Response to letter by Dr. Marc Hershenson (exposure of airway smooth muscle cells to cigarette smoke extract)

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TO THE EDITOR: We thank Drs. Hershenson and Chung for their insightful comments regarding our recent paper on mitochondrial fragmentation and dysfunction in human airway smooth muscle (ASM) induced by cigarette smoke extract (CSE) (1). They raise the point that CSE and the concentrations used in cell studies may not precisely reflect what happens with inhaled cigarette smoke (CS) that actually reach the ASM layer in vivo, given the intervening epithelial layer. They recommend that researchers in the field confirm in vitro data with experiments in vivo (e.g., examination of ASM tissue in CS-exposed animals). We certainly agree with Drs. Hershenson and Chung on this last point, which is well recognized by investigators working in ASM, other cell types, and in vitro systems in general.

The question of whether CS or specific components have direct effects on ASM is certainly valid. As Drs. Hershenson and Chung suggest, lipid-soluble components could indirectly reach the ASM via the circulation. However, we propose that although inhaled CS in vivo first affects the epithelium, a loss of epithelial barrier function with chronic exposure (3, 4) permits direct access of CS to the underlying ASM. Reactive oxygen species (ROS) may then be generated locally within the ASM. CS may also indirectly affect ASM, for example via epithelial production of proinflammatory mediators such as TNF-α (5) that are known to induce ROS. Indirect CS effects could also occur by metabolites from epithelial detoxification of CS, e.g., via cytochrome P-450 (2, 6). Thus multiple events may occur concurrently in vivo to allow easier access of CS or its components to ASM.

Although the suggestion made by Drs. Hershenson and Chung about applying “physiological” concentrations of CS components to ASM cells is also valid, from a practical standpoint it may be difficult to determine what such concentrations should be, and which of the myriad of components should be examined. Assuming that a particular CS component can be assayed within airway tissue, it is difficult to precisely quantify ASM levels per se, particularly if components accumulate to different extents based on permeability or lipid solubility. Therefore, we posit that an initial approach of using CSE, as numerous other studies have done, is a good initial step toward understanding CS effects on ASM.

Regardless of how CS or its components reach the ASM, we certainly agree with Drs. Hershenson and Chung regarding the need to correlate in vitro findings to the in vivo situation. Ongoing studies in chronic CS-exposed mice do suggest changes in ASM mitochondrial fission and fusion proteins that correlate to our published in vitro work (Aravamudan et al. unpublished observations). The local, ASM concentration of CS, or involvement of specific CS components, remain to be established. The questions raised by Drs. Hershenson and Chung provide an impetus to pursue these issues.

REFERENCES


