Bronchial hyperresponsiveness in children

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BRONCHIAL HYPERRESPONSIVENESS IN CHILDREN

Bronchial hyperresponsiveness is an integral part of childhood asthma, yet little is known about how or why the airways of asthmatics are hyperresponsive to a variety of stimuli. There are both excitatory and inhibitory neural supplies to airway smooth muscle. Also cholinergic ganglia have many receptors, stimulation of which inhibit release of acetyl choline. An imbalance between the excitatory and inhibitory influences could contribute to bronchial hyperresponsiveness. An increase in airway smooth muscle mass or sensitivity could potentially contribute to hyperresponsiveness, however, the contractile properties of asthmatic muscle in vitro do not differ from normal. A defect in epithelial function or integrity could expose airway receptors and smooth muscle to environmental stimuli. Airway inflammation can cause epithelial damage and be associated with increased airway responsiveness.

In children, relationships exist between measurements of bronchial responsiveness and severity of asthma if one examine group data. However, the relationship is much less certain for any individual. In population studies 10–30% of children with no history of asthma will have a positive histamine challenge test, and as many with clinical asthma will have negative tests. Despite this current treatment of asthma consists of two parts: 1. treatment of acute symptoms with bronchodilators; and 2. prophylactic treatment aimed at decreasing airway inflammation and hopefully decreasing airway responsiveness.

BRONCHIAL RESPONSIVENESS IN CHILDREN

Bronchial hyperresponsiveness is an integral part of childhood asthma, yet we know very little about how or why the airways of asthmatics are hyperresponsive to a variety of stimuli. In this talk I will briefly review some of the potential mechanisms of bronchial hyperresponsiveness and then try to tie bronchial hyperresponsiveness into the clinical picture we call asthma.

Mechanisms that may play a role in bronchial hyperresponsiveness

There are at least four potential sites in the respiratory system that could contribute to bronchial hyperresponsiveness.

− Neural control of the airways,
− Airway smooth muscle,
− Airway epithelium,
− Airway inflammation and inflammatory mediators.
Neural control of the airways

There is an abundant nerve supply to airway smooth muscle in “cartilaginous” bronchi. Four types of nerves may be involved in the normal control of airway smooth muscle:

1. Parasympathetic vagal cholinergic excitatory nerves

These nerves control the “resting” tone of the muscle, cause contraction of cartilaginous airways, and stimulate bronchial mucous secretion. Their ganglia have many receptors, stimulation of which can modify cholinergic transmission. The primary sensory receptor is the “irritant” receptor which is activated by many stimuli, e.g. mechanical (dust), chemical (SO₂, cigarette smoke), inflammatory mediators (histamine, prostaglandins), and others including, pulmonary oedema, microemboli, anaphylaxis, etc.

2. Sympathetic adrenergic inhibitory nerves

It is difficult to show any direct innervation of airway smooth muscle by these fibres, but they may regulate Acetylcholine release from parasympathetic nerves by an action on the parasympathetic ganglia.

3. Parasympathetic non-adrenergic inhibitory system (NAIS)

These fibres seem to be distributed preferentially to large to mid sized airways. Vasoactive intestinal peptide is the likely neurotransmitter. The bronchial “C” fibres are the likely sensory receptors. VIP receptors have been identified on airway smooth muscle, submucosal glands, and endothelial cells. Stimulation of the NAIS system leads to relaxation of constricted airway smooth muscle, mucous secretion, and vasodilatation.

4. Parasympathetic non-cholinergic excitatory system

This system is thought to be comprised of sensory fibres containing Substance P. It seems to have a greater density in small airways and stimulation may result in hyperaemia, oedema, contraction of smooth muscle, and mast cell degranulation.

The neural control is ideally placed to play a central role in producing bronchial hyperresponsiveness. This could result from a disturbance of the balance between excitatory and inhibitory systems; speculation that infants are born with responsive airways and that those who go on to have asthma fail to lose this resposiveness. Other studies have suggested that children aged 5-6 respond to lower doses of inhaled agonist than do older children or adults. However, many technical factors, including the dose of agonist delivered to the airways, the site of deposition within the airways and the test used to measure the response have to be standardized before one can draw valid conclusions.

Relationship between bronchial responsiveness of clinical asthma

While, as a group, children with asthma are more likely to have a positive response to tests of bronchial responsiveness that those without asthma, on an individual level the relationship is not so close. In population studies 10-30% of children with no history of asthma will have a positive histamine challenge test, and as many with clinical asthma will have negative test.

Table 1 shows data collected from two populations of children in NSW, totaling approximately 2300 children. These figures represent cumulative prevalences, ie if a child has ever had
asthma diagnosed he will be included in the asthma group. These data show that while a histamine challenge test is more likely to be positive in the asthma group, there are many children who we would consider to have asthma, who do not have positive histamine challenge tests.

There is also a relationship, on group data, between the level of histamine responsiveness and the requirements for asthma treatment, with those requiring more treatment being more sensitive to histamine. However, this relationship is also very loose if one examine individual’s data.

There is much debate as to which test of bronchial responsiveness best separates the asthmatic population form the non-asthmatics. Recent work suggests that the inhalation of hypertonic saline, potentially a more “natural” stimulus, may better separate the asthmatic and non-asthmatic populations because only those with asthma seem to respond. However, no population studies have yet been done in children and at this time histamine challenge remains the “gold-standard”.

**Treatment of bronchial hyperresponsiveness**

Asthma is now generally considered to be an inflammatory disease and there is appears to be a link between airway inflammation and bronchial hyperresponsiveness.

Sympathomimetics and theophylline do not decrease bronchial hyperresponsiveness. Cromoglycate can prevent the increase in bronchial hyperresponsiveness seen in grain handlers during the grain season. However, despite its ability to control clinical asthma in some subjects but the results of trials aimed at demonstrating a decrease in bronchial hyperresponsiveness in asthmatics are disappointing. Inhaled steroids have been demonstrated to decrease the sensitivity to the test on bronchial responsiveness, but oral steroids have not.

It seems reasonable that all children who required continuous treatment for asthma should have a prophylactic agent included in their treatment regimen. The choice lies between cromoglycate or inhaled steroids. Both can be effective in controlling asthma, and an abnormal number or distribution of nerves; or a disturbance of the normal regulation of neurotransmission, e.g. via receptors on the airway ganglia. Beta-2, alpha-2 and M-2 (muscarinic) receptors have been found on cholinergic airway ganglia. Stimulation of these receptors inhibits cholinergic transmission. Recently, an increase in substance p-containing nerves and a decrease in VIP-containing nerves have been demonstrated in the airways of asthmatics, when compared to non-asthmatic adults. Much work still needs to be done in this area.

**Airway Smooth Muscle**

People dying from asthma have been demonstrated to have increased smooth muscle in their airways. A greater muscle mass may be expected to produce more shortening in vivo for a given stimulus. Also thickening of the airway wall may lead to narrowing of the airway lumen. This would lead to a greater increase in airway resistance for a given degree of muscle shortening ($R a 1/r^4$). However it is unlikely that people with mild to moderate asthma have an increased amount of airway smooth muscle, yet they have increased bronchial responsiveness.
An increase in smooth muscle sensitivity would produce a greater response to a given stimulus and could lead to what is recognized as bronchial hyperresponsiveness. However, no differences have been demonstrated in vitro in the contractile properties of airway smooth muscle from asthmatics and non-asthmatics. There has been a recent suggestion that relaxation may not be normal in smooth muscle from asthmatics, but more work is needed to confirm this.

**Airway Epithelium**

The normal role of the epithelium is to act as a mechanical barrier to prevent irritant substances reaching the receptors and smooth muscle beneath. It also secretes a variety of substances including bronchodilator prostaglandins and a “relaxant” factor. People dying from asthma have been noted to have widespread epithelial destruction, raising the possibility that loss of the normal epithelium may contribute to bronchial hyperresponsiveness. However, measurements of epithelial permeability in vivo have failed to show increased epithelium permeability in subjects with mild to moderate asthma.

Thickening of the airway wall, both epithelium and smooth muscle could lead to increased responsiveness to a given stimulus from purely geometric factors. When airway smooth muscle contracts, the epithelium “folds” as the airway narrows. If the epithelium is thicker to begin with, the airway lumen will be narrowed more, for the same degree of muscle shortening. As airway resistance is inversely proportional to the fourth power of the radius, the resistance will rise much more in an airway with a thickened epithelium. Thus a thickened epithelium could act an “amplification” mechanism and make the airway appear more responsive.

**Airway Inflammation**

Airway inflammation leads to: epithelial damage; vasodilatation; increased epithelial permeability and interstitial oedema; increased mucous secretion; muscle contraction; increased vagal reflex activity; increased airway wall thickness; and increased bronchial responsiveness. Airway inflammation can be induced by viral infection, exposure to antigen, etc.

Epithelial biopsy from mild asthmatics frequently show: epithelial abnormalities, with a thickened epithelium, basement membrane and submucosa; lots of activated eosinophils, fewer neutrophils, and increased T4 lymphocytes; and margination of inflammatory cells in the blood vessels. However, these inflammatory changes are not invariably present in asthmatics.

Inflammatory mediators can be released from mast cells, eosinophils, neutrophils and possible endothelial cells. The precise role of the various inflammatory mediators in bronchial hyperresponsiveness is unknown. The mediators that are currently thought to be important include: the products of arachidonic acid metabolism (including prostaglandins and leukotrienes); histamine; major basic protein (released from eosinophils); and platelet activating factor (released from many cells including mast cells, platelets, basophils).

The most studied model of airway inflammation is the response of a susceptible subject to an antigen challenge. Following an antigen challenge one of three responses may be seen: an early fall in lung function with spontaneous recovery over 1–2 hours; a late fall in lung function occurring 4–12 hours after challenge without an early response; or a combined early and late
response. The early response is due to an IgE-dependent mast cell degranulation, which can be prevented by pre-treatment with salbutamol or cromoglycate. The late response seems to be stimulated by the recruitment of inflammatory cells, especially eosinophils, into the airway wall, possibly attracted by the release of PAF. The late response, but not the early response, is associated with an increase in non-specific bronchial responsiveness. Speculation is that major basic protein, released from eosinophils may be related in this process, however, the mechanism is far from clear. Treatment with cromoglycate or corticosteroids prior to antigen challenge can prevent both the late response and the increase in bronchial responsiveness.

Airway inflammation is certainly a part of asthma, but what is not clear is whether the inflammation is the cause of, or the result of bronchial hyperresponsiveness.

**Assessment of Bronchial Hyperresponsiveness**

Many challenge tests have been devised to test bronchial responsiveness. The most common are the pharmacologic tests, including inhalation of histamine or methacholine, and the non-pharmacologic tests including exercise, isocapnic hyperventilation, and inhalation of hypo- or hypertonic aerosols. These tests are all non-specific test of bronchial responsiveness. However, they have proved useful in helping to define the asthmatic population. The distribution of bronchial responsiveness follows either a uni-modal distribution, skewed to the left or a bi-modal distribution. There is not a clear distinction between people with mild asthma and non-asthmatic individuals. Subjects who are allergic to a specific antigen can be challenged by having them inhale that antigen.

Recent studies in normal infants have demonstrated that virtually all infants have responsive airways to a variety of stimuli; including cold air, histamine, and methacholine. This led to the choice between the two depends largely on personal preference and experience. Cromoglycate has no side effects whereas inhaled steroids uncommonly can cause oral candidiasis and hoarse voice if not inhaled correctly. It therefore seems reasonable to try cromoglycate first and switch to inhaled steroids if the symptoms are not controlled.

**Table 2**

<table>
<thead>
<tr>
<th>Relationship between Bronchial Hyperresponsiveness and Asthma</th>
<th>+ve</th>
<th>-ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosed Asthma</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Wheeze</td>
<td>39%</td>
<td>61%</td>
</tr>
<tr>
<td>Exercise Wheeze</td>
<td>53%</td>
<td>47%</td>
</tr>
<tr>
<td>Night Cough</td>
<td>34%</td>
<td>64%</td>
</tr>
<tr>
<td>Any Resp. Symptom</td>
<td>37%</td>
<td>63%</td>
</tr>
<tr>
<td>No asthma/resp. symptom</td>
<td>10%</td>
<td>90%</td>
</tr>
</tbody>
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