Hypocapnia, mitochondria and surfactant secretion

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Surfactant, a phospholipoprotein produced and stored by alveolar type II (ATII) cells, lowers surface tension in the alveolus and distal airways and is essential for normal lung mechanics and gas exchange.[1] Decreases in surfactant production induced by prematurity or disease cause alveolar collapse, hypoxemia and reductions in lung compliance, thereby requiring greater distending pressures to inflate the lung and increases in the work of breathing.[2] Prior studies dating back >30 years have shown that alveolar hypocapnia causes depletion of lamellar bodies in ATII cells and decreases surfactant production.[3] However, the mechanism(s) underlying the effect(s) of hypocapnia on surfactant secretion by ATII cells are not well understood.

The paper by Kiefmann *et al*[4] in *Thorax* sheds light on molecular mechanisms which may contribute to the effects of alveolar hypocapnia on surfactant production in vivo. The authors examined surfactant secretion, cytosolic and mitochondrial calcium and alveolar volume and compliance in two rodent preparations: isolated, blood-perfused rat lungs and rabbits in which the pulmonary artery was ligated to produce unilateral lung dead space. Calcium concentrations were determined in rat ATII cells in situ by intravital fluorescent microscopy. Importantly, ATII cells have abundant mitochondria as an energy source for production and secretion of pulmonary surfactant.[1] The calcium signals in the mitochondria regulate key cellular functions such as energy production and cell death.[5] The transport of calcium across the inner mitochondrial membrane is an essential signalling pathway for cellular metabolic functions. The calcium uniporter complex mediates mitochondrial calcium uptake, a process that buffers excess cytosolic calcium and regulates mitochondrial metabolism. Studies with isolated mitochondria indicate that they can accumulate large amounts of calcium.[6]

The basis for the current study is an earlier publication by this group using isolated rat ATII cells in vitro to examine the effects of hypocapnia on cytosolic and mitochondrial calcium.[7] The authors demonstrated that hypocapnia increased mitochondrial calcium uptake leading to the production of reactive oxygen species and ATII cell apoptosis. The current study by Kiefmann *et al*[4] shows that severe hypocapnia (ie, venous PCO_2 <10 mm Hg) in these reduced preparations decreased surfactant production and cytosolic calcium but increased mitochondrial calcium in ATII cells. Moreover, decreases in surfactant secretion correlated with the calcium shift from the cytosol to mitochondria. Alveolar application of rotenone, an inhibitor of complex I of the mitochondrial respiratory chain, completely blocked hypocapnia-induced reduction of surfactant production and cytosolic calcium and increased mitochondrial calcium uptake. Moreover, ruthenium red, an inhibitor of the mitochondrial calcium uniporter, produced similar effects. Finally, the authors found that in rabbits in which the pulmonary artery was ligated, hypocapnia reduced surfactant protein secretion in the bronchoalveolar lavage fluid, alveolar volume and lung compliance. Hypocapnia-induced changes were inhibited by adding CO_2 into the inspired gas in the pulmonary artery-ligated lung. This study supports the idea that hypocapnia-induced reductions in surfactant secretion in vivo result from decreases in cytosolic calcium and increases in mitochondrial calcium uptake.

Further studies are needed to fill in important gaps. First, the authors analyzed the effects of a severe and unphysiological reduction in venous PCO_2, that is, to <10 mm Hg. It is not known whether alveolar hypocapnia of lesser magnitude produces similar, 'dose-dependent' effects on cytosolic and mitochondrial calcium. Second, the effects of the opposite condition, that is, hypercapnia, are unknown and need to be studied. Specifically, does hypercapnia reduce mitochondrial calcium uptake and thus stimulate surfactant production? This is relevant both in subjects with hypercapnic respiratory failure from severe obstructive lung disease and subjects receiving 'permissive hypercapnia' produced in the setting of severe acute respiratory distress syndrome (ARDS) by low ventilator-delivered tidal volumes.[8 9] Finally, the present study used rats and rabbits. It remains to be seen if hypocapnia produces similar effects on human primary ATII cells in vitro.

Nonetheless, there are several potentially important pathophysiological implications of these findings. For example, reductions in surfactant production are believed to contribute importantly to the pathological changes seen in the lung in ARDS. Of interest, the authors assert that hypocapnia produced by 'perfusion failure' in at least some lung regions in ARDS would produce an attendant decrease in surfactant secretion. The subsequent reductions in lung compliance in these regions would increase the risk of barotrauma when alveolar distending pressures are high. Barotrauma promotes lung injury and therefore plays an adverse role in ARDS outcome.[10 11] Accordingly, an increased understanding of the regulation of surfactant production and secretion by ATII cells is likely to yield clinical benefits in ARDS as well as other lung diseases.

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