



REVIEW

Sweet talk: insights into the nature and importance of glucose transport in lung epithelium

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ABSTRACT: For over 50 years, glucose has been recognised to cross the lung epithelial barrier and be transported by lung epithelial cells. However, until recently, research into these processes focused on their effects on lung liquid volume. Here, we consider a newly identified role for pulmonary glucose transport in maintaining low airway surface liquid (ASL) glucose concentrations and propose that this contributes to lung defence against infection.

Glucose diffuses into ASL via paracellular pathways at a rate determined by paracellular permeability and the transepithelial glucose gradient. Glucose is removed from ASL in proximal airways via facilitative glucose transporters, down a concentration gradient generated by intracellular glucose metabolism. In the distal lung, glucose transport via sodium-coupled glucose transporters predominates. These processes vary between species but universally maintain ASL glucose at 3–20-fold lower concentrations than plasma.

ASL glucose concentrations are increased in respiratory disease and by hyperglycaemia. Elevated ASL glucose in intensive care patients was associated with increased *Staphylococcus aureus* infection. Diabetic patients with and without chronic lung disease are at increased risk of respiratory infection. Understanding of mechanisms underlying lung glucose homeostasis could identify new therapeutic targets for control of ASL glucose and prevention and treatment of lung infection.

KEYWORDS: Airway epithelium, alveoli, facilitative glucose transporter, glucose, lung, sodium-coupled glucose transporter

Our understanding of the role of glucose transport in the lung and the mechanisms that regulate glucose movement across the human lung epithelium lags far behind that of the gut and kidney. Since the mid-1960s, it has been known that there are energy-dependent, sodium-coupled glucose transporter (SGLT) and energy-independent, facilitative glucose transporter (GLUT) pathways for glucose uptake in the lung [1], and that glucose can permeate the alveolar epithelial barrier [2]. However, much subsequent research in this area was focused on the role of pulmonary SGLT transport as a modifier of lung liquid volume [3, 4], and the effects of starvation and diabetes on glucose transport [1, 5]. It is only recently that we and others have begun to investigate glucose transport as an important mechanism for maintaining a nutrient-depleted environment in the lung lumen to limit the growth of pathogenic organisms.

NORMAL GLUCOSE CONCENTRATIONS IN AIRWAY SURFACE LIQUID

Glucose concentrations are 3–20 times lower in the fluid that lines the lung epithelium (airway surface liquid; ASL) than in plasma. This is in contrast to conditions in the gut and kidney, where luminal glucose concentrations regularly exceed plasma glucose concentrations [6, 7]. In humans, glucose concentrations were found to be <1 mM in nasal ASL [8] and mean \pm SD 0.4 ± 0.2 mM in the lower respiratory tract, 12.5 times lower than plasma concentrations, which are normally maintained at ~ 5 mM [9]. In a perfused, fluid-filled, adult rat lung model, ASL glucose was estimated to be 0.5 mM when perfusate glucose was 10 mM [4]. In a chronically catheterised sheep fetus between 122 and 143 days gestation, lung liquid glucose was <0.01 mM and plasma glucose 0.19 mM [3]. *In vitro* studies in resistive human lung epithelial cell monolayers grown at an air–liquid interface have

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supported these *in vivo* observations. In immortalised human airway cells (line H441) with 10 mM glucose in the basolateral medium, apical ASL glucose was 0.24 ± 0.07 mM [10]. In primary cultures of human bronchial epithelial cells (HBECs) with 16.6 ± 0.4 mM glucose in the basolateral medium, ASL glucose was 2.2 ± 0.5 mM [11].

PROCESSES THAT DETERMINE ASL GLUCOSE CONCENTRATIONS

ASL glucose concentrations are the net result of diffusion of glucose from blood and interstitial fluid across the respiratory epithelium into the ASL, and removal of glucose from ASL by epithelial glucose transport processes. Glucose diffusion is determined by epithelial permeability to glucose, the trans-epithelial glucose gradient and surface area. Glucose removal is determined by cellular glucose uptake and metabolism (fig. 1) [4, 12–14].

GLUCOSE DIFFUSION INTO ASL

Movement of glucose from the blood and interstitial fluid into the ASL occurs primarily by paracellular pathways. Early *in vivo* studies found that rabbit respiratory epithelium and pig tracheal epithelium were permeable to L-glucose, an isoform of glucose that is neither transported nor metabolised. In rat lungs, increasing paracellular permeability with protamine increased luminal glucose concentrations [15, 16]. More recent work has shown that L-glucose, applied to the basolateral side of resistive human airway epithelial cell monolayers grown on permeable filters at an air–liquid interface, moved into the apical compartment in a time- and concentration-dependent manner, consistent with paracellular diffusion [10–12]. Moreover, apical appearance of L-glucose increased exponentially with a decrease in transepithelial electrical resistance [10, 12]. These findings imply that glucose diffuses passively across the epithelium *via* paracellular pathways, and that this process is affected by the permeability of epithelial tight junctions to glucose and by the glucose concentration gradient (fig. 1).

Paracellular pathways

Tight junctions between epithelial cells predominantly determine the permeability of the epithelium [17]. They comprise transmembrane proteins, including junctional adhesion molecules, claudins and occludins, which are linked to cytoskeletal proteins and each other by scaffolding proteins, such as zonula occludens (ZO) proteins. The protein components and their localisation contribute to the formation of different populations of size- and charge-limiting transcellular diffusion pathways. These pathways have been broadly classified into pore and leak types [18–22]. The pathway(s) by which glucose crosses the epithelial tight junction barrier are currently unknown.

ZO-1, occludin and claudins are the main junction proteins determining paracellular permeability [21, 22]. Claudins are critical for tight junction formation, affecting both pathways and charge selectivity of tight junction pores. In airway epithelial cells, differential expression of claudin-1, 3 and 5 alters epithelial permeability to large molecules. Claudin-2 is important for cation conductivity but has no effect on the flux of mannitol (which is similar in size to glucose) [23–25]. Overexpression of occludin increases epithelial permeability to small hydrophilic molecules while reducing ion movement [26]. The role of tight junctions in regulating glucose movement through epithelial tight junctions in the lung will undoubtedly be complex. However, identification of proteins and signalling pathways that restrict glucose movement could provide potential therapeutic targets to reduce glucose in ASL.

Transcellular pathways

There is some evidence that glucose can move by transcellular pathways from the blood and interstitial fluid into the ASL. PEZZULO *et al.* [11] compared bidirectional flux of L-glucose, which diffuses by paracellular pathways as it is not transported, and 2-deoxyglucose (2-DOG), which can be transported and moved by paracellular and transcellular pathways. 2-DOG flux in both the basolateral-to-apical and apical-to-basolateral directions was identified, indicating the presence of

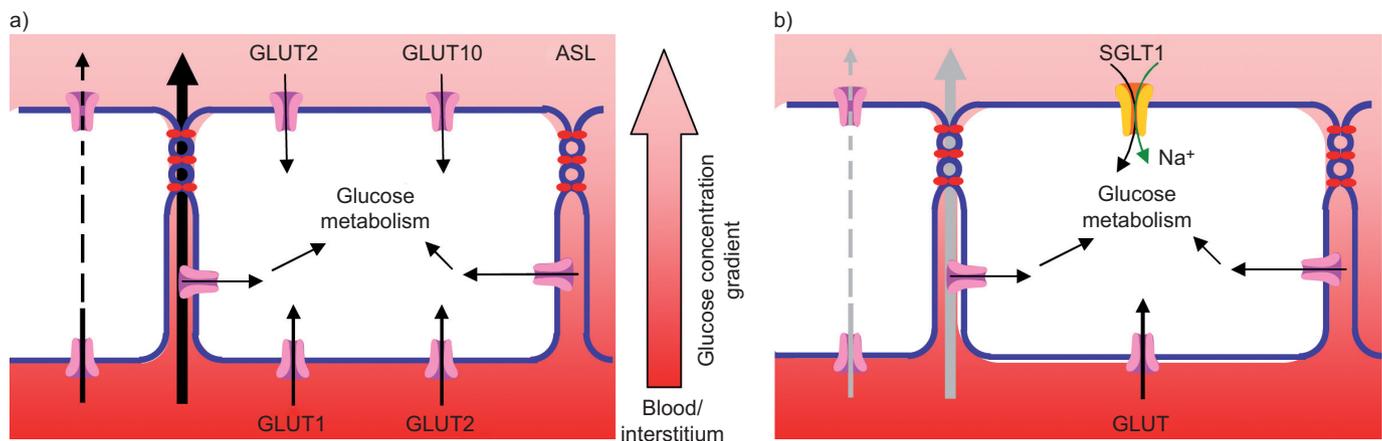


FIGURE 1. Current model of the mechanisms controlling glucose concentrations in the surface liquid lining the airway and distal lung epithelium. a) In the airway epithelium, the glucose concentration of the airway surface liquid (ASL) is the net effect of paracellular diffusion (and, to a lesser extent, the transcellular flux of glucose) from the blood and interstitial fluid across respiratory epithelium into the ASL, and removal of glucose from ASL by uptake into epithelial cells. Glucose uptake across the apical membrane is mediated by facultative glucose transporter (GLUT)2 and GLUT10, and across the basolateral membrane by GLUT2 and GLUT1. b) In the distal (alveolar) lung epithelium, glucose uptake across the apical membrane is *via* sodium-coupled glucose transporter (SGLT)1 and the basolateral membrane *via* unidentified GLUTs.

transcellular pathways for glucose movement across airway epithelium (fig. 1).

Transepithelial glucose gradient

The airway epithelium maintains the glucose concentration gradient, with blood/interstitial glucose concentrations being higher than ASL glucose concentrations (see earlier) [3, 8, 9]. However, if this gradient is increased by elevation of blood and interstitial glucose concentrations, this increases movement of glucose into ASL. In healthy human volunteers, experimental elevation of blood glucose from ~5 mM to 12–15 mM increased glucose in nasal ASL from <1 to 4.8 ± 2.2 mM [27] and in lower respiratory tract ASL from 0.36 ± 0.27 to 0.75 ± 0.39 mM [9]. In support of these findings, people with diabetes mellitus had elevated nasal (median 4 mM, interquartile range 2–7 mM) [8] and lower respiratory tract (1.2 ± 0.7 mM) ASL glucose concentrations [9].

THE ROLE OF GLUCOSE TRANSPORT IN LIMITING ASL GLUCOSE

As glucose is able to diffuse across airway epithelium, with time, ASL glucose might be expected to equilibrate with blood glucose concentrations. As this is not the case, additional mechanisms must exist to remove glucose from the ASL and/or restrict diffusion and transcellular transport. In the next section, we will expand on the nature and role of glucose transport in lung epithelium.

Glucose transporters

Glucose transport across mammalian cell membranes is mediated either by facilitative GLUTs (encoded by the SLC2 gene family) or by SGLTs (SLC5 gene family). Glucose moves through GLUTs by passive diffusion down a concentration gradient generated by hexokinases (HKs) and glucokinases, which phosphorylate intracellular glucose. By contrast, SGLT-mediated transport is driven by sodium and glucose gradients and, therefore, can move glucose against its concentration gradient.

The human SLC2 family consists of 14 known isoforms (SLC2A1–14) encoding glucose transporter proteins, each with different tissue expression patterns, substrate (sugar) specificity and transport kinetics. According to their sequence homology, GLUTs can be divided into three distinct classes: class I comprises the well-characterised transporters GLUT1–4 [28–31] and GLUT14 (a gene duplication of GLUT3) [32]; class II includes the fructose transporter GLUT5 [33], and GLUT7 [34], GLUT9 [35] and GLUT11 [36]; class III comprises the recently identified transporters GLUT6 [33], GLUT8 [37], GLUT10 [38], GLUT12 [39] and the proton-driven human myoinositol transporter (GLUT13) [40]. Their affinities for glucose vary greatly. GLUT2 has a lower affinity for glucose than other members of the glucose transporter family (Michaelis constant (K_m) of ~32 mM when expressed in *Xenopus* oocytes [41], while GLUT10 has the highest affinity (K_m ~0.3 mM) [42]. The human SLC5 gene family consists of 11 isoforms (SLC5A1–11), of which SLC5A1 (SGLT1) [43] and SLC5A2 (SGLT2) [44] are known to encode SGLTs.

TABLE 1 Facultative glucose transporter (GLUT) and sodium-coupled glucose transporter (SGLT) expression in human cultured epithelial cells, human bronchial tissue and whole lung

Transporter	Human cultured epithelial cells						Bronchial tissue		Whole lung	
	H441				HBECs		mRNA	Protein	mRNA	Protein
	Nonpolarised		Polarised		mRNA	Protein				
	mRNA	Protein	mRNA	Protein			mRNA	Protein		
GLUTs										
GLUT1	+	-	-	-	+	+	+	-	+	-
GLUT2	+	+		+	+	-	+	+		
GLUT3	-	-	-	-	+	-	+	-	+	-
GLUT4	+	+		-	+	-	+	-		-
GLUT5					+		+	-	+	-
GLUT6					+		+			
GLUT7					+		+			
GLUT8					+	-	+			
GLUT9					+		+			
GLUT10				+	+	+	+		+	
GLUT11					+		+			
GLUT12					+		+			
SGLTs										
SGLT1					+	-	+			+
SGLT2					+	-	+			+

HBEC: human bronchial epithelial cells; +: present; -: absent.

GLUT- and SGLT-mediated glucose transport have been well characterised in many tissues and cell types, although relatively little is known about their roles in the lung. Understanding of this is greatly complicated by regional, species and developmental differences in pulmonary glucose transport.

Glucose transport in airway epithelium

In human airway epithelium (trachea, bronchi and bronchioles), GLUTs are the predominant glucose transporter type expressed (tables 1 and 2). GLUT10 is present in immortalised human airway epithelial cells (H441) [10], and GLUT2 protein was detected in both apical and basolateral membranes of H441 and in epithelial cells in human bronchial biopsies [13]. In primary cultured HBECs, GLUT10 was present in the apical membrane but GLUT1 protein was detected in basolateral membrane [11]. In H441 cell monolayers, phloretin (an inhibitor of GLUT-mediated transport) inhibited apical glucose uptake and increased appearance of D-glucose in the apical compartment [12]. In HBEC monolayers, 2-DOG (a substrate for GLUT but not SGLT transport) was taken up across the apical membrane [11]. Taken together, these findings indicate that apical glucose uptake through GLUTs plays an important role in maintaining low ASL glucose concentrations.

As GLUTs only transport glucose down its concentration gradient, this poses the question as to how GLUTs can maintain low ASL glucose concentrations. Two mechanisms have been proposed from recent research. First, glucose taken up into airway epithelial cells is metabolised rapidly [12]. This would maintain low intracellular glucose concentrations, providing a

driving force for glucose uptake across basolateral and apical membranes. Rapid metabolism of glucose would also be predicted to limit transcellular movement of glucose that could occur given the basolateral-to-apical glucose concentration gradient. Secondly, glucose uptake from the basolateral membrane and intercellular clefts could modify glucose concentration in localised microdomains and decrease glucose concentration gradients close to routes of paracellular diffusion. In support of this, basolateral phloretin increases appearance of glucose in the apical compartment of polarised H441 cell monolayers [12]. In this scenario, combined paracellular and transcellular glucose movement would be less than cell glucose uptake, allowing generation of low ASL glucose concentrations [11, 12]. We also speculate that the different apical and basolateral localisation of GLUTs may play an important role in regulating glucose uptake from these apical and basolateral domains. For example, the low K_m of GLUT10 compared with the higher K_m s of GLUT1 and GLUT2 would preferentially favour glucose uptake from the apical side at low glucose concentrations. These findings indicate that airway epithelial GLUTs could be targeted to enhance depletion of glucose in ASL in respiratory disease. Moreover, it could be envisaged that genetic mutations that decrease glucose transporter function could lead to compromised airway glucose homeostasis and result in recurrent pulmonary or upper airway infections.

Both of these hypotheses predict that glucose metabolism in airway epithelial cells is a key driver of GLUT transport and determinant of ASL glucose concentrations. Once taken up into the cell, conversion of glucose to glucose-6-phosphate is

TABLE 2 Facultative glucose transporter (GLUT) and sodium-coupled glucose transporter (SGLT) expression in whole lung, and bronchial and alveolar[#] epithelium in fetal and adult stages

Transporter	Whole lung				Bronchial epithelium				Alveolar epithelium			
	Fetal		Adult		Fetal		Adult		Fetal		Adult	
	RNA	Protein	RNA	Protein	RNA	Protein	RNA	Protein	RNA	Protein	RNA	Protein
GLUTs												
GLUT1	+	[50, 51]	+	[50]	+	[51, 52]						
GLUT2												
GLUT3												
GLUT4												
GLUT5												
GLUT6												
GLUT7												
GLUT8												
GLUT9												
GLUT10												
GLUT12												
SGLTs												
SGLT1												
SGLT2												

Expression in rats unless otherwise stated. +: present; -: absent. #: type II cells; *: pig; §: mouse; f: rabbit; ##: sheep.

catalysed by HKs. As glucose phosphorylation is considered to be the rate-limiting step in glucose metabolism [62, 63] this is likely to be an important process in lung glucose homeostasis. HKI, HKII and HKIII have been identified in rat lung [52, 64], and HKII is present in human lung tumours and A549 alveolar epithelial cells [65, 66]. How HK activity might regulate glucose uptake, transepithelial glucose transport and glucose concentrations in ASL has yet to be explored. However, it could be speculated that upregulation of HK activity would increase glucose uptake and reduce ASL glucose. There is already interest in activators and inhibitors of hexokinase activity for the treatment of diabetes. These enzymes may also provide potential therapeutic targets for the treatment and prevention of lung disease associated with elevated ASL glucose.

In human airway epithelium, sodium-coupled glucose transport does not appear to contribute to maintenance of low ASL glucose concentrations. SGLT protein has not been detected in human airway epithelium (table 1). In human tracheal epithelium mounted in Ussing chambers, short-circuit current (I_{sc}) was not increased by luminal glucose or reduced by phlorizin (an SGLT inhibitor) [11]. There was no consistent effect of apically applied phlorizin on glucose uptake or I_{sc} in human cell monolayers. Ussing chamber studies comparing sheep and human tracheal epithelium (from diseased lung) showed phlorizin produced a small reduction in I_{sc} in ovine airways (~5%), but had no significant effect in human tissue [67].

While GLUTs dominate apical glucose transport in the surface epithelium of the airways, there is some enticing evidence that SGLTs could be present in the submucosal glands (SMGs). In polarised cultures of serous SMG cells (Calu-3 cells), the addition of phlorizin (200 μ M) inhibited ~20% of basal I_{sc} , which could be mimicked by removal of glucose from the apical bath solution [54], consistent with the presence of apical sodium-coupled glucose transport in these cells [68, 69]. Whether SGLTs are present in submucosal glands *in vivo* remains to be tested but it seems unlikely so far that they have a significant contribution to airway glucose transport given the lack of functional evidence (see earlier).

Glucose transport in distal lung epithelium

In distal lung (alveolar) epithelium, sodium-coupled glucose transport appears to be the major mechanism responsible for apical glucose uptake from the lumen. As studies have not been performed in human distal lung epithelium, understanding of this area comes from animal studies.

SGLT1, but not SGLT2, mRNA has been identified in distal lung epithelium from adult rats [55, 60], and from mouse and human whole-lung tissue [49, 56]. BODEGA *et al.* [61] recently identified SGLT protein in type I and II alveolar cells of rat and sheep lung. However, SGLT1 protein could not be detected in adult rabbit lung tissue. In rat, rabbit and sheep distal lung, glucose removal from the lumen is prevented by phlorizin, which inhibits SGLTs [3, 4, 70]. SGLT-mediated transport has been demonstrated in freshly isolated alveolar type II (ATII) cells from guinea pig [70]. In airway epithelial cells, the intracellular sodium concentration is low (~23 mM) compared with the sodium concentration in the ASL (~120 mM) or blood plasma (~140 mM) [71, 72]. SGLT utilises this sodium gradient to drive glucose uptake from ASL

(low glucose) to the interstitium and blood (high glucose) against its concentration gradient.

By contrast, there is little evidence of luminal GLUT-mediated transport by the distal lung epithelium. Phloretin in the lung instillate did not inhibit glucose or fluid absorption from rabbit [15, 73] or rat whole lung [4], and there was little luminal 2-DOG (GLUT-specific) uptake in fetal sheep lung [3]. However, both phlorizin and phloretin inhibit glucose uptake in isolated ATII cells from guinea pig lung [70], indicating that GLUTs could be present on the basolateral membrane.

The observation that airway and alveolar epithelium utilise diverse glucose transport mechanisms has led to speculation as to the role of apical glucose transport in different lung regions. In the airway, which is the first line of defence against infection, generation of low ASL glucose concentrations may be crucial for maintenance of airway sterility. In the distal lung, where gas exchange occurs, sodium-coupled glucose transport may be an important driver of fluid reabsorption and regulation of ASL volume, with generation of low ASL glucose concentrations as a secondary beneficial effect. Developmental changes in lung epithelial glucose transport also indicate differences in the role of these transport processes in the fetal and adult lung.

Developmental differences in lung glucose transport

Developmental changes in lung glucose transporter expression have best been characterised in rat lung (table 2). In fetal rats, GLUT1 mRNA expression increases to maximal levels at gestational day 20 and falls to very low levels by postnatal day 8 [51]. Immunohistochemical staining of the rat fetus from gestational day 13 to 21 shows weak GLUT12 expression in the epithelial cell membrane of bronchioles at gestational day 19, which increases in intensity by day 21. Consistent with mRNA expression studies, GLUT1 protein was also observed in the airways at gestational day 19, decreasing in intensity at day 21 [57]. GLUT1 protein has also been detected in the alveolar epithelium of the fetal rat, although to date, GLUT1 protein has not been identified in either the airways or distal lung of the adult rat [59]. SGLT1 mRNA expression has been seen in the distal lung of both fetal and adult rats [55, 56].

In fetal sheep, the maximum rate of phlorizin-sensitive glucose uptake from the lung lumen increased with gestational age [3], indicating increased pulmonary expression of SGLTs towards birth. In humans, amniotic fluid glucose concentrations fall towards the end of pregnancy [74], consistent with increased pulmonary glucose reabsorption.

It is interesting to speculate on the role of glucose transport in fetal lungs. In fetal sheep, both addition of glucose to lung liquid [3] and maternal hyperglycaemia decrease net lung liquid secretion, probably by driving glucose-coupled sodium absorption. However as glucose concentrations are very low in normal fetal lung liquid, this process is unlikely to be a major determinant of lung sodium transport unless there is gestational diabetes. An alternative role could be to scavenge glucose from amniotic fluid, which could have the dual functions of conserving nutrients and reducing the risk of infection.

Species and tissue differences in lung glucose transport

The investigation of lung glucose transport in humans *in vivo* is challenging, so animal and cell culture models have been used

to explore this field. There are important differences in the expression and function of transporters between species, cell types and experimental conditions that should be appreciated when choosing a model.

Species differences

Where it has been investigated, adults of most species have been found predominantly to express GLUT transporters in airway and SGLT in distal lung epithelium. Glucose uptake by isolated primary guinea pig ATII epithelial cells could be reduced both by phlorizin and by phloretin, indicating that not only SGLTs but also GLUTs are present in guinea pig distal lung cells [70]. By contrast, in adult sheep, glucose uptake across the tracheal epithelium can be inhibited by phlorizin and requires external sodium, consistent with sodium-coupled glucose transport [75]. Similarly, in isolated equine tracheae, phlorizin addition to the apical (but not the basolateral) membrane produced a significant decrease in *I_{sc}* [76]. However, these differences between guinea pig and sheep/horse more likely reflect the experimental preparation. In intact epithelium, SGLT is predominantly present on the luminal membrane, but in isolated cells, there is a contribution from basolaterally localised GLUTs.

Cell types

Most *in vitro* studies of human airway epithelial glucose transport have used immortalised H441 cells or primary cultured HBECs. H441 cells derive from a papillary adenocarcinoma of the bronchiolar epithelium. When cultured at an air-liquid interface, these cells form an absorptive epithelial monolayer, exhibit vectorial ion transport processes, and have similar morphological and phenotypic characteristics to human bronchiolar epithelium [77]. Both H441 cells and HBECs express GLUTs and do not exhibit SGLT expression. However, there may be differences in the GLUT isoform expressed, with H441 cells predominantly expressing GLUT2 and GLUT10 [10, 13] and HBECs expressing GLUT1 and GLUT10 [11].

Experimental conditions

Experimental conditions in both animal and *in vitro* studies may influence channel expression and function. In animals, investigation of distal lung glucose transport requires use of a fluid-filled lung model, which may alter transport processes. In cell culture, nonpolarised H441 cells express GLUT4, which was not detected in H441 cells polarised at an air-liquid interface [13].

EFFECTS OF ELEVATED ASL GLUCOSE CONCENTRATIONS

So what are the implications of lung glucose homeostasis for human health and disease? Clinical observation has shown that ASL glucose concentrations are normally ~12.5 times lower in human ASL than in plasma. However, ASL glucose concentrations are elevated in respiratory disease and when blood glucose is elevated. Nasal glucose concentrations are undetectable (<1 mM) in healthy volunteers, but detectable in 90% of people with diabetes mellitus (median 4 mM, interquartile range 2–7 mM) [8]. Ventilated patients on intensive care are more likely to have glucose detectable in bronchial aspirates when they have elevated blood glucose [7]. ASL glucose concentration, estimated using an exhaled breath condensate technique (breath glucose), was found to be 0.4 ± 0.2 mM in healthy volunteers but was elevated to 2.0 ± 1.1 mM in patients with cystic fibrosis,

1.2 ± 0.7 mM in patients with diabetes mellitus and by the greatest amount (4.0 ± 2.0 mM) in people with both cystic fibrosis and diabetes mellitus [9]. In patients undergoing bronchoscopy, glucose was found to be elevated in bronchoalveolar lavage fluid (BAL) from patients with chronic obstructive pulmonary disease (COPD) and chronic severe asthma compared with levels in BAL fluid from healthy controls [78, 79]. These scenarios involve hyperglycaemia as a result of stress, and type I and type II diabetes mellitus. Any specific effect(s) of these individual disorders on glucose transport and homeostasis is, as yet, unclear. However, this may be important to understand, particularly with type II diabetes becoming more prevalent in the Western population.

There is both direct and indirect evidence that elevated ASL glucose concentrations promote lung infection. The respiratory pathogens *Staphylococcus aureus* and *Pseudomonas aeruginosa* both utilise glucose as a growth substrate [80]. Patients intubated and ventilated in an intensive care unit who have detectable glucose in bronchial aspirates are more likely to have methicillin-resistant *S. aureus* isolated from aspirates than those without detectable glucose [81]. Diabetes mellitus is a predisposing factor for nasal colonisation with *S. aureus* [82]. Patients with COPD who also have diabetes mellitus are more likely to have Gram-negative organisms cultured from their sputum than those without diabetes [83]. During acute exacerbations of COPD, increasing admission blood glucose concentrations are associated with increasing an likelihood of isolating *S. aureus* and multiple pathogens from sputum [79]. The growth of *P. aeruginosa* was found to be increased in the lungs of hyperglycaemic mice *in vivo* [11]. In humans with cystic fibrosis, coexisting diabetes mellitus is associated with an increased risk of infection with multiple antibiotic-resistant *P. aeruginosa* [84]. Cystic fibrosis patients with diabetes mellitus had more pulmonary exacerbations [85], which were less likely to respond to intravenous antibiotics [86], than those without diabetes.

QUESTIONS FOR THE FUTURE

While there are several mechanisms that regulate glucose homeostasis across the pulmonary epithelium, glucose transport undoubtedly plays a key role in maintaining a low glucose concentration in the ASL and, thus, restricting the growth of respiratory pathogens. This newly identified role for glucose transport raises some important questions, particularly regarding our classic understanding of GLUT-mediated transport. For example, is GLUT abundance regulated in response to changes in ASL glucose concentration? Why are SGLTs only detectable in the distal lung (SGLT can transport glucose against its concentration gradient, which would more efficiently reduce glucose in ASL)? In addition, in the gut, SGLTs are proposed to have an important role as glucose sensors with consequent upregulation of GLUT-mediated transport [87]. What are the roles of the different transporters, especially GLUT1, GLUT2 and GLUT10, in pulmonary glucose homeostasis? Is pulmonary glucose transport compromised in respiratory disease and diabetes (particularly in type II diabetes), and does this contribute to increased ASL glucose and infection? Finally, could we target glucose transport in the lung to ameliorate some of the consequences of respiratory disease?

STATEMENT OF INTEREST

None declared.

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