A one-horse race can have only one winner

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TO THE EDITOR: The spectrum of reactions to my Viewpoint (3) regarding the role of the airway smooth muscle (ASM) in creating airway hyperresponsiveness akin to asthma has raised several interesting points (see Ref. 4). First, I must begin with a critical clarification. A few of the responders appear under the impression that I suggested the ASM was the “horse” we should dismount or stop chasing as it is not the main culprit in causing hyperresponsiveness. This is not my claim. The ASM may very well be the main culprit. The horse I referred to was that the causative step leading to airway hyperresponsive is a reduced ability to dynamically stretch the ASM during tidal breathing and a DI, which then triggers the necessary alteration in ASM phenotype. Have we been overly predisposed to design experiments and interpret data singularly along these lines? I provided arguments suggesting that this specific trajectory may be the wrong “leading” horse in the race, that data from intact airway airways are inconsistent with such because the in situ strains during typical transmural pressures are insufficient, and that whole organism data could be explained with other mechanisms and are not exclusively supportive of only this “horse.” Hence, the diminished response to a DI in patients with asthma and the clear evidence that humans with asthma have a diminished capacity to dilate their airways compared with those without asthma may be a consequence rather than a cause. Our inclination for it having been a cause rather than a consequence had been driven, perhaps, by an over willingness to leap from isolated ASM experiments to whole organism ones. There are some other reactions I need to address. Dr. Seow’s (see Ref. 4) response seemed concerned with parenchymal stiffening during airway provocation. However, it is unlikely that this is an important phenomena in the whole lung. Indeed, a study from our group (2) using gases of distinct density affirmed that the preponderance of the changes in lung resistance postchallenge was due to the airways and virtually none was due to changes in the tissue properties. Dr. Noble and colleague’s (see Ref. 4) response raises a legitimate concern of whether transmural pressures for isolated airways compare well to in situ. But Harvey et al. (1) used rather large pressure swings near the limits of what is likely achievable in situ and still was unable to invoke substantive bronchoprotection or bronchodilatation. Dr. Skloot and colleagues (see Ref. 4) raise some interesting whole organism data, but perhaps the exercise data and the obesity data can also be explained by length adaptation and/or atelectasis mechanisms rather than the impact of ASM dynamic stretching. So, there remains an understandable propensity to want to design experiments and explain our data with only a single “horse” in the race. I profess that we likely need to run a more challenging and less predictable race with more horses, and I for one might take better odds on some of the others.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

K.R.L. drafted manuscript; K.R.L. edited and revised manuscript; K.R.L. approved final version of manuscript.

REFERENCES


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