You Are What You Eat: Diet-Dependent Changes in Pulmonary Surfactant

Pulmonary surfactant is a complex mixture of phospholipids, proteins, and neutral lipids, including cholesterol, that is synthesized, secreted, and primarily recycled by alveolar type II (ATII) epithelial cells (1). Surfactant is essential to maintain normal lung function; by lowering the surface tension of the alveolar lining fluid, surfactant facilitates alveolar expansion on inspiration and prevents alveolar collapse at the end of expiration (2). In adults, abnormalities in surfactant composition and/or function are a key pathophysiologic feature of many pulmonary diseases, including pneumonia, acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease, and pulmonary fibrosis (3). Interestingly, however, and for reasons that remain unclear, improving outcomes with surfactant replacement therapy in adults has proven to be more challenging (4).

Synthesis of surfactant lipids and proteins clearly depends on the appropriate availability of nutrients. However, the effects of dietary changes on surfactant composition and function have not been investigated in depth. In their paper in this issue of the *Journal*, Schipke and colleagues (pp. 379–390) investigated the impact of feeding mice starch-rich, sucrose-rich, and fat-rich diets for 30 weeks relative to a standard fiber-rich diet (5). They found that the resulting hypercholesterolemia and hyperinsulinemia are associated with altered lung mechanics in mice fed sucrose- or fat-rich diets, although *ex vivo* surfactant function decreased only in the latter group. In line with these functional changes, surfactant phospholipid composition was significantly altered in all three treatment groups, although there were also clear differences in the predominant phospholipid species between mice fed high-carbohydrate diets and those fed excess fat. Finally, dietary modifications were associated with changes in gene expression in ATII cells and, in the case of mice fed a high-starch diet, alterations in ATII cell ultrastructure.

The relative contribution of surfactant dysfunction to the alterations in lung mechanics is most clearly seen in the animals receiving the fat-rich diet, as demonstrated by significantly reduced surfactant adsorption, increased hysteresis, and altered pressure–volume curves. Notably, changes resulting from a sucrose-rich diet were very similar but insufficient to achieve significance regarding a decrease in adsorption. The corresponding compositional changes to surfactant lipids are highlighted by significant, but relatively small, changes in the proportion of saturated, monounsaturated, and polyunsaturated fatty acids. Although an overabundance of polyunsaturated fatty acids has been associated with reduced surface activity, the increased amounts in this model are unlikely to fully explain the observed functional changes in adsorption and lung mechanics; it has generally required significantly higher concentrations of polyunsaturated fatty acids, cholesterol, or lysophospholids to significantly affect surface tension–lowering activity (6, 7). Other changes in surfactant composition, such as total surfactant recovery, major phospholipid subclasses present (as a percentage of total lipids), cholesterol content, and proportions of other neutral lipids, can and likely will be explored in this model and potentially yield further insights.

These observations may have some important experimental implications in mouse models of pulmonary disease. Although most researchers feed their study subjects standardized chow, many cardiovascular and cancer studies employ modified (often high-fat) diets, and this may be an additional experimental variable that needs to be borne in mind when interpreting changes in lung function in these animals (8, 9). More importantly, it is possible that surfactant function could be altered by changes in food intake associated with either incorporation of unpalatable chemicals in the chow or the onset of experimentally induced disease. For example, the inclusion of tamoxifen in the diet to induce gene knockout often results in initial inappetence, particularly in older mice (10). Likewise, mice with acute influenza pneumonia stop eating altogether (11); if the impact of dietary alterations on surfactant is rapid, this alone could account for some of the lung function abnormalities, such as reduced lung compliance, reported in infected mice. Indeed, it is possible that an acute change in diet could have a greater impact on surfactant lipids than a chronic change; the observed alterations in gene expression could reflect long-term adaptation to a modified diet. Hopefully, future studies will shed additional light on how changes in diet modify surfactant composition and function over time.

The potential clinical implications of dietary intake leading to alterations in surfactant composition and function are clear. Although extreme for the sake of mechanistic clarity and analysis, the experimental diets used in these studies reflect dietary habits associated with the obesity crisis. Obesity is a well-established risk factor for common respiratory disorders associated with surfactant dysfunction, including ARDS and asthma (12, 13). During both the H1N1 influenza outbreak in 2009 and the currently ongoing pandemic from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the severity of ARDS and mortality among patients with obesity were significantly increased (12, 14). Altered surfactant as a principal mechanism leading to the increased susceptibility of this vulnerable population is plausible and provides a basis for considering obesity as a predictor for enriched responsiveness to surfactant replacement therapy in future clinical trials.

The experiments described in this article also provide insights into the mechanisms underlying altered surfactant lipid metabolism

Originally Published in Press as DOI: 10.1165/rcmb.2020-0582ED on January 11, 2021

in mice fed high-carbohydrate and high-fat diets. Dietary modification resulted in significant changes in gene expression profiles in isolated ATII cells; unsurprisingly, overall effects of high-starch and high-sucrose diets were more similar to each other than to those of high-fat diet feeding. One prominently upregulated gene in all three groups was *abca1*, which encodes a membrane-expressed lipid transporter that is essential for the export of phospholipids and cholesterol from the basolateral surface of ATII cells. Transcription factors that regulate lipid biosynthesis, such as *srebf1* and *cebpα*, were also induced. Interestingly, effects of diet on *pcyt1a*, which encodes the rate-limiting enzyme in *de novo* phospholipid synthesis, were much more limited. This suggests that the effects of dietary modification on surfactant phospholipid composition are primarily due to acyl chain remodeling, and increased expression of the acyltransferase *lpcat1* is consistent with this mechanism. However, as the authors note, it is not clear whether changes in gene expression and surfactant composition are a direct effect of dietary modification on ATII cells or secondary to systemic metabolic changes associated with obesity, hypercholesterolemia, and/or hyperinsulinemia in these mice. Hopefully, their future studies will shed light on this issue.

As rates of obesity (15) and type II diabetes mellitus (16) continue to rise, the importance of further understanding how these conditions directly and indirectly impact lung function will become more essential to public health. Well-controlled studies such as that of Schipke and colleagues (5) are beginning to provide valuable mechanistic insight into the interplay between diet and lung function that could lead to novel strategies for therapeutic intervention in patients, particularly when they are faced with additional lung stressors such as pulmonary infections. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

R. Duncan Hite, M.D.
Department of Internal Medicine
University of Cincinnati
Cincinnati, Ohio

Ian C. Davis, D.V.M., Ph.D.
Department of Veterinary Biosciences
The Ohio State University
Columbus, Ohio

References

1. Whitsett JA, Weaver TE. Alveolar development and disease. *Am J Respir Cell Mol Biol* 2015;53:1–7.
2. Autilio C, Pérez-Gil J. Understanding the principle biophysics concepts of pulmonary surfactant in health and disease. *Arch Dis Child Fetal Neonatal Ed* 2019;104:F443–F451.
3. Agudelo CW, Samaha G, Garcia-Arcos I. Alveolar lipids in pulmonary disease: a review. *Lipids Health Dis* 2020;19:122.
4. Meng SS, Chang W, Lu ZH, Xie JF, Qiu HB, Yang Y, *et al*. Effect of surfactant administration on outcomes of adult patients in acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. *BMC Pulm Med* 2019;19:9.
5. Schipke J, Jütte D, Brandenberger C, Autilio C, Perez-Gil J, Bernhard W, *et al*. Dietary carbohydrates and fat induce distinct surfactant alterations in mice. *Am J Respir Cell Mol Biol* 2021; 64:379–390.
6. Agassandian M, Mallampalli RK. Surfactant phospholipid metabolism. *Biochim Biophys Acta* 2013;1831:612–625.
7. Hite RD, Seeds MC, Jacinto RB, Grier BL, Waite BM, Bass DA. Lysophospholipid and fatty acid inhibition of pulmonary surfactant: non-enzymatic models of phospholipase A_2 surfactant hydrolysis. *Biochim Biophys Acta* 2005;1720:14–21.
8. Wali JA, Jarzebska N, Raubenheimer D, Simpson SJ, Rodionov RN, O'Sullivan JF. Cardio-metabolic effects of high-fat diets and their underlying mechanisms-a narrative review. *Nutrients* 2020;12: 1505.
9. Peck B, Schulze A. Lipid metabolism at the nexus of diet and tumor microenvironment. *Trends Cancer* 2019;5:693–703.
10. Chiang PM, Ling J, Jeong YH, Price DL, Aja SM, Wong PC. Deletion of *TDP-43* down-regulates *Tbc1d1*, a gene linked to obesity, and alters body fat metabolism. *Proc Natl Acad Sci USA* 2010;107: 16320–16324.
11. Groves HT, Higham SL, Moffatt MF, Cox MJ, Tregoning JS. Respiratory viral infection alters the gut microbiota by inducing inappetence. *mBio* 2020;11:e03236-19.
12. Hibbert K, Rice M, Malhotra A. Obesity and ARDS. *Chest* 2012;142: 785–790.
13. Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol* 2018;141:1169–1179.
14. Lemyze M, Courageux N, Maladobry T, Arumadura C, Pauquet P, Orfi A, *et al*. Implications of obesity for the management of severe coronavirus disease 2019 pneumonia. *Crit Care Med* 2020;48: e761–e767.
15. Hales CM, Fryar CD, Carroll MD, Freedman DS, Ogden CL. Trends in obesity and severe obesity prevalence in US youth and adults by sex and age, 2007-2008 to 2015-2016. *JAMA* 2018;319: 1723–1725.
16. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, *et al*. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 2001;24:1936–1940.