The multiscale manifestations of airway smooth muscle contraction in the lung

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AIRWAY HYPERRESPONSIVENESS is a hallmark feature of asthma and is defined as an excessive decrement in lung mechanical function following challenge with standard doses of a smooth muscle agonist, such as methacholine. Accordingly, understanding the mechanisms underlying airway hyperresponsiveness is seen as central to understanding the pathogenesis of asthma itself. Here is where things get complicated, however, as there are numerous different mechanisms that could potentially account for hyperresponsiveness, from abnormalities of the airway smooth muscle to variations in the mechanical load opposing smooth muscle shortening to geometric effects, such as airway wall thickening (5, 12, 15). In reality, these different mechanisms probably coexist to varying degrees in any given asthmatic subject. In fact, asthma is a complex disease, and synergy between multiple mechanisms of hyperresponsiveness may be where the action really lies (3).

In any case, one of the most effective ways to reverse bronchoconstriction in a normal animal or human subject is to inflate the lungs briefly and deeply (1). This is thought to stretch the airway smooth muscle through dilation of the airway walls. Similarly, the responsiveness of the airways to challenge with a smooth muscle agonist is substantially reduced by increasing either transpulmonary pressure (1, 6) or tidal volume (13). Curiously, however, some asthmatic subjects will actually worsen their bronchoconstriction with a deep breath (1), for reasons that remain unclear, but which potentially involve any of the mechanisms that have been identified as potentially underlying airway hyperresponsiveness. The issue is not easily resolved by studying the intact human or animal, so many researchers have taken a reductionist approach to addressing the matter. In particular, there has been a great deal of recent research on the dynamic force-length behavior of activated smooth muscle is markedly reduced by imposed length oscillations, LaPrad et al. asked the obvious question: Is a corresponding effect observed when smooth muscle is located in situ in the airway wall?

Surprisingly (or maybe not surprisingly), the answer came back “no”. Regardless of how they varied the amplitude of the transmural pressure oscillations, LaPrad et al. found no effect on the net level of airway constriction to standard doses of acetylcholine. This is not what one would have expected. Variations in transmural pressure across the airway wall cause oscillations in airway radius, which presumably cause associated oscillations in the lengths of the smooth muscle cells, which are aligned more or less circumferentially within the airway wall tissue. If directly oscillating airway smooth muscle strips attenuate their contractile ability, why not when they are oscillated within the airway wall? LaPrad et al. do not provide a definitive answer on this point, although they allude to the possibility that the geometrical arrangement of the smooth muscle cells within the wall and the coupling of the cells to the wall tissue may somehow be involved (10).

This particular question remains an area for future research, but it highlights how biological systems are so often recalcitrant to the reductionist approach. Indeed, the same message comes from studies in whole lungs in vivo; again, there is relatively little evidence of the strain rate-induced reductions in active force that are so evident at the level of the smooth muscle strip (4).

The real lesson to be learned from the study of LaPrad et al., therefore, is that we still cannot tell a priori how behavior will cross length scales in biological systems. One day we may have computational models that explain accurately and reliably why some microscopic behaviors cross multiple length scales (e.g., isolated smooth muscle contracts, and the result is seen all the way up to the whole lung), while others do not (e.g., the strain rate...
suppression of force discussed above appears only to be significant at the level of the muscle strip). That day may be a long way off, however. In the mean time, the only way to find out how biological systems behave at different length scales is to do the necessary experiments and see what happens. Actually, this is a fortunate state of affairs, because it has kept a community of scientists happily occupied with interesting research questions for decades, and I doubt anybody is going to spoil the fun anytime soon.

REFERENCES


