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# Hyperglycaemia and pulmonary infection

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Pathophysiological stress from acute illness causes metabolic disturbance, including altered hepatic glucose metabolism, increased peripheral insulin resistance and hyperglycaemia. Acute hyperglycaemia is associated with increased morbidity and mortality in patients in intensive care units and patients with acute respiratory disease. The present review will consider mechanisms underlying this association. In normal lungs the glucose concentration of airway secretions is approximately 10-fold lower than that of plasma. Low airway glucose concentrations are maintained against a concentration gradient by active glucose transport. Airway glucose concentrations become elevated if normal homeostasis is disrupted by a rise in blood glucose concentrations or inflammation of the airway epithelium. Elevated airway glucose concentrations are associated with and precede increased isolation of respiratory pathogens, particularly methicillin-resistant *Staphylococcus aureus*, from bronchial aspirates of patients intubated on intensive care. Markers of elevated airway glucose are associated with similar patterns of respiratory infection in patients admitted with acute exacerbations of chronic obstructive pulmonary disease. Glucose at airway concentrations stimulates the growth of respiratory pathogens, over and above the effect of other nutrients. Elevated airway glucose concentrations may also worsen respiratory disease by promoting local inflammation. Hyperglycaemia may thus promote pulmonary infection, at least in part, by an effect on airway glucose concentrations. Therapeutic options, including systemic control of blood glucose and local manipulation of airway glucose homeostasis, will be considered.

**Hyperglycaemia: Stress: Infection: Lung diseases: Insulin**

## Stress, acute illness and hyperglycaemia

Stress can be defined as 'a pathological process resulting from the reaction of the body to external forces and abnormal conditions that tends to disturb the organism's homeostasis' (National Library of Medicine, 2005). The present review will focus on the effect of the stress of acute illness on carbohydrate metabolism and the consequences of stress-induced hyperglycaemia, particularly in the lungs.

### *Normal carbohydrate metabolism*

Blood glucose concentrations are normally maintained at about 4·0–5·5 mmol/l, the optimal concentrations for brain function (Meisenberg & Simmons, 1998). Blood glucose is supplied by dietary carbohydrates for a few hours after a meal, and subsequently maintained by hepatic glucose production (see Fig. 1(a)). The liver synthesises glucose both by the degradation of glycogen and by gluconeogenesis from non-carbohydrate precursors, including amino acids, lactic acid and glycerol. The relative contributions of hepatic glycogenolysis and gluconeogenesis to glucose production are hormonally regulated. Glucagon stimulates glycogenolysis in a rapid potent time-dependent manner that wanes as glycogen stores are depleted (Magnusson *et al*. 1995). Glucagon also has a slower less-potent stimulatory effect on gluconeogenesis that is limited by the availability of gluconeogenic substrates (Chhibber *et al*. 2000). Adrenaline stimulates glycogenolysis directly (Chu *et al*. 1996) and increases gluconeogenesis indirectly by enhancing peripheral substrate release (Chu *et al*. 1997). Cortisol stimulates gluconeogenesis through direct hepatic effects (Exton *et al*. 1976). These three hormones have an

**Abbreviation:** ICU, intensive care unit.

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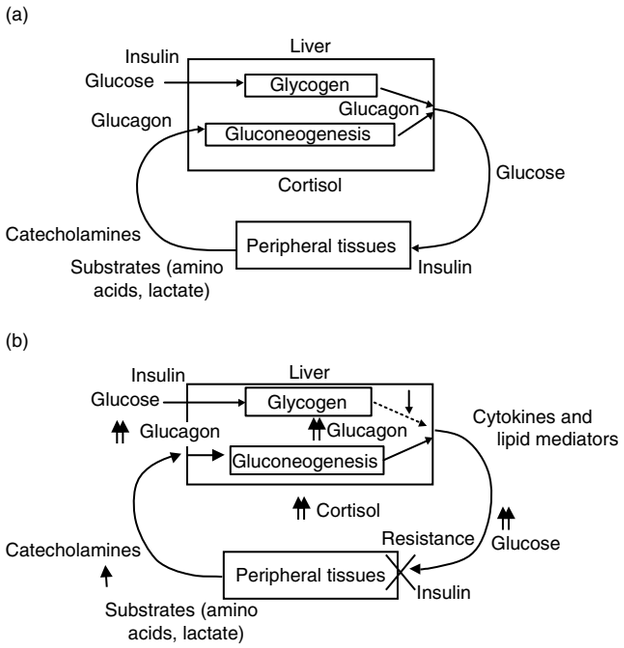


**Fig. 1.** Carbohydrate metabolism. (a) Normal carbohydrate metabolism. Blood glucose is maintained at approximately 4·0–5·5 mmol/l. After a meal glucose is supplied by dietary carbohydrates, and increased insulin concentrations stimulate hepatic glucose storage as glycogen and peripheral glucose utilisation. At other times blood glucose is maintained by glycogenolysis and gluconeogenesis, regulated by glucagon. Gluconeogenesis requires substrates (amino acids, lactic acid, lipids) that are released from peripheral tissues in response to catecholamines. (b) Carbohydrate metabolism during acute stress. Increased concentrations of glucagon and cortisol stimulate gluconeogenesis, which is fuelled by increased peripheral substrate release that is driven by increased catecholamine concentrations. Inflammatory mediators, including cytokines, also induce reversible insulin resistance, resulting in failure to suppress hepatic glucose production and reduced glucose uptake in peripheral tissues. The net effect is hyperglycaemia. ↑, Increased concentrations; ↓, ⇢, reduced conversion of glycogen to glucose.

additive effect on glucose production (Lecavalier *et al.* 1990; Gustavson *et al.* 2003), particularly as adrenaline mobilises substrates for gluconeogenesis, which is enhanced by glucagon and cortisol. The actions of insulin oppose the effects of glucagon, catecholamines and cortisol. Insulin stimulates glucose-consuming pathways and suppresses glucose-producing pathways in the liver, as well as stimulating glucose uptake by peripheral tissues.

### *Carbohydrate metabolism in acute illness*

In acute illness glucose production is increased and peripheral glucose clearance is decreased, resulting in elevated plasma glucose concentrations (see Fig. 1(*b*)). This response appears to be mediated by a combination of neurohumoral changes, cytokine production and the release of lipid mediators (McGuinness, 2005). Elevation of serum concentrations of glucagon, adrenaline and cortisol is observed in response to a variety of pathophysiological stresses (Rolih & Ober, 1995), and infusion of these hormones in combination reproduces the marked hyperglycaemia, hyperinsulinaemia and accelerated glucose metabolism of acute illness (McGuinness *et al.* 1999). The contribution of individual hormones to stress hyperglycaemia has proved difficult to quantify, as in physiological models interventions to stimulate or block one hormone change the concentrations and effects of the other hormones. In the context of these limitations adrenaline has been shown to stimulate glucose production and inhibit glucose utilisation, in part by inhibiting pancreatic insulin secretion (McGuinness *et al.* 1999). Glucagon appears to divert glucose and gluconeogenic precursors from glycogen to glucose production, thus contributing to net hepatic glucose output (McGuinness *et al.* 1994*a*). Hepatic insulin resistance, with failure to suppress gluconeogenesis despite hyperglycaemia and increased circulating insulin levels, further contributes to the increased glucose production (Van den Berghe, 2004).

The induction of reversible insulin resistance by acute stress reduces peripheral glucose utilisation. Patients with sepsis show a reduction in glucose utilisation during hyperglycaemic clamping compared with controls, despite similar plasma insulin concentrations (White *et al.* 1987). Insulin resistance in acute stress has been attributed to inflammation and cytokine production. In mice the infusion of the proinflammatory cytokine IL-6 both reduces insulin-stimulated glucose uptake in skeletal muscle and blunts suppression of hepatic glucose production by insulin activity (Kim *et al.* 2004). Infusion of IL-10, an anti-inflammatory cytokine, prevents IL-6-induced defects in insulin action and signalling activity (Kim *et al.* 2004). In rats the infusion of the proinflammatory cytokine TNF-α reduces insulin sensitivity within 24 h and induces insulin resistance over 4 d (Ruan *et al.* 2002). TNF-α neutralisation increases by 68 % the rate of glucose infusion required to maintain euglycaemia in rats during hyperinsulinaemic euglycaemic clamp studies, stimulating glucose uptake by skeletal muscle (Borst *et al.* 2004). Furthermore, TNF-α-deficient knock-out mice with diet-induced obesity respond to an exogenous dose of insulin or glucose much more efficiently than wild-type mice expressing TNF-α (Hotamisligil, 1999). The mechanism of cytokine-induced insulin resistance is not fully understood, but may be the result of a direct effect on insulin receptor signalling. Increased cytokine concentrations stimulate the generation of 'suppressor of cytokine-signalling' proteins, which act as negative-feedback inhibitors of cytokine signal transduction (Mao *et al.* 1999). 'Suppressor of cytokine-signalling' proteins have been shown to inhibit insulin receptor tyrosine phosphorylation and downstream signal transduction (Senn *et al.* 2003) and to degrade insulin receptor substrate (Rui *et al.* 2002).

### *Definition of hyperglycaemia*

As the understanding of the pathophysiological consequences of hyperglycaemia has increased, the definition of hyperglycaemia has changed. The diagnosis of diabetes mellitus requires either that fasting blood glucose should be ≥7·0 mmol/l on two or more occasions or that random blood glucose should be ≥11·0 mmol/l on one occasion,

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combined with symptoms of diabetes (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003). A number of studies investigating the effect of glucose in acute illness have therefore defined acute hyperglycaemia as blood glucose of ≥11 mmol/l (Malmberg *et al*. 1995; Umpierrez *et al*. 2002; McAlister *et al*. 2005). However, evidence of adverse effects of blood glucose above physiological concentrations (>6·0 mmol/l) but below diabetic concentrations (<11·0 mmol/l) in acute illness has led investigators to consider any blood glucose concentration above physiological concentrations to be hyperglycaemia in acute stress (Capes *et al*. 2001; Van den Berghe *et al*. 2001).

### *Hyperglycaemia and poor outcomes from acute illness*

Hyperglycaemia, by either definition, is extremely common in acute illness. It has been reported (Umpierrez *et al*. 2002) that 38% of adults admitted acutely to general hospital wards were found to have hyperglycaemia, defined as blood glucose at admission or fasting blood glucose of ≥7 mmol/l or two random blood glucose measurements of ≥11·1 mmol/l. In one-third of the group with elevated blood glucose the hyperglycaemia had been newly diagnosed, and in-hospital mortality was found to be higher in this group (16%) than in those with established diabetes mellitus (3%) or normal blood glucose (1·7%; Umpierrez *et al*. 2002). Furthermore, hospital stay was reported to be longer and intensive care unit (ICU) admission more frequent in those patients with newly-diagnosed hyperglycaemia. Other studies have shown that hyperglycaemia (various definitions) is also associated with adverse outcomes from acute myocardial infarction (Capes *et al*. 2000), ischaemic or haemorrhagic stroke (Capes *et al*. 2001), surgery (Hill Golden *et al*. 1999) and trauma (Yendarumi *et al*. 2003). Blood glucose control with insulin improves outcomes from myocardial infarction (Malmberg *et al*. 1995) and ICU admission following cardiothoracic surgery (Van den Berghe *et al*. 2001). Regression analysis has found that control of glucose levels, rather than insulin dose, is responsible for the clinical benefits observed (Finney *et al*. 2003; Van den Berghe *et al*. 2003). These findings imply that elevated glucose concentrations have a direct detrimental effect on outcomes.

### *Potential mechanisms*

Hyperglycaemia could have adverse effects in acute illness through cellular glucose overload and oxidative stress. In acute illness cytokines, hormones and hypoxia up regulate expression and membrane localisation of glucose transporters in many cell types (Van den Berghe, 2004). Cellular glucose overload results in increased glucose metabolism, in turn increasing superoxide and peroxynitrite production, which may impair mitochondrial activity (Van den Berghe, 2004). In support of this finding, ultrastructural abnormalities have been observed in hepatic mitochondria obtained at liver biopsy from patients in the ICU with hyperglycaemia, whereas virtually no mitochondrial abnormalities are detected in patients in whom normoglycaemia is maintained therapeutically (Vanhorebeek *et al*. 2005). The mitochondrial toxicity of glucose in diverse cells could account for the broad spectrum of organ and tissue dysfunction associated with hyperglycaemia in acute illness (Van den Berghe *et al*. 2001).

Acute hyperglycaemia is associated with increased risk of infection (Khaodhiar *et al*. 1999; Vriesendorp *et al*. 2004), and insulin therapy to normalise blood glucose reduces septicaemia by 46% and the need for prolonged antibiotic therapy by 35% compared with conventional therapy (Van den Berghe *et al*. 2001). Systemic immune defects in patients with diabetes include decreased neutrophil and macrophage chemotaxis, phagocytosis and killing, and impairment in complement and cytokine responses to infection (Geerlings & Hoepelman, 1999). Similar systemic immune dysfunction could contribute to increased infection risk in acute hyperglycaemia. Additionally, elevated glucose concentrations could have local effects on host immunity or bacterial growth, which could promote infection.

## Hyperglycaemia and pulmonary infection

Two recent studies have shown that acute hyperglycaemia is associated with poor outcomes from hospital admission for pulmonary infection. Patients with hospital-acquired pneumonia who have a blood glucose concentration of >11 mmol/l have an increased risk of death and in-hospital complications compared with those with a blood glucose concentration of ≤11 mmol/l (McAlister *et al*. 2005). An increase in blood glucose concentration of 1 mmol/l is associated with a 3% increase in the risk of in-hospital complications (McAlister *et al*. 2005). It has been found that 50% of patients admitted with acute exacerbations of chronic obstructive pulmonary disease have a blood glucose concentration of ≥7·0 mmol/l (Baker *et al*. 2006). Relative risk of death or prolonged hospital stay is greatest in those patients with the highest blood glucose concentrations (highest blood glucose quartile *v*. lowest blood glucose quartile; relative risk 1·97 (95% CI 1·33, 2·92), $P<0·0001$) and increases by 14% with each 1 mmol/l increase in blood glucose concentration (Baker *et al*. 2006). In patients with acute exacerbations of chronic obstructive pulmonary disease multiple pathogens and *Staphylococcus aureus* are isolated from sputum more frequently as blood glucose concentrations increase, raising the question as to whether hyperglycaemia could directly influence airway infection.

### *Glucose concentrations in airway surface liquid*

The air spaces in the lung are lined with a thin layer of fluid (airway surface liquid). The volume and composition of airway surface liquid are carefully regulated and are critical for lung defence. Animal studies have shown that the glucose concentration of airway surface liquid is 3–20-fold lower than that of plasma (Barker *et al*. 1989; Icard & Saumon, 1999). Glucose has not been detected in nasal secretions from healthy human volunteers using modified

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glucose oxidase sticks (lower limit of detection approximately 0·5 mmol/l; Philips *et al*. 2003). Liquid from normal human lower airways, sampled non-invasively by exhaled breath condensate collection, contains 0·4 (SD 0·2) mmol glucose/l (Clark *et al*. 2004).

*Hyperglycaemia.* Airway glucose concentrations become elevated when blood glucose is raised. Glucose concentrations are 1–9 mmol/l in nasal secretions from patients with treated diabetes mellitus and 1–11 mmol/l in bronchial aspirates from patients in the ICU with stress hyperglycaemia (Philips *et al*. 2003). The relationship between blood and airway glucose concentrations has been clarified in healthy volunteers using a modified hyperglycaemic clamp technique (Wood *et al*. 2004*b*). Glucose is not detected in nasal secretions at baseline (blood glucose 5 mmol/l), but becomes detectable in nasal secretions within 10 min of blood glucose elevation to 12 mmol/l (Wood *et al*. 2004*b*). Nasal glucose reaches a maximum concentration of 4·8 (SD 2·2) mmol/l then falls to control values when blood glucose is allowed to return to baseline. A blood glucose 'threshold' of 6·7–9·7 mmol/l has been identified, above which glucose becomes detectable in nasal secretions (Wood *et al*. 2004*b*). Liquid from the lower airways of patients with diabetes (sampled as exhaled breath condensate) contains 1·2 (SD 0·7) mmol/l glucose as compared with 0·4 (SD 0·2) mmol/l glucose in airway surface liquid from healthy volunteers ($P<0·0001$; Clark *et al*. 2004). Glucose concentrations in lower-airway secretions also increase in response to experimental hyperglycaemia (Clark *et al*. 2006).

*Inflammation.* Airway glucose concentrations are elevated when the airway epithelium is inflamed. Glucose is detected at 1–2 mM in nasal secretions from healthy volunteers during acute viral rhinitis and disappears with resolution of the symptoms (Philips *et al*. 2003). Glucose concentrations are elevated in liquid from the lower airways of patients with cystic fibrosis who have airway inflammation and normal glucose tolerance (Brennan *et al*. 2006). The effects of inflammation and hyperglycaemia appear to be additive, as glucose concentrations are elevated further in liquid from the lower airways of patients with cystic fibrosis who also have diabetes mellitus (Brennan *et al*. 2006).

*Airway glucose homeostasis.* The observation that glucose concentrations are 10-fold lower in human airways than in plasma implies that glucose is actively removed from the airway lumen against the glucose concentration gradient. Animal studies have indicated that glucose is removed from the airway lumen by $Na^+$-dependent glucose transporters in the apical membrane of airway epithelial cells (Barker *et al*. 1989; Saumon *et al*. 1996). Glucose transport from the lumen by $Na^+$-dependent glucose transporters is driven by a $Na^+$ gradient that is generated by $Na^+$-$K^+$ ATPase pumps in the basolateral membrane of epithelial cells (Fig. 2(a)). Animal airway epithelial cells also express the facilitative GLUT (Devaskar & de Mello, 1996), although the polarity of expression and function of the GLUT in airway epithelium has not been fully elucidated. It has been shown that $Na^+$-dependent glucose transporter-1 and GLUT2 are expressed at mRNA and protein level in human nasal epithelium and in immortalised cell lines from the proximal (H441) and distal (A549) airway (Wood *et al*. 2004*a*), implying that glucose homeostasis is similar in human airways. In support of this notion $Na^+$-dependent glucose transporter-1

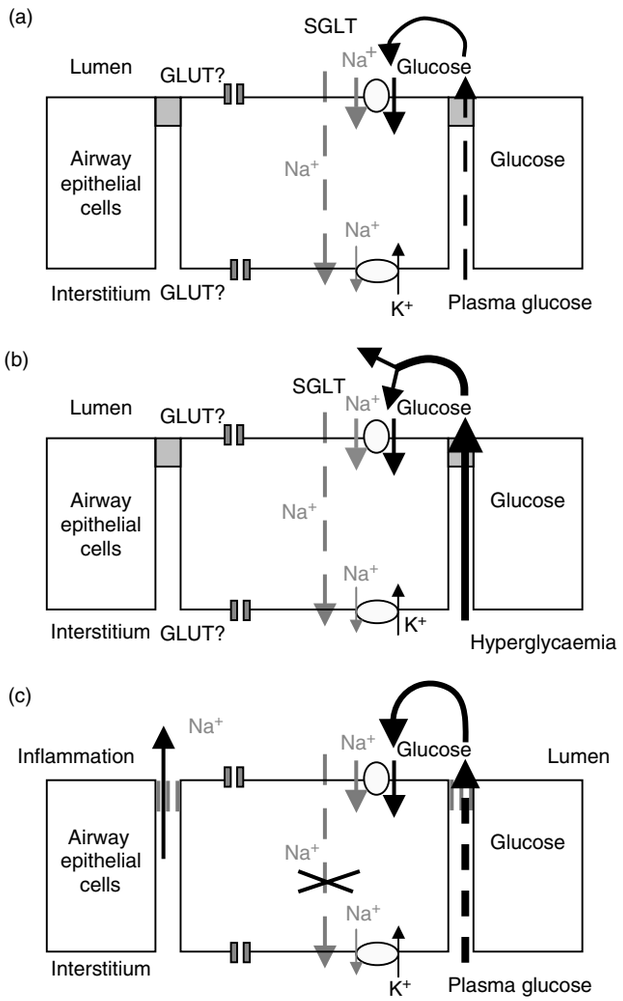


**Fig. 2.** Proposed model of airway glucose homeostasis. (a) Airway glucose homeostasis: the airway epithelial cells are interspersed with tight junctions, forming a resistant epithelium. Glucose moves down its concentration gradient from plasma to lumen across the epithelium, probably by paracellular diffusion. Glucose is removed from the airway lumen by sodium ion-dependent glucose transporters (SGLT) present in apical membranes of epithelial cells, maintaining low lumen glucose concentrations. SGLT transport is driven by a sodium ion gradient generated by $Na^+$-$K^+$ ATPase pumps in the basolateral membrane. Facilitative GLUT are also expressed by airway epithelial cells, although their polarity of expression and function is not known. (b) Hyperglycaemia: when blood glucose is raised the concentration gradient for glucose from plasma to the lumen increases and more glucose diffuses into the airway lumen. At blood glucose concentrations of >6·7–9·7 mm (Wood *et al*. 2004*b*) lumen glucose concentrations exceed the capacity of glucose transport and airway glucose concentrations rise. (c) Inflammation: the permeability of the airway epithelium is increased, possibly as a result of structural changes in tight junctions, thus dissipating the transepithelial sodium ion gradient, reducing glucose absorption by SGLT and elevating airway glucose concentrations.

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mRNA (Ishikawa *et al*. 2001), but not protein (Devaskar & de Mello, 1996), and GLUT2 protein (Ito *et al*. 1998) expression have been demonstrated in non-cancerous regions of human lung obtained at autopsy from patients with primary lung carcinomas. A proposed model of glucose homeostasis in human airways is shown in Fig. 2(a). In this model the effect of hyperglycaemia on airway glucose concentrations is explained by increased movement of glucose into the airway lumen, which overwhelms transport processes that remove glucose from airway secretions (Fig. 2(b)). Inflammation could elevate airway glucose concentrations by increasing airway permeability, which would both increase glucose movement into the lumen and reduce the $Na^+$ gradient driving glucose transport out of the lumen (Fig. 2(c)).

## Glucose and infection in the airways

### *Association studies*

Glucose in airway secretions is associated with the acquisition of respiratory infection in patients in the ICU who are intubated (Philips *et al*. 2005). Patients with glucose present in bronchial aspirates are more likely to have pathogenic bacteria detected in sputum (relative risk 2·4 (95% CI 1·5, 3·8)), particularly methicillin-resistant *S. aureus* (relative risk 2·1 (95% CI 1·2, 3·8)), than those without bronchial glucose. Furthermore, glucose in airway secretions on admission to the ICU are associated with subsequent acquisition of methicillin-resistant *S. aureus* (relative risk 1·8 (95% CI 1·1, 3·6)), implying that glucose precedes infection. It has also been found that multiple respiratory pathogens and methicillin-resistant *S. aureus* are isolated more frequently from sputum of patients admitted with acute exacerbations of chronic obstructive pulmonary disease and hyperglycaemia, although direct measurements of airway glucose were not made (Baker *et al*. 2006).

### *Glucose and bacterial growth*

Glucose in airway secretions could promote respiratory infection through direct effects on bacterial growth. Bacteria utilise saccharides both as substrates for catabolic reactions to provide energy for growth and as C for the biosynthesis of new cellular material (Mortlock, 1998). *S. aureus* and *Pseudomonas aeruginosa*, which are important causes of nosocomial (hospital-acquired) respiratory infection in patients with stress-induced hyperglycaemia, both possess transporters that allow cellular uptake of D-glucose and are able to metabolise D-glucose (Reizer *et al*. 1988; Adewoye & Worobec, 2000). In laboratory culture glucose at concentrations found in airway secretions (0·5–10 mmol/l) promotes a dose-dependent increase in the growth of *S. aureus* (Brennan *et al*. 2004) and 0·56 mmol glucose/l supports growth of *P. aeruginosa* without other nutrients (Chance & Mawhinney, 2000).

### *Glucose and bacterial pathogenicity*

Changes in the environmental nutrient composition can alter bacterial gene expression, leading to changes in virulence. Laboratory culture of mucoid strains of *P. aeruginosa* in high glucose concentrations (approximately 50 mmol/l) induces *algD* transcription, increasing the production of alginate, a viscous exopolysaccharide that causes pulmonary deterioration in cystic fibrosis (Ma *et al*. 1997). Glucose at pathophysiological concentrations stimulates both *P. aeruginosa* (11·1 mmol/l) and *S. aureus* to form biofilms, adherent slime-encased bacterial communities that allow bacterial survival and antibiotic resistance (Kievit *et al*. 2001).

### *Glucose and airway inflammation*

Glucose in airway secretions could moderate the inflammatory response to infection. Serum concentrations of proinflammatory cytokines, including IL-6, soluble IL-6 receptors (Esposito *et al*. 2002; Muller *et al*. 2002; Yu *et al*. 2003) and TNF-α (Esposito *et al*. 2002; Yu *et al*. 2003), are elevated in patients with impaired glucose tolerance compared with controls with normal glucose tolerance. Experimental elevation of blood glucose in patients with normal glucose tolerance when they are clinically stable (Esposito *et al*. 2002) or during sepsis (Yu *et al*. 2003) stimulates acute increases in plasma IL-6 and TNF-α. Plasma IL-8 increases after an oral glucose load in patients with impaired glucose tolerance (Straczkowski *et al*. 2003). The stimulatory effect of glucose on IL-6 and TNF-α production is ameliorated by glutathione infusion, implying that an oxidative mechanism is involved (Esposito *et al*. 2002). In addition, advanced glycation end products, formed by a non-enzymic reaction of glucose with protein $NH_2$ groups, up regulates IL-8 and TNF-α production by human monocyte-derived macrophages (Pertynska-Marczewska *et al*. 2004). There is no published information on the effects of glucose on cytokine production in the airway. However, respiratory pathogens increase airway epithelial expression of proinflammatory cytokines, including IL-6, IL-8 and TNF-α (Khair *et al*. 1994), which could be further up regulated by elevated airway glucose, increasing inflammation and disease severity.

## Nutritional and therapeutic implications

### *Nutritional support and stress hyperglycaemia*

In folklore one version of the advice relating to the treatment of infections suggests ‘If you feed a cold, you’ll have to starve a fever later’. Recent research into altered response to nutritional support during acute stress perhaps provides new validity for this old saying. In individuals receiving enteral and parenteral nutritional support without acute stress glucose is handled predominantly by the liver (McGuinness, 2005). Physiological studies in dogs have demonstrated that the liver takes up approximately 50% of the glucose delivered as chronic total parenteral or enteral nutrition (McGuinness *et al*. 1998; Chen *et al*. 2000). Glucose that is taken up by the liver is predominantly converted to lactate, a substrate that can be taken up by peripheral tissues independently of insulin, thus ensuring effective glucose disposal (McGuinness *et al*. 1998). In

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human subjects studies of liver metabolism are limited by a lack of access to the hepatic and portal veins. However, during prolonged moderate experimental hyperglycaemia–hyperinsulinaemia 40% of the infused glucose is taken up by the splanchnic region, implying a similar role for the liver in glucose disposal in human subjects during nutritional support (Sidossis *et al*. 1999).

In acute stress the adaptation of the liver to nutritional support is markedly impaired. Net hepatic glucose uptake and lactate output are markedly decreased (McGuinness *et al*. 1998). Additionally, glycogen deposition is reduced and suppression of hepatic glucose production is impaired (McGuinness *et al*. 1995). The hormonal changes in acute stress contribute to the abnormal response to nutritional support. Elevated glucagon concentrations impair net hepatic glucose uptake (McGuinness *et al*. 1994*b*). Additionally, glucagon stimulates glucose production by gluconeogenesis (McGuinness *et al*. 1994*a*), which may increase during parenteral or enteral nutrition because of increased supplies of precursor amino acids and lipids. 'Feeding', i.e. nutritional support, thus exacerbates the extent of hyperglycaemia seen during acute stress (Patino *et al*. 1999). This augmented hyperglycaemia may further increase the risk of secondary infection and up regulate the inflammatory response, thus inducing a 'fever later'. This process may be particularly relevant in 'colds', as airway epithelial permeability is increased during viral rhinitis (Philips *et al*. 2003). Inflammation combined with hyperglycaemia results in additional elevation of airway glucose concentrations (Brennan *et al*. 2006), in turn increasing the risk of acquiring bacterial respiratory infection (Philips *et al*. 2005). Patino *et al*. (1999) have demonstrated the effectiveness of 'starving the fever later', as patients receiving hypoenergetic–hyperproteic total parenteral nutrition regimens on a surgical ICU have a more physiological clinical course with less metabolic stress than those receiving high-energy loads.

### *Insulin*

Despite increased insulin resistance in acute stress (White *et al*. 1987), insulin therapy is effective in the normalisation of blood glucose and reduction of adverse outcomes in acute illness. In a prospective study of 1548 patients admitted to a cardiothoracic surgical ICU (Van den Berghe *et al*. 2001) intensive blood glucose control with insulin (blood glucose 4·4–6·1 mM) has been shown to reduce intensive care mortality by 43%, in-hospital mortality by 34%, septicaemia by 46% and the need for prolonged antibiotic therapy by 35% compared with conventional therapy (blood glucose 10–11·1 mM). Similar results have been seen in a more heterogeneous population of critically-ill adults on a general ICU (Krinsley & Grissler, 2005), with blood glucose control to <7·2 mM reducing in-hospital mortality by 29% and ICU length of stay by 11%. The beneficial effects of intensive insulin therapy are related to metabolic control, as reflected by normoglycaemia, rather than the infused insulin dose (Van den Berghe *et al*. 2003). However, insulin may also have benefits that are independent of its effects on blood glucose. In the surgical ICU study (Van den Berghe, 2004) intensive insulin therapy was shown to be associated with an improvement in dyslipidaemia, higher skeletal muscle protein content, reduced inflammation (as indicated by lowered C-reactive protein and mannose-binding lectin levels) and down-regulation of the adhesion molecules intercellular adhesion molecule-I and E-selectin. Insulin may also have direct effects on the airway, which may be of importance in the prevention or treatment of pulmonary infection.

### *Insulin in the airway*

In patients in the ICU systemic insulin therapy is associated with the clearance of glucose from bronchial aspirates (BJ Philips, personal communication). This finding may simply be attributable to an effect of insulin on blood glucose. However, physiological insulin concentrations stimulate the uptake of 2-deoxyglucose by rat alveolar type II epithelial cells (Sugahara *et al*. 1984), implying a possible role for insulin in the up-regulation of pulmonary glucose clearance. Insulin could also have direct effects on infection and inflammation. Insulin therapy reduces pulmonary influenza A viral titres in diabetic mice (Reading *et al*. 1998) and reduces sputum examinations positive for *Haemophilus influenzae* and *Streptococcus pneumoniae* in patients with cystic fibrosis-related diabetes (Lanng *et al*. 1994). There have been no studies of the effect of insulin on airway inflammation. However, systemic insulin has anti-inflammatory effects, mediated through the suppression of major proinflammatory transcription factors (Dandona *et al*. 2005), and potentially could have anti-inflammatory effects in the airway. Imminent licensing of inhaled insulin preparations will provide the opportunity for further exploration of the direct effects of insulin on glucose clearance, infection and inflammation in the airway.

## Conclusion

Stress hyperglycaemia is common in acute illness and is associated with increased risk of poor outcome from respiratory infection. It has been shown that the glucose concentration in the airway increases as blood glucose rises and that elevated airway glucose concentrations are associated with the acquisition of respiratory infection, at least in intensive care. Further studies are required to determine whether elevated glucose concentrations are truly detrimental in airway secretions and to establish the place of therapies that lower airway glucose concentrations in the treatment of airway infection and inflammation.

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