How should airway smooth muscle be punished for causing asthma?

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ASTHMA IS A COMPLEX DISEASE that has varied manifestations, is often difficult to treat, and indeed is even a challenge to define. Nevertheless, there are some features of asthma that are characteristic. Key among these is airways hyperresponsiveness (AHR), defined as an abnormally large mechanical response to challenge with a bronchial agonist such as acetylcholine. Exactly why asthmatic individuals exhibit AHR is still not clear. Obviously, airway smooth muscle (ASM) is involved in the response to bronchial challenge, but an abnormal response does not automatically mean that the ASM itself has to be abnormal. The link between ASM activation and subsequent changes in lung mechanics is also influenced by, for example, the mechanical loads opposing muscle shortening, and by geometric factors such as the thickness of the airway mucosa, all of which have the potential to affect bronchial responsiveness enormously (4). Nevertheless, ASM still remains a principal suspect as the culprit in asthma (11).

One of the key pieces of evidence that has long driven the suspicion that ASM is abnormal in asthma is that asthmatic and normal individuals seem to respond very differently to a deep breath. Whereas the airway constriction elicited following bronchial challenge in normal individuals is almost completely reversed by a deep lung inflation, bronchoconstriction is worsened by such a maneuver in at least in some asthmatic individuals (1). These findings, which remain poorly understood, have lead to a great deal of interest in the general question of how lung volume (or, equivalently, transpulmonary pressure) affects airways responsiveness. Studies have shown in both humans and animals (1) that airways responsiveness is exquisitely sensitive to acute changes in lung volume. Presumably, as volume increases, so does the tension in the alveolar walls that are attached to intrapulmonary airways, which in turn opposes the narrowing of the airway lumen. This phenomenon has also been accurately reproduced in computational models (2, 3), so the acute effects of lung volume on airways responsiveness in the normal lung are now well characterized, even if the mechanisms involved are not universally agreed on.

Another consequence of the widespread interest in deep breaths and asthma has been a large number of in vitro studies on various preparations of ASM (1). These studies have revealed that ASM is much more complex and dynamic than is immediately apparent from whole organ or in vivo studies, or than would have been guessed a priori from what is known about skeletal muscle. In particular, it has been shown in recent years that ASM has a remarkable ability to adapt its force-generating capacity to changes in length (7). Coupled with previous knowledge about the fact that smooth muscle can exist in several different active states, known as the latch hypothesis (1), it now seems clear that the way ASM operates in the lung at any particular point in time ought to be highly dependent on what lung volume has been doing previously. Accordingly, there is considerable interest in obtaining evidence of ASM plasticity in vivo. So far, animal studies of this nature have not revealed particularly startling effects (10), although this may reflect the fact that the animals used were normal and that the interventions applied were extremely acute.

Attempting to model a chronic disease such as asthma in acute animal preparations is a perennial problem. It is already hard enough to make headway in the understanding of human disease by studying it in a species that has four legs and tail. One would think we should avoid limiting relevance even further by taking shortcuts driven by expediency and cost, yet this typifies most animal disease models. In this regard, the study in this issue of the Journal of Applied Physiology by Xue et al. (12) is particularly important. These authors somehow managed to convince a group of ferrets to go about their business for nearly 3 wk while wearing vests and being tracheostomized so that the chronic effects of lung volume change on AHR could be assessed. This is an experimental tour de force in itself, but more than that it shows that we can, and indeed should, be working on ways to extend the chronicity, and hence the human relevance, of animal models of lung disease.

Xue et al. (12) found that chronically elevated lung volume caused a marked reduction in bronchial responsiveness to acetylcholine in vivo, in the isolated organ, and in isolated strips of ASM in vitro. The only other study that I am aware of looking at how such chronic volume change affects airways responsiveness is that by McClean et al. (8), who reduced volume in sheep with a corset and found responsiveness to be increased. The studies of Xue et al. (12) and McClean et al. (8) together thus indicate that ASM behavior in vivo is affected by the length at which it is chronically maintained. The teleological implications of this are very unclear, especially as we cannot agree whether smooth muscle is a good thing to have in the lungs or not (6, 9). The clinical implications, however, are easier to fathom in view of the number of common conditions that cause lung volume to be either chronically increased (e.g. chronic obstructive lung disease) or decreased (e.g. obesity).

Time will tell whether the results from these animal studies bear out in human patients with chronically altered lung volumes. In the meantime, however, we face the fascinating question of why airways responsiveness should be so affected by only a modest chronic increase in lung volume. Xue et al. (12) showed that the reductions in responsiveness in their ferrets were accompanied by reductions in myosin light chain phosphorylation, which they took as a general indication of reduced ASM activation. They offer a very brief but tantalizing speculation that this could be somehow due to a reorganization of cytoskeletal and contractile proteins. Perhaps chronic lengthening of ASM causes its contractile machinery to shift from a more parallel to a more serial juxtaposition, which might be expected to reduce its maximum force-generating capacity. Whatever the case, this is a subject worthy of careful
further investigation. And who knows? Maybe it will lead to a novel approach to treating asthma. After all, some who find ASM guilty of causing asthma have sentenced it to death by microwave irradiation (5). Perhaps torture by stretching on the rack would be a more effective punishment.

REFERENCES


