Fullerene derivatives protect against oxidative stress in murine macrophage line cells and ischemia-reperfused lungs

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THE ARTICLE by Ya-Wen Chen et al. (1) in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology represents an experimental model that should be used when possible to determine whether similar mechanisms cause damage in monolayers of endothelial and epithelial cells compared with isolated perfused lungs of the same species that are subjected to ischemia-reperfusion (I/R) or inflammation. It is possible that lung cells grown in culture may respond differently than lung cells in their natural environment to inflammatory responses, because both TNF-α and IL-10 are known to be released in intact lungs subjected to I/R, although the former is an inflammatory cytokine, whereas the latter is an anti-inflammatory cytokine (8). Damage that occurs to the endothelial or epithelial barrier subjected to I/R will obviously be determined by these cytokines and others relative to the endothelial or epithelial barrier subjected to I/R or inflammation. It is possible that lung cells grown in culture may respond differently than lung cells in their natural environment to inflammatory responses, because both TNF-α and IL-10 are known to be released in intact lungs subjected to I/R, although the former is an inflammatory cytokine, whereas the latter is an anti-inflammatory cytokine (8). Damage that occurs to the endothelial or epithelial barrier subjected to I/R will obviously be determined by these cytokines and others relative to J) interactions between cytokines, etc., 2) concentrations of all anti-inflammatory and inflammatory cytokines activated in the process, 3) time of the cytokine release, and 4) past history of endothelial and epithelial cell lines relative to their exposure to the inflammatory responses, i.e., an intact lung would likely have epithelial and endothelial cells that have been exposed to different tissue cytokines and have different respective receptors on their surfaces that could be quite different compared with cells grown in culture that have not been exposed daily to insults that intact animal lungs are exposed to in their environment on a daily basis (2, 3, 7).

This paper by Chen et al. evaluates the problem of whether isolated cells are different than intact lung cells in a well-defined inflammatory study in which a “fullerene derivative,” which is a compound that protects against oxidant stress in both isolated RAW (a murine macrophage line) cells and perfused rat lungs, is subjected to oxygen radical and I/R endothelial damage. This is obviously a serious problem that occurs in human lung transplantation and has been addressed in several publications (5). Clearly, the fullerene derivative protected RAW cells in a dose-dependent fashion by decreasing the reactive oxygen species produced by compounds against oxygen radical damage produced by exposing them to nitroprusside and hydrogen peroxide. In addition, Chen et al.’s paper also shows that both sodium nitroprusside and H2O2 reduced the normal mitochondrial membrane potential and cell viscosity using flow cytometry, and these changes were greatly reduced when the fullerene derivative was present.

In the isolated lung studies, both SNP and I/R caused increases in pulmonary arterial and capillary pressures during I/R, as measured by the double occlusion method, and this vascular effect was reversed by treating the lungs with the fullerene derivative. An interesting, but odd, finding was that fullerene derivatives used at high concentrations also caused lung injury! This caveat indicates that any study that evaluates the ability of a substance to oppose or block oxygen radical formation in lungs must always be used in a dose-response fashion to determine the beneficial dose and whether the antioxidant treatment can also produce damage at higher doses.

In Chen et al.’s study, fullerene was a very potent anti-inflammatory compound in both RAW cells and isolated lungs exposed to either oxygen radicals or I/R. Although this paper contains important new data and uses an excellent experimental design to better understand the mechanisms involved in the damaging process, future studies must also evaluate the inflammatory response in a broader fashion by also defining the production of inflammatory factors such as TNF-α, interferon-γ, IL-1, and anti-inflammatory factors such as IL-10 (2–4, 6, 7). In future studies, the authors should evaluate how blocking various cytokines, and their receptors on cells, and how various vasoactive drugs affect lung cells exposed to oxidative damage. There is absolutely no doubt that I/R causes significant endothelial and epithelial damage in intact lungs. However, the mechanisms responsible for producing the inflammatory response in lungs and isolated endothelial cells will require a more in-depth analysis of the various cytokines and chemokines released by each experimental model to determine their importance in producing lung damage. Also the mechanisms responsible for fullerene and other anti-inflammatory compounds to affect the release and actions of the various cytokines and chemokines released in I/R and other inflammatory processes must be studied in detail because 1) we are now dealing with systems that allow us to live and reproduce in our environment and this is also true for all animals; 2) however, the inflammatory response in animals may be different compared with humans, because we have evolved under different environmental conditions (9); 3) isolated cells may certainly mimic intact cells in organs in some or even many aspects, but it must be shown that this holds true for each experimental condition studied in our laboratories, because their environments may greatly affect their inflammatory response compared with in vivo cells.

This short editorial is certainly not intended to discourage the reader from doing studies similar to those done by Chen et al., because we now are in the greatest decade of understanding cell biology in the history of mankind. As we begin to decipher how our body and its cells respond as they are exposed to different environmental factors, we will be better able to understand how our bodies can become both infected and oppose infections as our inflammatory system continues to evolve to better cope with our changing environmental conditions.
REFERENCES


