The importance of biomechanical feedback in the generation of asthma

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THOSE OF US WHO PURSUE BIOLOGICAL research do so mainly because of the intellectual satisfaction derived from making discoveries. But we are blessed with generous grants from our governments whose motivations are more practical and include improving the health of our populations, promoting new therapies, and enhancing the knowledge on which future practical discoveries can be made. Thus it is refreshing to read the occasional basic research paper describing a mechanism in a way that its practical importance is obvious. Such is the case with the paper by Connolly et al. (1) in this issue of the Journal of Applied Physiology.

People who suffer from asthma soon learn that taking and holding a deep inspiration can provide some measure of relief. The several mechanisms contributing to this relief are likely to include 1) resetting the length of the activated smooth muscle by tearing off attached cross bridges so that if they reattach, it will be at a longer muscle length and 2) reducing the cooperative effect of multiple attached crossbridges and thus reducing the number of sites for cross bridge reattachment. On the other hand, they also learn that the relief provided by this maneuver attenuates with repeated use, so that they should use it sparingly, if at all, to avoid hyperinflated lungs.

The paper discussed here examines this behavior in isolated airway smooth muscle cells grown on Silastic membranes and finds that repeated 10% stretches of these cultured cells for up to 10 days reduced resistance to stretch, in both the cyclically stretched and nonstretched cells, but that the chronically oscillated cells recover their resistance to stretch three times more rapidly than the unstretched cells. Of the possible mechanistic explanations for this behavior perhaps the most likely is an increase in myosin light chain kinase activity in the chronically oscillated cells, and this was confirmed by the authors’ biochemical assay.

This relatively simple finding could have enormous practical implications, some of which might be investigated with the same techniques. For example, there is belief that asthma begets more asthma. To the extent that this is so, would blocking of light-chain kinase prevent the transition from early childhood wheezing to chronic asthma. A trustworthy answer to this question could only be obtained with the clinical gold standard of a placebo-controlled, randomized, double-blind study, but substantial preliminary progress might be made with the same laboratory model used by the authors. Such laboratory experiments might address the very important practical issues of the strength and duration of treatment required to interrupt the progression to chronic asthma. Thus I view the present report as a first installment in what I hope will become a series of studies defining the pathways leading to chronic asthma and strategies for blocking these pathways.

A final point to be made from these observations is that responses described have the characteristics of positive feedback, and there are two general characteristics of positive feedback that may be of particular relevance in the treatment of asthma. The first is that once started, the feedback is self-sustaining, and the second is that the output of the system increases rapidly to its maximum. These considerations suggest a mechanistic explanation for the clinical saw that the treatment of an asthma attack should be sufficiently vigorous to end all symptoms, i.e., to break the feedback loop, and that it should continue until all signs and symptoms of bronchospasm have fully abated.

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DISCLOSURES

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REFERENCES