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Title:

DELETERIOUS IMPACT OF HYPERGLYCEMIA ON CYSTIC FIBROSIS AIRWAY ION TRANSPORT AND EPITHELIAL REPAIR

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What was your research question?

Our main goal was to better understand the alterations of the function of the lung lining (composed of epithelial cells) due to high blood sugar (hyperglycemia) in the context of cystic fibrosis related diabetes (CFRD), a deleterious complication of cystic fibrosis (CF).

Why is this important?

With an ageing population of people with CF, we begin to see other complications, including cystic fibrosis related diabetes (CFRD). CFRD increases with age, reaching up to 40% in CF adults and is associated with a faster progression of the lung disease. In fact, many lines of evidence indicate that diabetes, even in patients without CF, is associated with reduced pulmonary function compared to those without diabetes. However, we don't understand how high blood sugar levels affect lung function.

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What did you do?

CFRD has been associated with higher lung damage and bacterial infection, suggesting a weakened defense against infection. We then hypothesised that hyperglycemia may impact on lung functions critical for lung integrity and defense. The first line of defense against pathogens, called mucociliary clearance – the 'wafting' action of the lining of the airway to remove microorganisms, depends on the activity of proteins transporting ions like sodium, potassium and chloride, through epithelial cells. Our previous works also pointed toward a role of these channels in lung repair after injury. We thus investigated the effect of exposure to high glucose concentrations, mimicking the diabetic conditions, on airway cells from patients with and without CF.

What did you find?

Our data first showed that hyperglycemia decreased both chloride and potassium transport. Moreover, the ability of the lung lining to repair after injury was reduced after exposure to high glucose. We recently showed that new small molecules, called CFTR correctors, developed to correct the basic CFTR default not only allowed to partially recover CFTR function but also improved CF airway lining repair. We then assessed if this strategy would be still effective under hyperglycemic conditions. Our results showed that CFTR rescue was not significantly altered by high glucose. However, the wound healing rates in corrected CF airway epithelia were lower in high glucose compared with normal glucose conditions.

What does this mean and reasons for caution?

Altogether, our results indicate that hyperglycemia impairs both ion transport and epithelial repair in airway lining cells. These two major processes could contribute to the decline in pulmonary function in diabetic patients in both non-CF and CF patients. Moreover, hyperglycemia may dampen the beneficial effect of CFTR correctors on airway lining repair.

In brief, our results demonstrate the importance to control hyperglycemia in order to reduce the negative effect upon lung function.

What's next?

It would be interesting to further investigate how and why hyperglycemia impacts on lung functions. We are also convinced that it would be important to take into account the diabetic component in clinical trials evaluating the efficiency of new CFTR correctors on lung function in CF patients, through comparisons between non-diabetic CF patients and CFRD patients with or without proper sugar control.

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