on the adrenal medulla [15]. Infusions of NPY have been shown to inhibit adrenaline secretion evoked by preganglionic nerve stimulation in phined rats [14]. However, in man the chromaffin cells of the adrenal medulla contain smaller amounts of NPY [12] and a physiologically important interaction between NPY and adrenaline release remains to be established. In the present study we determined plasma NPY-LI levels by an immunoenzymeassay preceded by two different sample work-up methods, as the sample work-up procedure might influence the results. The acid ethanol extraction is the one previously used with this assay [15]. Regardless of the plasma sample work-up procedure we found no elevation of plasma NPY-LI after bronchoconstriction induced by histamine or allergen. Thus, we cannot confirm the claim [15] that bronchial obstruction increases NPY release. Therefore, unless NPY was released locally in the adrenal medulla and not elsewhere, there is no support for a modulatory role of NPY on adrenaline release.

Since bronchoconstriction is not a major stimulus for sympatho-adrenal activity in asthmatics or in healthy subjects the earlier findings of modest increases in plasma levels of noradrenaline [9, 15] and NPY-LI [15] in acute severe asthma do not seem to be related to bronchial obstruction per se. Other factors, such as exhaustion and anxiety following a longer period of severe asthmatic symptoms are probably involved. Since plasma NPY-LI is elevated during exercise [10, 11], the increased work of breathing may also be of importance for the finding of increased plasma NPY-LI in acute severe asthma. During exercise, elevation of plasma NPY-LI is correlated to elevation of noradrenaline but not adrenaline [10, 11], suggesting that NPY release during exercise originates from sympathetic nerves and not from the adrenal medulla. Daniel and co-workers [15] also found a correlation between increases of NPY-LI and noradrenaline. Thus, the present and previous findings are compatible with a hypothesis that both the NPY-LI and the noradrenaline response to acute severe asthma are caused by the increased work of breathing.

There were highly significant increases of plasma noradrenaline levels and heart rate in the four healthy subjects (C-group) in whom no bronchoconstriction (as assessed by PEF) was achieved. The two subjects who inhaled the highest doses of methacholine exhibited side effects such as sweating, increased salivation and headache. Hence, it is probable that the activation of sympathetic mechanisms after methacholine inhalation in the C-group was caused by systemic effects of methacholine. Such systemic effects of methacholine inhalation may also explain the insignificant tendency towards greater increases of plasma catecholamine levels in healthy subjects (to whom considerably higher doses of methacholine were administered) than in the asthmatic subjects.

It is interesting to note that significant bronchoconstriction was observed (sGaw reductions of 56 and 69%) in two of the four subjects in the C-group who did not reach the requirements with regard to reduction of PEF. These two subjects had symptoms consistent with those of airflow obstruction at the highest methacholine concentration, even though no obstruction was revealed by PEF-measurements (7 and 12%, respectively). Thus, in our subjects we had eight responders with regard to PEF and ten responders with regard to sGaw. Since we based our criterion for bronchoconstriction on a 20% decrease in PEF and had a sex-and-age matched control group we chose to present data with the "PEF-responders" in the control group. However, calculating on ten controls ("sGaw-responders") did not change the results of the statistical analyses or interpretation of data. The reasons for the discrepancies between PEF and sGaw are not clear, but it is likely that PEF, being an effort-dependent parameter, can remain high if bronchoconstriction is overcome by increased effort in such subjects. Another explanation could be that alterations of sGaw and PEF reflect events in airways of different diameters. Thus, inhaled methacholine might influence only the largest...
airways in certain subjects, thereby influencing sGW to a greater extent than PEF. A third possibility is that the
deep inspiration which is needed to measure PEF might
duce transient bronchodilatation [25].

The post-challenge courses for recovery of heart rate
and, to some extent, plasma noradrenaline levels, dif-
nered between the A-M and C+ groups. As stated above,
it can not be excluded that some sympathetic activation
may have occurred, although this was not detected as
alterations of plasma noradrenaline concentrations. Our
findings that heart rate and plasma noradrenaline
remained slightly elevated after the bronchial provocation
in the asthmatic subjects, despite an inverse towards
pre-challenge values in the control subjects, suggests
that some sympathetic activation might have been
produced by bronchoconstriction. The reason for this
difference is not clear, but uneven ventilation/perfusion
may have contributed.

Circulating noradrenaline does not influence bronchial
tone [8, 26] or bronchial reactivity [8]. Thus, adrenaline
is the most interesting of the catecholamines with regard
to regulation of bronchial tone. It is well-known that
circulating adrenaline, released from the adrenal medulla,
acts as a hormone with bronchodilatation properties.
Furthermore, we have shown that circulating adrenaline
can prevent allergen-induced bronchoconstriction [7].
The present results, however, do not support the idea
that endogenously produced circulating adrenaline is of any
major importance as a counter-regulator in connection
with acute bronchoconstriction, as all three methods of
eliciting bronchoconstriction failed to elevate plasma
adrenaline to any appreciable extent.

In conclusion, bronchoconstriction is not an important
stimulus for sympathetic-adrenal activation and there is no
significant difference between asthmatic and non-
asthmatic subjects in this respect. Hence, the finding
that adrenaline is not a counter-regulatory hormone in
connection with bronchoconstriction seems to represent a
general phenomenon, rather than a defective response in
asthmatic subjects. Furthermore, we failed to substanti-
ate the idea that NPY might be involved in broncho-
constriction and/or the defective adrenaline response to
bronchoconstriction.

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