Editorial Review

Factors contributing to bronchial hyper-responsiveness in asthma

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INTRODUCTION

Asthma is a condition characterized by recurrent breathlessness, cough or wheeze caused by variable or intermittent narrowing of intrapulmonary airways [1]. All asthmatic individuals have hyper-responsive intrathoracic airways and because of this most experience acute attacks of bronchoconstriction at times. A great deal of work has been done to understand this hyper-responsive state of the airways and this article summarizes some of this work. However, by way of introduction and to put this type of acute bronchial reaction in context we will describe the various other forms of bronchial narrowing that occur in asthma and their significance. It will be seen that although acute bronchoconstrictive reactions are relatively easy to study in the laboratory, the less acute obstructive reactions are more important in the morbidity and mortality of this condition. It is hoped that studies of acute bronchoconstriction may give insight into fundamental bronchial abnormalities in asthma that will be of relevance to our wider understanding of this condition.

On the basis of time-course we classify bronchial obstruction as follows:

1. Acute obstruction: of sudden onset and brief duration (minutes).
2. Sub-acute obstruction: of slower onset (hours) and longer duration (days and weeks).
3. Chronic obstruction: varying little from day to day and continuing for months and years.

In addition, there is an exaggerated diurnal variation of airway calibre in asthma that is superimposed on the above types of obstruction. For this reason, airways obstruction and symptoms are usually worse at night or on waking in the morning [1].

Acute bouts of obstruction occur in most asthmatic subjects, and may be the sole manifestation of their condition. These attacks are often caused by exercise or by breathing smoky or otherwise polluted air, and when attacks occur at a low threshold they are an important cause of disability. This is particularly true in children in whom strenuous exercise is such an important part of everyday life. These attacks are self-limiting and, although distressing, are not usually life-threatening. Exceptionally, very severe acute bronchial obstruction may be fatal, usually in the context of anaphylaxis. The principal cause of acute obstruction is contraction of smooth muscle in the bronchial wall, as demonstrated by its prevention or rapid abolition by β2-adrenoceptor agonist drugs [2] that are known to relax bronchial smooth muscle [3].

Most deaths from asthma are a consequence of an overwhelming sub-acute obstructive reaction. The duration of the fatal attack is usually hours, not minutes [4]. Non-fatal attacks usually last for several days even with aggressive treatment, but without this may last for weeks. Sub-acute attacks may develop against a background of poor asthma control, but equally may develop without warning or apparent cause in subjects who are well-controlled or asymptomatic.

Sub-acute obstruction responds poorly to β2-adrenoceptor agonist agents (although this poor response may be life-saving), demonstrating that bronchial smooth muscle contraction is only partially responsible for bronchial narrowing. In patients who die in an asthmatic attack there is obstruction of bronchial lumena by gelatinous plugs consisting of inspissated bronchial secretions, inflammatory exudate and cells, and denuded epithelium. In addition, the lumena are narrowed by thickening of the bronchial wall by inflammatory oedema, infiltration with inflammatory cells and hyperaemia [5, 6]. Although the precipitating cause is often unknown in the individual case, two precipitants of attacks are well recognized: allergy and infection.

Inhalation of antigen usually causes an acute broncho-obstructive reaction of brief duration (minutes). However, in a proportion of cases this reaction is followed, after an
unobstructed interval of several hours, by sub-acute obstruction ('late response') [7].

Chronic airway obstruction, occurring for months and years with little variation, is an important cause of disability in a proportion of asthma sufferers. The immediate response to $\beta_2$-adrenoceptor agonist drugs is disappointing, but obstruction may be completely or partially relieved by treatment with corticosteroids or by removing the patient from chronic antigen exposure [8]. In many patients some degree of obstruction remains after maximal therapy, suggesting permanent structural changes in the airways. Epidemiological studies [9] have shown that even in mild asthma chronic airflow obstruction may develop slowly. The mechanism of these permanent changes is unknown, but it is clearly of major importance to know the factors involved and whether the process is modifiable by asthma treatment.

Sub-acute and chronic obstruction in asthma is clearly of major importance to the morbidity and mortality of the condition, but these forms of obstruction are much more difficult to study in the laboratory than the acute obstructive reaction. Post-mortem studies of asthmatic subjects who have died for reasons unconnected with asthma have demonstrated an active inflammatory process in the bronchial wall even when asthma was reasonably controlled at the time of death [10]. It is extremely difficult to study this inflammation in life but some progress may be expected when highly specific and safe antagonists of inflammatory mediators are developed. Laboratory studies of asthmatic subjects have therefore tended to concentrate on the acute reaction, its provocation and prevention in the hope of identifying basic bronchial abnormalities in the asthmatic airway.

PROVOCATION OF ACUTE BRONCHOCONSTRICTION

In the laboratory, acute obstructive reactions can be produced by a wide range of physical, physicochemical, chemical and pharmacological bronchial stimuli. These include smooth muscle agonists such as methacholine, inflammatory mediators such as histamine or prostaglandins, bronchial irritants such as sulphur dioxide, physical stimuli such as cooling or drying the airways, and promoters of bronchial inflammation such as ozone or antigens. Both the stimulus and the broncho-obstructive response may be quantified and hence this type of bronchial provocation lends itself to laboratory investigation to a much greater extent than the more chronic forms of obstruction, or those that occur at night.

One major insight into the mechanisms of asthma has been gained by studies of the acute bronchial obstructive reaction: asthmatic subjects are hyper-responsive to a wide variety of bronchial stimuli. More specifically, the asthmatic subject bronchoconstricts to a stimulus that has no effect on a non-asthmatic subject. This hyper-responsiveness is at the root of most acute broncho-obstructive reactions.

GENERAL CHARACTERISTICS OF BRONCHIAL HYPER-RESPONSIVENESS

Hyper-responsiveness is virtually universal in asthma. There is evidence that the abnormality is both inherited and acquired [11]. There is an overlap of degree of responsiveness between the asthmatic and non-asthmatic populations with atopic non-asthmatic individuals tending to show an intermediate level of responsiveness [12]. Responsiveness shows diurnal variation [13, 14] and may increase after antigen exposure [15], viral infections [16] and exposure to irritant gases [17]. There are relationships within subjects between responsiveness to different provoking agents: there is a close relationship between the responsiveness of individuals to histamine and methacholine [18]. Responsiveness correlates crudely with the severity of asthma as measured by the need for treatment [19]. In all subjects $\beta$-adrenergic stimulating drugs decrease responsiveness acutely [2]. $\beta$-Adrenergic blocking drugs increase responsiveness in asthmatic subjects but have no effect in normal subjects [20].

MEASUREMENT OF RESPONSIVENESS

Over the past 15 years it has become standard to define human bronchial responsiveness by means of dose-response curves [21, 22]. Usually the bronchial agonist is given as an aerosol by inhalation, and the bronchoconstrictor response is measured by a change in forced expiratory volumes or flows (maximal or partial), or by a change in airways resistance ($R_{aw}$), conductance ($G_{aw}$) or specific conductance ($sG_{aw}$) $sG_{aw} = 1/Raw \times V_{s}$, where $V_{s}$ is the thoracic gas volume). No measuring technique has shown an overwhelming advantage over the others [23]. We use $sG_{aw}$ measured in the constant volume body plethysmograph, as our index of airway calibre change. Compared with the commonly used forced expiratory volume in 1 s ($FEV_1$), $sG_{aw}$ is more sensitive to small changes in calibre, is less arduous for the subject, and avoids the artefacts seen with $FEV_1$ resulting from taking a deep breath to total lung capacity [24, 25]. Conversely, $FEV_1$ is more reproducible, easier for the operator and much cheaper to perform.

To produce a dose-response curve it is necessary to give increasing doses of the provocative agent and to repeatedly measure response. Most commonly the bronchial doses are given in a cumulative fashion with doubling doses being given at intervals of 3–5 min. The aim is to start at a low agonist dose that produces no bronchial narrowing, and to progressively increase the dose until the subject is aware of moderate chest tightness, at which point the calibre measurement will register a significant airway narrowing. Responsiveness is defined in terms of the dose required to produce a certain degree of bronchial narrowing. For tests using $FEV_1$ it is usual to define $PC_{20}$, the provocative concentration required to produce a 20% fall in $FEV_1$. Such a change would be outside the usual range of variability of $FEV_1$ during a baseline period of observation. For tests using $sG_{aw}$, which is
less reproducible, PD_{35}, the provocative dose causing a 35% fall in conductance is measured.

One major area of uncertainty concerns the comparison of dose–response curves which start from different airway calibres. Bronchial narrowing from an FEV\textsubscript{1} of 4 L to 3.2 L or from 1 L to 0.8 L are both reductions of 20%, but in one the absolute change is four times the other. Do these responses represent equivalent degrees of bronchoconstriction? If they are equivalent, then the slope of the log dose–response curve which starts from an FEV\textsubscript{1} of 4 L must be four times as steep as that which starts from 1 L, so that when 'normalized' to the same starting FEV\textsubscript{1} slopes will be the same. With $s\text{Gaw}$ measurements of histamine and methacholine dose–response curves, we have shown that this is the case. The starting level of conductance is a scaling factor for the subsequent response under all the circumstances we have examined. That is, the slope of the response is proportional to the starting $s\text{Gaw}$. Thus the slope is less in asthma than in normal subjects directly in proportion to airway conductance before challenge [26]. Similarly, on different occasions the slope of the response varies in the same individual in proportion to changes in conductance; if the subject is bronchodilated before challenge with atropine or salbutamol, the slope is increased in proportion to the increase to baseline conductance [26, 27]; prior bronchoconstriction has the opposite effect [28].

This means that when dose–response curves are 'normalized' to the same starting conductance value (i.e. when the response is expressed as a percentage change from the starting value) all curves become approximately parallel. The position of the curve on the dose axis may therefore reasonably be described in terms of a single value such as PD\textsubscript{35}. Viewed in this way bronchial hyper-responsiveness in asthma consists of a paralleled displacement to the left of the agonist dose–response curve. Competitive and functional antagonists, such as atropine or salbutamol, produce a dose-dependent rightward shift of the dose–response curve [26, 27].

To our knowledge, the validity of PC\textsubscript{20} in this regard has not been demonstrated, particularly in regard to comparisons between individuals. In fact, the slope of the histamine dose–response curve, when response is measured by FEV\textsubscript{1}, is a function of responsiveness. More responsive subjects have steeper slopes [29].

**DELIVERY OF BRONCHOCONSTRICTOR AGENTS TO THE BRONCHIAL WALL**

One very unsatisfactory feature of testing in vivo of bronchial response to inhaled drugs is the uncertainty over the quantity of drug reaching bronchial smooth muscle. Several lines of evidence would suggest that bronchial response is a function of both the quantity of drug penetrating into the tracheobronchial tree and also its site of deposition. Thus, Wanner et al. [30] showed that in normal subjects histamine responsiveness was related to the quantity of histamine retained in the lungs. Ruffin et al. [31] demonstrated that when histamine was deposited preferentially in central bronchi it was far more effective at causing bronchoconstriction than when it was distributed evenly to the whole tracheobronchial tree.

We have recently examined the relationships between lung dose, site of deposition and responsiveness [32]: We mixed the bronchial agonist, methacholine, with \textsuperscript{99m}Tc-labelled diethylenetriaminepenta-acetic acid (\textsuperscript{99m}Tc-DTPA) so that pulmonary deposition could be visualized and quantified with a gamma camera. The method of inhalation was standard to many laboratories: the subject inspired slowly from functional residual capacity to around total lung capacity, without breath holding, and the aerosol was released automatically at the beginning of inspiration. The particle size of the aerosol produced by the jet nebulizer was well characterized and was similar to that described for other jet nebulizers.

The percentage of nebulized dose reaching the lungs was highly variable (1–20%), but a similar wide range was seen in normal and asthmatic groups. There was no significant difference between groups in mean lung dose achieved. The distribution of aerosol within the lung did, however, differ between groups, with asthmatic subjects usually showing patchy central distribution and normal subjects a more even peripheral and central distribution. Frequently, scans showed 'hot spots' in the region of lobar, segmental or sub-segmental bronchi, which are divisions of the tracheobronchial tree where air flow resistance per bronchial division is progressively increasing [33]. Thus in many subjects the highest aerosol deposition occurred (probably due to a turbulent airflow) at points in the tracheobronchial tree of relatively high resistance. Narrowing these high-resistance segments will have a greater effect on total airway resistance than a similar degree of narrowing elsewhere. Thus this type of bronchial challenge, particularly in asthmatic subjects, is probably dominated by deposition in and narrowing of central intrapulmonary bronchi. Interestingly, we detected very little activity over the trachea or main bronchi despite the fact that we performed anterior gamma camera scans.

We were, however, unable to show a significant relationship between the quantity or pattern of aerosol deposition and methacholine sensitivity. Asthmatic subjects with central airways deposition tended to be more sensitive than subjects with peripheral deposition, but the relationship was not statistically significant. We believe that this is because there are numerous other factors controlling methacholine sensitivity apart from drug deposition and that the effect of deposition is lost in this 'noise'. For this reason we have also examined the responsiveness of subjects to an agent whose effects are more simply determined by drug concentration, a pharmacological antagonist compound. The blocking effect of a competitive pharmacological antagonist depends upon its concentration at its receptor and the association coefficient of the antagonist–receptor complex [34]. Atropine is a competitive antagonist at the cholinergic muscarinic receptor and produces a dose-dependent antagonism of methacholine-induced bronchoconstriction in vivo that is compatible with its main action being competitive antagonism [35]. In non-asthmatic subjects a given dose of atropine produces...
a similar degree of antagonism in the bronchi, whether given by inhalation or intravenously [36], but in asthma larger degrees of blockade may be seen with inhaled but not intravenous atropine [36, 37]. This suggests that inhaled atropine achieves higher local concentrations in these subjects than in others. We have shown that the degree of antagonism achieved with a given dose of inhaled atropine correlates significantly with the dose depositing in central airways [32]. This demonstrates that total deposition in the lung and its pattern are factors influencing bronchial response to an inhaled substance. However, the influence on agonist responsiveness is limited, and intersubject variation of deposition explains only a small proportion of the intersubject variance of agonist responsiveness.

**IS BRONCHIAL RESPONSIVENESS A FUNCTION OF INITIAL AIRWAY CALibre?**

Fig. 1 demonstrates several reasons why bronchial responsiveness may be expected to be a function of airway calibre. (1) With narrow airways greater responsiveness may be a consequence of central deposition of inhaled aerosol. (2) Bronchial smooth muscle in the constricted bronchus may be in a state of enhanced activation (due to inflammatory mediators or neural influences) and this may be associated with hyper-responsiveness [38]. (3) Narrowing may be a consequence of bronchial wall-thickening or luminal mucus-plugging, and this may enhance the degree to which the bronchial lumen is narrowed for a given degree of bronchoconstriction [39].

**Relationship between resting airway calibre and responsiveness**

This question looks at all three reasons mentioned above. Asthmatic subjects have narrow airways and increased responsiveness when compared with normal subjects, and therefore when data from asthmatic and normal populations are analysed together there are significant inverse correlations between airway calibre and responsiveness [26, 40]. However, the relationship is not well defined, and thus within a normal or asthmatic group of subjects no such relationship can be discerned. These findings are compatible with the notion that calibre and responsiveness are altered by the same factors, but not necessarily by the same extent.

**Effect of prior bronchoconstriction on bronchial responsiveness**

In these experiments we used a bronchoconstrictor agent, methacholine, to produce sustained bronchoconstriction and we then challenged the subjects with a second agent, histamine [28]. We were therefore examining the first two reasons above. We performed these experiments on normal subjects who were bronchoconstricted by methacholine to the extent of a 40% reduction of sGaw, taking them well into the conductance range that we see in mild asthma. This degree of prior bronchoconstriction had no discernible effect on bronchial responsiveness to histamine. From our studies and those of other workers on aerosol deposition we would expect that the histamine aerosol would have deposited more centrally due to the prior bronchoconstriction, and this would tend to enhance bronchial responsiveness. Clearly, as we have previously concluded, this is not a dominant factor determining responsiveness. In addition, this experiment strongly argues against baseline airway calibre as being an important factor per se.

**Effect of prior bronchodilatation on bronchial responsiveness**

It is more difficult to be categorical about the effect of bronchodilatation because drugs used to produce this effect, such as anticholinergic or β-adrenoceptor agonists, may reduce responsiveness independently of any change in airway calibre [41]. However, a large dose of atropine (4.5 mg; 12.3 μmol) caused a 37% and a 83% increase in airway conductance in normal and asthmatic subjects.
respectively, but caused only a 3.5-fold shift in the dose–response curve to histamine [26]. This decrease of responsiveness could be due to factors other than bronchodilatation, for example antagonism of reflex vagal bronchoconstriction [42] or an antihistaminic effect of atropine [43]. If the whole decrease in responsiveness were a direct consequence of bronchodilatation we can conclude that this is a small change for a large degree of bronchodilatation. The conclusions from this observation are similar to those with prior bronchoconstriction: that the effect of airway calibre on drug deposition has a limited effect on responsiveness, and that baseline airway calibre itself has little effect on responsiveness by any other mechanism.

THE CAUSE OF HYPER-RESPONSIVENESS: AN HYPOTHESIS

The bronchial response to an inhaled particulate agonist is achieved by a number of series and parallel steps (Fig. 1). In laboratory studies it is usual only to measure the dose or concentration of the provoking agent that is nebulized (‘input’), and its effect on bronchial calibre, measured in terms of airflow or airways resistance (‘output’). Between the ‘input’ and the ‘output’ of the system is a seemingly impenetrable ‘black box’ of great complexity [44]; probably no two ‘black boxes’ are quite alike. The total intersubject difference in non-specific bronchial responsiveness within the population is more than 1000-fold, but when attempts have been made to study single links in the chain of events described in Fig. 1 intersubject differences have generally been small. This may be, in part, because the populations used to study these phenomena do not include the highly responsive severe asthmatic patients who are too sick to be studied. Equally it seems probable that the wide intersubject differences in responsiveness result from multiple small differences at different stages in the sequence of events described in Fig. 1. Thus we may consider two subjects, one normal and the other with asthma. The asthmatic subject is 1000 times more sensitive to inhaled methacholine than the normal subject. The asthmatic subject’s hyper-responsiveness could hypothetically be due to several factors: first, he may deposit more methacholine in his central tracheobronchial tree than the normal individual due to decreased airway calibre or other mechanism [30, 32, 45]. For the sake of our argument we will say that he deposits 10 times more. Secondly, his bronchial smooth muscle may be 10 times more sensitive to methacholine due to the presence of excitatory inflammatory mediators or other factors, and therefore responds at one-hundredth of the inhaled dose that was required by the normal subject. If, in addition, we postulate that due to bronchial wall-thickening and mucus-plugging of the asthmatic bronchus, it takes only one-tenth of the normal amount of muscle contraction to increase resistance by a given amount, then this degree of bronchoconstriction will be reached at one-thousandth of the methacholine inhaled dose in the asthmatic subject as compared with the normal subject. In this regard we know that aerosol deposition varies between individuals by at least 20-fold ([32]; see above); bronchial smooth muscle, in vitro, from patients with bronchitis shows a between-subject range of sensitivity to histamine and methacholine of approximately 30-fold [46, 47]; partial plugging of airways will inevitably mean that resistance will become more sensitive to changes in smooth muscle contraction [39]. In addition, it would seem inevitably that mediator release and the strength of bronchoconstrictor reflexes will vary between individuals. Thus it may be a mistake to seek for the cause of bronchial hyper-responsiveness: there are probably several causes in each individual.

CONCLUSIONS

Bronchial hyper-responsiveness is a marker of an underlying bronchial abnormality in asthma. Response to a variety of agonist and antagonist substances can be defined. The abnormality in asthma is that response occurs at a lower dose than in non-asthmatic subjects, but in other regards the response of normal and asthmatic subjects are similar, albeit scaled to a lower airway calibre in the asthmatic subjects. Future work should define more clearly the quantitative importance of the various factors involved in the mechanism of bronchial hyper-responsiveness.

Hyper-responsiveness is most marked in patients with the most severe asthma [19]. Thus it would seem that there is a relationship between the tendency to develop acute bronchoconstrictive reactions and the tendency to more prolonged forms of obstruction. The link is probably bronchial inflammation. However, it remains an open question as to whether studies of the acute bronchoconstrictive response will be of substantial use in understanding the more prolonged forms of obstruction that cause most debility and virtually all deaths in asthma.

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