Word counts: text, 2,500; abstract, 220.

**Airway glucose homeostasis: a new target in the prevention and treatment of pulmonary infection**

Short title: Airway glucose homeostasis and pulmonary infection

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**Funding information**

Professors Baker and Baines have received funding from the Medical Research Council (UK) MR/K012770/1; MR/J010235/1, British Lung Foundation COPD 10/7 and the Wellcome Trust (UK) WT075049AIA; 088304/Z/09/Z for some of the work described in this review

**Conflicts of interest**

The authors do not perceive any conflicts of interest relevant to the preparation of this manuscript

**Abbreviations list**

AMP, adenosine monophosphate

ASL, airway surface liquid

BAL, bronchoalveolar lavage

CF, cystic fibrosis

COPD, chronic obstructive pulmonary disease

GLUT, facilitative glucose transporters

MRSA, Meticillin-resistant *Staphylococcus aureus*

PPAR, peroxisome proliferator-activated receptor

SGLT, sodium glucose cotransporters

**Abstract**

In health, the glucose concentration of airway surface liquid (ASL) is 0.4mM, around 12 times lower than blood glucose concentration. Airway glucose homeostasis is a set of processes that actively maintain low ASL glucose concentration against the transepithelial gradient. Tight junctions between airway epithelial cells restrict paracellular glucose movement. Epithelial cellular glucose transport and metabolism removes glucose from ASL. Low ASL glucose concentrations make an important contribution to airways defence against infection, limiting bacterial growth by restricting nutrient availability.

Both airway inflammation, which increases glucose permeability of tight junctions, and hyperglycaemia, which increases the transepithelial glucose gradient, increase ASL glucose concentrations, with the greatest effect seen where they co-exist. Elevated ASL glucose drives proliferation of bacteria able to use glucose as a carbon source, including *Staphylococcus aureus*, *Pseudomonas aeruginosa* and gram-negative bacteria. Clinically this appears to be important in driving exacerbations of chronic lung disease, especially in patients with comorbid diabetes mellitus. Drugs can restore airway glucose homeostasis by reducing permeability of tight junctions (e.g. metformin), increasing epithelial cell glucose transport (e.g. beta agonists, insulin) and/or by lowering blood glucose (e.g. dapagliflozin). In cell culture and animal models these reduce ASL glucose concentrations and limit bacterial growth, preventing infection. Observational studies in humans indicate that airway glucose homeostasis modifying drugs could prevent chronic lung disease exacerbations if tested in randomised trials.

**Keywords:** Airway epithelium; glucose; *Staphylococcus aureus*, *Pseudomonas aeruginosa*; metformin.

Microbial communities in the lung are determined by three main factors: immigration, elimination and local reproduction1. In health, the dominant factors are immigration, by microaspiration, inhalation and direct spread; and elimination, by cough, mucociliary clearance, innate and adaptive immunity (figure 1). As healthy lungs are a relatively nutrient-poor environment for bacteria, reproduction plays only a minor role in determining community composition. In lung disease, epithelial and endothelial injury allows an increase in abundance of nutrients in the lung lumen, promoting bacterial growth. As bacteria vary in their ability to use different nutrient sources this causes differential growth, altering the composition of the microbial community and driving inflammation and injury. In this review, we consider the role of glucose homeostasis in restricting nutrient availability in the airway. We explore factors that disrupt airway glucose homeostasis and review the impact of these in promoting bacterial growth and infection. We present evidence that drugs that restore glucose homeostasis reduce bacterial growth in the airway and examine the clinical potential of these new therapies in the prevention and treatment of pulmonary infection.

**Glucose homeostasis and the lung**

In health, glucose concentrations in fluid lining the airway epithelial surface (airway surface liquid, ASL) are maintained at ~0.4mM, despite a strong transepithelial gradient for movement of glucose from the blood (4.9-6.1mM glucose)2. The principal mechanisms limiting ASL glucose concentrations include epithelial tight junctions, and glucose transport and metabolism (figure 2).

Tight junctions in airway epithelium are made up of proteins including junctional adhesion molecules, claudins and occludins, which are linked to cytoskeletal proteins and each other by scaffolding proteins such as zonula occludens. These junctions generally preclude paracellular movement. However the junctions contain pore and leak pathways, determined by abundance and localisation of constituent proteins, which allow paracellular diffusion of selected molecules3. Airway epithelial tight junctions are poorly permeable to glucose, although some paracellular glucose diffusion into ASL occurs4,5. The pathways by which glucose crosses the tight junctions are currently unknown. However claudin 1 and occludin appear to be important in determining tight junction glucose permeability in cultured airway epithelial cell monolayers6.

In the airway epithelium, the predominant glucose transporters expressed are facilitative glucose transporters (GLUTs). These allow passive diffusion of glucose across cell membranes, driven by a gradient generated by rapid intracellular glucose metabolism. GLUTs are expressed in both apical (lumen-facing) and basolateral (blood/interstitium-facing) airway epithelial cell membranes. GLUT-mediated glucose uptake across the apical membrane directly reduces glucose concentrations in ASL. Uptake across the basolateral membrane may modify local glucose concentrations, reducing glucose concentration gradients for movement of glucose into ASL4,5. In the distal lung, sodium coupled glucose transport isoform 1 (SGLT1) predominates in alveolar luminal membranes and drives glucose clearance from ASL by utilising both intracellular glucose and Na+-driven gradients7.

**Factors disrupting airway glucose homeostasis**

ASL glucose concentrations are increased by airway inflammation and by hyperglycaemia, particularly where these co-exist.

*Inflammation*. In humans, ASL glucose concentrations are increased from normal values (0.4±0.2mM)2 by a variety of airway pathologies, including: viral rhinitis (1 (1-2)mM)8; chronic rhinosinusitis (1.6±0.1mM)9; cystic fibrosis (CF) (nasal secretions 1-3mM10, lower airways 2.0±1.1mM2); and chronic airways inflammation (bronchoalveolar lavage glucose concentrations 4x healthy volunteers)11. In epithelial cell monolayers, paracellular glucose flux was increased by either treatment with proinflammatory mediators12 or infection with *Staphylococcus aureus*13 or *Pseudomonas aeruginosa*14. Similarly, glucose flux was increased across the tracheal epithelium of mice treated with lipopolysaccharide13. In cultured airway epithelial cell monolayers, *Pseudomonas aeruginosa* infection reduced the abundance of tight junction proteins claudin-1 and occludin between the cells and induced the appearance of occludin cleavage fragments6. This was associated with an increase in paracellular glucose flux. It is worth noting that, in epithelial cell monolayers, inflammation also increased the abundance of GLUT transporters and GLUT-mediated glucose uptake12. Although this was insufficient to prevent a rise in ASL glucose concentrations, it raises the interesting possibility that dynamic regulation of GLUT transporters could mitigate the increased flux of glucose into ASL during inflammation.

*Hyperglycaemia.* People with diabetes mellitus have increased nasal (4(2-7)mM)8 and lower airway (1.2±0.7mM)2 glucose concentrations. In healthy volunteers, an experimental increase of ~10mM in blood glucose induced an increase in glucose concentrations of <1mM to 4.8±2.2mM in nasal secretions15 and 0.4±0.3 to 0.8±0.4mM in lower airways secretions2. This was reversed when normoglycaemia was restored. In patients intubated on intensive care, blood glucose concentrations were positively associated with glucose concentrations in bronchial aspirates8. People with airway inflammation (CF) and diabetes had greater ASL glucose (4.0±2.1mM), than people with either CF (2.0±1.1mM) or diabetes (1.2±0.7mM) alone2. ASL glucose concentrations increase *in vitro* and in animal models when glucose concentrations are elevated in basolateral media or blood respectively. For example in airway epithelial cell monolayers, elevation of basolateral glucose from 5mM to 15mM increased ASL glucose by up to 3mM12,14,16. Glucose concentrations are 2 to 8 times higher in bronchoalveolar lavage samples from diabetic compared to non-diabetic rodents13,17,18,19.

**Airway glucose homeostasis and infection**

Disruption of airway glucose homeostasis increases the availability of glucose as a nutrient source in the lung lumen. This has potential to support proliferation of bacteria able to use glucose as a carbon source, increasing bacterial loads and altering bacterial communities. Evidence from *in vitro*, animal and human studies indicates that elevated ASL glucose stimulates proliferation of *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other gram negative bacteria. In humans this is associated with clinical infections, including rhinosinusitis and exacerbations of chronic lung disease.

*Airway epithelial cell-bacterial co-cultures*. Apical growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa* increases when basolateral glucose concentrations are elevated in co-cultures using a variety of glucose concentrations, cell types and bacterial strains5,13,14. The effect of elevating basolateral glucose on apical bacterial growth can be replicated by pharmacological blockade of GLUT transport5. It can be prevented by substituting L-glucose (a non-metabolisable, non-transportable glucose analogue) for D-glucose14 or using bacteria with mutated carbohydrate transport genes16. Taken together, these findings indicate that elevated ASL glucose is directly causing the observed increase in bacterial growth.

*Animal models*. In mouse and rat models of respiratory infection, diabetes mellitus is associated with increased pulmonary bacterial growth irrespective of rodent (mice or rats), form of diabetes (leptin receptor deficient (db/db), leptin deficient (ob/ob), streptozocin- or alloxan-induced) or bacteria (*Staphylococcus aureus* or *Pseudomonas aeruginosa*)5,13,18,19,20. As in co-culture models, elevated glucose concentrations in lung secretions appear directly to stimulate bacterial growth. Increased pulmonary proliferation of *Pseudomonas aeruginosa* in diabetic mouse lungs is dependent on its ability to use glucose as a nutrient source and does not occur in mutant bacterial strains where glucose uptake and utilisation genes have been deleted5. In diabetic rats, pulmonary proliferation of *Pseudomonas aeruginosa* was inhibited by isoproterenol, which stimulates glucose removal from ASL, and promoted by pharmacological inhibition of SGLT119.

*Humans*. Two studies in intubated patients on intensive care units found that elevated glucose concentrations in bronchial aspirates doubled the risk of subsequent identification of any pathogenic bacteria and of meticillin-resistant *Staphylococcus aureus* (MRSA) in respiratory secretions21,22. Airway glucose concentrations were increased in upper and lower airway secretions from patients with chronic obstructive pulmonary disease (COPD) following an experimental rhinovirus infection and, at day 15, correlated with airway bacterial load23. Although these are the only studies to have looked directly at the relationship between airway glucose concentrations and respiratory infection, studies of people with diabetes provide circumstantial evidence for a stimulatory effect of glucose on the respiratory growth of glucose-utilising pathogens. Both cross-sectional and longitudinal studies have indicated that diabetes is a risk factor for nasal colonisation with MRSA24,25. People with diabetes who have chronic rhinosinusitis are three times more likely to have *Pseudomonas aeruginosa* or other gram negative rods cultured from sinus samples obtained at surgery than those without265. In people with COPD, exacerbation frequency is positively correlated with fasting blood glucose27 and those with diabetes are more likely to exacerbate and have more frequent exacerbations than those without28. COPD patients with diabetes or acute hyperglycaemia are more likely to have gram negative organisms29, multiple pathogens and *Staphylococcus aureus*30 cultured from sputum during exacerbations. In CF, diabetes is an independent risk factor for pulmonary exacerbations31. Poor glycaemic control was positively correlated with the number of respiratory infections32. CF patients with diabetes or impaired glucose tolerance are more likely to be colonised with *Pseudomonas aeruginosa*33, *Burkholderia cepacia*34 and *Stenotrophomonas maltophilia*35, pathogens particularly associated with increased exacerbation frequency and accelerated lung decline.

**Restoration of airway glucose homeostasis**

Where airway glucose homeostasis is disrupted by hyperglycaemia and/or inflammation, drugs that reduce epithelial tight junction permeability, increase epithelial glucose transport and/or reduce blood glucose concentrations can restore homeostasis and restrict the availability of glucose as a nutrient source (figure 3). This reduces bacterial growth in experimental models and has therapeutic potential in the prevention and treatment of pulmonary infections in humans.

*Epithelial tight junctions*

Metformin, a biguanide, is the drug that has been most extensively studied in this context. It is an insulin sensitiser which exerts at least some of its actions through activation of AMP-activated protein kinase (AMP-kinase). In airway epithelium, metformin is anti-inflammatory36 and reduces permeability by altering tight junction protein expression (discussed below). As it also lowers blood glucose in people with type 2 diabetes37, although slowly over weeks rather than days, it thus has several beneficial effects on airway glucose homeostasis.

In epithelial cell monolayers, metformin increased transepithelial electrical resistance in an AMP-kinase dependent manner13 and increased expression of the tight junction proteins claudin 1 and occludin6. Metformin reduced the rise in ASL glucose concentrations caused by raising basolateral glucose from 10mM to 40mM by ~50%13. In epithelial cell-bacterial co-culture models, metformin pre-treatment ameliorated both *Staphylococcus aureus-*13 and *Pseudomonas aeruginosa*-induced6 increases in paracellular glucose permeability and limited the occludin cleavage and reduction in claudin 1 abundance seen with *Pseudomonas aeruginosa*. In animal models, 3 days of metformin treatment reduced lung glucose concentrations (bronchoalveolar lavage (BAL)) in diabetic mice to the level seen in non-diabetic mice, without altering blood glucose concentrations18. Metformin reduced glucose flux across mouse trachea, indicating that reduced epithelial tight junction permeability was a contributing mechanism13.

The restriction in ASL glucose concentrations seen with metformin is associated with a reduction in bacterial growth at the epithelial surface. In airway epithelial cell monolayers, metformin pre-treatment inhibited the apical growth of *Staphylococcus aureus*13 and *Pseudomonas aeruginosa*14 in a dose-dependent manner and prevented the increase in bacterial growth usually induced by increasing basolateral glucose concentrations. In diabetic mice, metformin pre-treatment reduced pulmonary proliferation of *Staphylococcus aureus*13 and *Pseudomonas aeruginosa*18 to levels seen in non-diabetic animals, despite having no effect on blood glucose.

Other candidates. In airway epithelial cell monolayers, glucocorticoids38, 1,25-dihydroxyvitamin D339, peroxisome proliferator-activated receptor (PPAR) gamma agonists40 and azithromycin41 have all been shown to increase expression of tight junction proteins and reduce epithelial permeability to ions and/or dextran. Azithromycin and vitamin D pre-treatment prevented the reduction in transepithelial resistance and tight junction protein rearrangement induced by inflammatory stimuli (*Pseudomonas aeruginosa* or toluene diisocyanate respectively)42,39. Insulin has recently been shown to promote airway barrier function, increasing transepithelial electrical resistance and reducing paracellular flux of small molecules43. Whilst all these drugs have potential to restrict movement of glucose into the ASL, limiting its availability to bacteria as a nutrient source, to our knowledge this has not been tested.

*Glucose transport*

Beta adrenoceptor agonists. Isoproterenol is a non-selective beta-adrenergic agonist, which exerts many of its actions through activation of the cyclic AMP-protein kinase A pathway. In rat distal lung, isoproterenol increased translocation of the sodium-glucose cotransporter isoform 1 (SGLT-1) to the luminal membrane19. In diabetic rats, this was associated with a 50% reduction in the glucose concentration of BAL. *In vitro,* proliferation of MRSA and *Pseudomonas aeruginosa* was reduced by 30-40% in BAL from diabetic rats pre-treated with isoproterenol compared to BAL from rats pre-treated with saline. Similarly, isoproterenol pre-treatment reduced *in vivo* proliferation of *Pseudomonas aeruginosa* in diabetic rat lungs.

Insulin. A recent study in primary human airway epithelial cells found that insulin treatment stimulated cellular glucose uptake43. This was inhibited by cytochalasin B, consistent with a requirement for GLUT translocation to the cell membrane. Glucose uptake across airway epithelial cell monolayers is also stimulated by treatment with pro-inflammatory mediators. These induced increased expression of GLUTs and increased GLUT-mediated glucose uptake across apical cell membranes12. The mechanism underlying inflammation-induced upregulation of GLUTs in airway epithelium has not been identified, but this represents a potential target for new treatments to lower ASL glucose concentrations.

*Blood glucose control*

Sodium-glucose cotransporter isoform 2 (SGLT-2) inhibitors. This relatively new class of anti-diabetic drugs lowers blood glucose by inhibiting glucose reabsorption in the renal tubules, resulting in increased glucose excretion in the urine. They reduce ASL glucose concentration by reducing the gradient for movement of glucose from blood into ASL. As these drugs are highly selective for SGLT-2 over SGLT-1, they do not directly affect glucose transport in the lung17.

In diabetic mice, 4 days of treatment with the SGLT-2 inhibitor dapagliflozin significantly reduced blood (from 21.6±19 to 11.4±0.7mM) and BAL (from 0.28±0.15 to 0.15±0.01mM) glucose concentrations17. In mice infected with *Pseudomonas aeruginosa*, bacterial counts at 24 hours were twice as high in BAL from diabetic as from non-diabetic mice. Pre-treatment of diabetic mice with dapagliflozin for 7 days before infection reduced bacterial counts in BAL from diabetic mice to levels seen in non-diabetic mice17.

*Mixed mechanisms*

Many of the drugs listed above have potential to lower ASL glucose concentrations by more than one mechanism. Metformin, PPAR gamma agonists and insulin all lower blood glucose concentrations, reducing the transepithelial gradient for movement of glucose into ASL. PPAR gamma agonists may also increase intracellular glucose metabolism, increasing local gradients for glucose uptake from ASL into airway epithelial cells.

**Clinical potential**

In experimental models, drugs that modify airway glucose homeostasis restrict availability of glucose in airway secretions, reducing bacterial proliferation. The next step in developing this new therapeutic approach is to test the ability of these drugs to prevent, or augment treatment, of pulmonary infection in humans. Observational studies and a few small clinical trials in humans support this approach.

In people with chronic lung disease and diabetes, those taking metformin or thiazolidinediones had less respiratory infections than those taking other medication. Patients with asthma and diabetes taking metformin had a 5-fold lower risk of asthma-related hospitalisation and 2-3 fold lower risk of any exacerbation44. Patients with COPD and diabetes taking thiazolidinediones had a 14% reduction in the number of exacerbations compared to those taking alternative oral anti-hypoglycaemics45. In people with cystic fibrosis with diabetes or pre-diabetes, several small clinical trials have shown that insulin treatment reduced annual exacerbation rates by 2-3 fold46,47.

**Conclusions**

Airway glucose homeostasis plays an important role in restricting nutrient availability in the lung lumen. Where this is disrupted by inflammation or hyperglycaemia, ASL glucose concentrations increase. This ‘nutrient imbalance’ promotes the proliferation of bacteria able to use glucose as a carbon source such as *Staphylococcus aureus*, *Pseudomonas aeruginosa* and other gram negative bacteria, driving infection. Drugs that restore airway glucose homeostasis can reduce bacterial proliferation, promoting elimination of bacteria by the immune system and preventing or augmenting treatment of infection. Observational studies in humans indicate that anti-diabetic drugs that modify airway glucose homeostasis could be better at preventing respiratory infection than those that only lower blood glucose. Airway glucose homeostasis modifiers could also prevent infection in people with chronic lung disease who have normal or impaired glucose tolerance not requiring anti-diabetic medication. Metformin and dapagliflozin have the best supporting experimental evidence of potential benefit as modifiers of airway glucose homeostasis and now need to be tested separately and in combination in clinical trials to determine the efficacy of this approach in prevention of respiratory infection.

**Acknowledgements**

Professors Baker and Baines have received funding from the Medical Research Council (UK) MR/K012770/1; MR/J010235/1, British Lung Foundation COPD 10/7 and the Wellcome Trust (UK) WT075049AIA; 088304/Z/09/Z for some of the work described in this review

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**Figure legends**

**Figure 1.** Microbial communities and airway glucose homeostasis. Bacteria (blue and orange circles) enter healthy airways by microaspiration, inhalation and direct spread and are cleared by cough, mucociliary clearance and the immune system. There is little local bacterial reproduction in the relatively nutrient-poor environment.

**Figure 2.** Airway glucose homeostasis and bacterial infection **A.** In health, airway surface liquid (ASL) glucose concentrations are maintained at around 12 times lower than blood concentrations by the poor glucose permeability of tight junctions between airway epithelial cells and by glucose uptake into cells. This occurs through facilitative glucose transporters (GLUT, airways) or sodium-glucose co-transporters (SGLT, alveoli) down localised concentration gradients driven by intracellular glucose metabolism. The nutrient poor environment of ASL restricts local reproduction of bacteria (blue and orange circles). **B.** Airway glucose homeostasis is disrupted by hyperglycaemia, which increases the gradient for glucose movement into ASL, and by airway inflammation, which alters tight junction protein expression and increases paracellular glucose leak. Despite upregulation of apical glucose transporters, ASL glucose concentrations increase. This promotes growth of bacteria able to use glucose as a carbon source (orange), increasing bacterial loads and altering bacterial communities.

**Figure 3.** ‘Airway glucose homeostasis modifiers’ as a new therapeutic approach for the prevention of pulmonary infection. In experimental models, drugs that A. increase expression of tight junction proteins, B. increase apical glucose uptake and C. lower blood glucose, cause a reduction in airway glucose concentrations and restrict growth of glucose-utilising pathogens in ASL. Clinical trials are now required to determine whether this can prevent, or augment treatment, of pulmonary infection in humans.

PPAR, peroxisome proliferator-activated receptor; ASL, airway surface liquid