EDITORIAL

NONSPECIFIC AIRWAY HYPERRESPONSIVENESS: MUSCLES AND MEDIATORS OR TUBES AND TETHERING?

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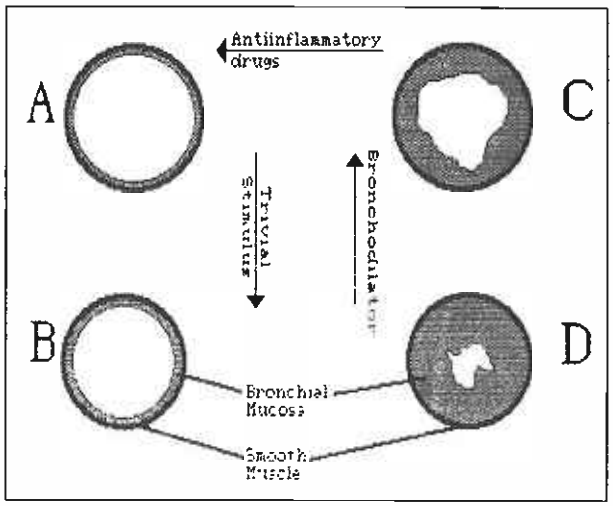
One of the key differences between asthmatics and normal subjects lies in their respective airways. Trivial stimuli which have no perceptible effect on normal airways could evoke a bronchoconstrictive response in asthmatic airways. This inordinate sensitivity is called nonspecific airway hyperresponsiveness (also nonspecific bronchial hyperreactivity)[1] and may be the reason why an asthmatic may develop a severe attack in the same environment where a normal subject remains unaffected. The nonspecific stimuli may be physical (exercise, cold air, dry air) or pharmacologic (histamine, methacholine).

What underlies this exaggerated airway response (usually measured as a fall in FEV_1, forced expired volume in the first second, or SGaw, specific conductance) in asthmatics? Is it abnormally hypercontractile airway smooth muscle? There is some evidence to suggest this on histopathological studies which show a degree of smooth muscle hyperplasia and hypertrophy in asthmatics[2]. However, when isolated airway smooth muscles of asthmatics are studied, there is a poor correlation between the sensitivity of the smooth muscle in vitro and the reactivity of the airway in vivo[3]. If the in vitro airway smooth muscles strips are not hyperreactive, why is the whole intact airway hyperreactive in vivo?

A possible explanation initially put forward by Bouhuys[4] and more recently developed by Hogg[5], follows. It has long been known that there is airway inflammation in asthmatics[6].



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The airway wall is thus thickened with inflammatory cellular infiltrate, exudate and mucus. However, the airway is thickened inwards, viz internal to the smooth muscle layer (see Fig). In a normal airway, a certain degree of airway smooth muscle shortening would decrease internal cross-sectional area slightly (see Fig: A-B). In the inflamed airway, the same degree of airway smooth muscle shortening would cause a great diminution of internal cross-sectional area because of the increased wall thickness (see Fig: C-D). While there is not a lot of difference in the flow resistance of airways A and C, there is a tremendous increase of flow resistance in airway D compared with airway B because resistance is inversely related to the fourth or higher power of radius.

If this is correct, then treating with bronchodilators viz sympathomimetics, merely moves the patient from state D to state C, shown as a rise in FEV_1, and the patient would still be prone to getting another asthmatic attack on the slightest provocation (ie. he can easily revert to state D). Antiinflammatory agents would however move the asthmatic from state C to state A, so that even when provoked by some nonspecific stimulus to the smooth muscle, he may remain asymptomatic because he would only have moved from state A to state B. This proneness to bronchoconstrict to trivial stimuli is measured by histamine or methacholine inhalation challenge and is expressed as $PD_{20}FEV_1$ (provocative dose that causes a 20% fall of FEV_1 from baseline). Thus a patient in state A will have a high $PD_{20}FEV_1$ ie. he is so stable that only a high dose of the pharmacologic agent will provoke an airway response. Conversely, a patient in state C will have a low $PD_{20}FEV_1$. The treatment of asthma should then be directed not just at the symptomatic bronchoconstriction but at the underlying airway inflammation. Topical steroid inhalers are believed to play this role.

Another intriguing hypothesis for nonspecific airway hyperresponsiveness, also a mechanistic one, was put forward by Macklem[7]. He proposed that the degree of airway narrowing resulting from airway smooth muscle contraction depends on the smooth muscle force which tends to constrict the airway, and the load against which the smooth must act. This load consists of the elastance of the airway, the elastance of the lung parenchyma, and the interdependence between the two[8]. If the load were great, the smooth muscle contraction would be mainly isometric and little airway constriction would result. If however, the load were small, or if the mechanical linkage between the airway and the parenchyma were uncoupled, smooth muscle contraction would be mainly isotonic and result in airway constriction. By studying methacholine induced airway constriction in normal subjects, they were able to demonstrate that the maximal airway response to methacholine was volume dependent, being greater at FRC minus 500ml than at FRC (functional residual volume). They explained that this was due to the higher elastic load at FRC than at FRC minus 500ml, possibly due to altered

interdependence between the airways and the parenchyma at the lower volume.

Woolcock et al[9] found that normal subjects had a plateau of bronchoconstrictor response to histamine inhalation challenge, whereas asthmatics did not. This means that whereas in asthmatics the airway continues to constriet with increasing doses of histamine, in normal subjects, after a certain degree of airway constriction, no further constriction will occur despite supramaximal stimulation. A normal subject is thus 'protected' from excessive constriction. This is compatible with Macklem's findings. Thus normal subjects may have a greater load against which the smooth muscle must act. Indeed the reduced elastic recoil found in asthmatics during an acute attack may be real and not artefactual as previously thought.

In summary, the first hypothesis explains airway hyperresponsiveness on the basis of increased internal wall thickness, presumably inflammatory. The second explains it on the basis of a balance of forces, between smooth muscle contraction on the one hand and parenchymal elastic recoil and linkage on the other. Both explanations are entirely mechanistic and neither needs to invoke smooth muscle hypercontractility nor excessive mediator release or sensitivity.

These two hypotheses are by no means the last word on airway hyperresponsiveness and asthma, but they do illustrate that hyperresponsiveness may not merely be muscles and mediators; the thickness of the tubes and their tethering should be considered as well.

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