Hyperglycaemia as part of the stress response: the underlying mechanisms

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Stress hyperglycaemia is a distinctive clinical feature of critical illness. Stress mediators, namely stress hormones, cytokines and the central nervous system, interfere with normal carbohydrate metabolism, especially in the liver and skeletal muscle. Central insulin resistance, defined as increased hepatic gluconeogenesis and glucose output despite abundant endogenous insulin levels, appears pivotal to the occurrence of stress hyperglycaemia. The skeletal muscle is refractory to insulin action too. Peripheral insulin resistance is predominantly attributed to inhibition of the skeletal muscle glycogen synthesis. Significantly increased non-insulin-mediated glucose transport into the skeletal muscle overrules defective insulin-mediated glucose transport. Inflammatory mediators and counter-regulatory hormones have been shown to impede crucial elements of the insulin-signalling pathway (insulin receptor substrates/IRS-1/phosphatidylinositol 3-kinase/Akt/Glucose Transporter 4). Still, exogenous insulin administration normalises blood glucose levels in this setting. Insulin treatment may counteract hepatic insulin resistance during acute critical illness. During prolonged critical illness, therapeutic insulin effects seem mediated by increased skeletal muscle glucose uptake and use.

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In healthy individuals, blood glucose levels are tightly regulated within the narrow range of 60–140 mg dl⁻¹. Although not entirely understood, several critical pathways involved in normal glucose control have been untangled.¹

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Dysregulated glucose homeostasis, irrespective of previously diagnosed diabetes, was already recognised as a hallmark of critical illness in the late 19th century. The hyperglycaemic condition in critically ill patients has been labelled stress hyperglycaemia.

Relating to critical illness, the term stress refers to the systemic response to severe injury or infection. This stress response is manifest as a syndrome consisting of hypermetabolism, a hyperdynamic cardiovascular state and inflammation. The occurrence of hyperglycaemia is part of the hypermetabolic condition in conjunction with increased oxygen consumption, hyperlactataemia and protein catabolism. The intensity of the stress response peaks several days after the initial insult and diminishes during recovery. A prolonged response may occur in patients who have persistent tissue hypoperfusion or an unresolved focus of injury or infection with the development of multiple organ failure causing prolonged critical illness.

Hyperglycaemia persists throughout acute and prolonged critical illness. This phenomenon has long been regarded as an adaptive and beneficial stress response: ensuring adequate cellular glucose uptake in non-insulin-dependent, obligatory glucose-consuming tissues such as the brain, phagocytes and reparative cells.

In 2001, however, the critical care community was forced to reconsider this dogma, as a large, randomised, controlled clinical study showed that preventing even moderate hyperglycaemia during critical illness substantially improved outcome. This Leuven study, performed in the surgical unit (SICU), was subsequently corroborated in long-stay patients of the medical unit (MICU), as well as in the Leuven paediatric unit (PICU). These single-centre studies elegantly showed that maintenance of normoglycaemia, with intensive insulin therapy (IIT), actually reduced morbidity and mortality in critically ill patients, provided tight glycaemic control is obtained. These studies have had a major impact worldwide and instigated a vivid discussion concerning the benefits and potential risks of implementing IIT in the varied ICU population.

Insights in how stress induces hyperglycaemia and how IIT controls blood glucose levels during critical illness are imperative to offer a theoretical foundation for the concept of tight glycaemic control in the ICU and to stimulate further research.

This review discusses normal glucoregulation and stress-induced metabolic alterations promoting hyperglycaemia, based on animal and human data. Next, the possible effects of exogenous insulin on carbohydrate metabolism in critical illness are highlighted.

**Regulation of blood glucose levels in healthy individuals**

**Glucose uptake and use**

Under basal conditions, the central nervous system (CNS) accounts for 80% of whole-body glucose use mainly by non-insulin-mediated glucose uptake (NIMGU), and the skeletal muscle for 20% of glucose use, half by insulin-mediated glucose uptake (IMGU), half by NIMGU. Postprandial glucose uptake is equally distributed between muscle, fat, the hepatosplanchnic bed and insulin-independent tissues (CNS and red blood cells (RBCs)).

Glucose uptake through the cellular membranes occurs by carrier-mediated facilitated diffusion. Three of the five identified isoforms, glucose transporter 1 (GLUT1), GLUT2 and GLUT4, are essential for glucose uptake. GLUT1, present in many tissues, is responsible for basal uptake. It has a high affinity for glucose, ensuring transport even in the setting of hypoglycaemia. GLUT1 is equally distributed between the plasma membrane and intracellular vesicles. GLUT2 mediates uptake and release of glucose by hepatocytes and regulates glucose-stimulated pancreatic insulin secretion. GLUT2 guarantees liver permeability for glucose. Glucose transport is not considered rate limiting for hepatic glucose uptake. By contrast, the GLUT4 isoform is the rate-limiting step in glucose uptake in IMGU-dependent tissues, such as skeletal muscle, cardiac muscle and adipose tissue.

Insulin binds to cell surface receptors, which results in autophosphorylation/activation of an intrinsic tyrosine kinase molecule of the insulin receptor (IR)β-subunit (Fig. 1). Activated tyrosine kinase subsequently phosphorylates messenger proteins, namely insulin receptor substrates (IRSs). IRS-1 associates with several proteins including the enzyme phosphatidylinositol (PI) 3-kinase. Under basal conditions, GLUT4 is concentrated in intracellular vesicles, with only about 5% appearing in the
plasma membrane. Insulin increases cellular glucose uptake by PI3-kinase-mediated GLUT4 translocation to the plasma membrane, as well as increased GLUT4 activity. Likewise, PI3-kinase mediates the metabolic effects of insulin, including activation of glycogen synthase, protein synthesis, lipogenesis and gene regulation in insulin-responsive cells, including inhibition of phosphoenolpyruvate carboxykinase (PEPCK), the key enzyme of gluconeogenesis. Although the targets of PI3-kinase action remain quite controversial, the serine/threonine kinase Akt represents one of the PI3-kinase downstream mechanisms.

Glucose production

Glucose production for the systemic circulation is limited to liver and kidney: only these organs contain significant glucose-6-phosphatase levels, the enzyme that catalyses the conversion of glucose-6-phosphate to glucose (Fig. 1). The liver provides glucose through glycogenolysis and gluconeogenesis (GNG). After an overnight fast, the contribution of glycolysis is roughly 50% of the overall hepatic glucose output, but drops to zero after 60 h of starvation. The human kidney does not contain an appreciable store of glycogen. Hence, renal glucose production is exclusively gluconeogenic.

Blood glucose regulation

In healthy individuals, euglycaemia is preserved by hormonal, neural and hepatic auto-regulatory mechanisms. Plasma insulin levels vary rapidly in response to fluctuations in glycaemia. Insulin reduces blood glucose levels through glucose uptake and glycogen synthesis, and suppression of GNG. Conversely, glucagon, catecholamines, cortisol and growth hormone raise blood glucose by enhanced glycogenolysis and GNG while inhibiting peripheral IMGU. Importantly, the secretion of these counter-regulatory hormones requires the presence of hypoglycaemia or vital stimuli (burn, trauma or sepsis). The enzymes glycogen phosphorylase and glycogen synthase, promoting glycogen breakdown and synthesis, respectively, are submitted to hormonal modulation (Fig. 1). Insulin stimulates glycogen synthase and inactivates glycogen phosphorylase. Glucagon and epinephrine have the opposite effect on glycogen metabolism. Insulin inhibits PEPCK gene transcription, whereas glucagon induces the synthesis of this gluconeogenic enzyme. Glucagon is the primary hormonal stimulator of hepatic GNG, without affecting renal GNG. Then again, epinephrine represents the primary stimulus for renal GNG.

Central and peripheral glucosensors monitor glucose availability and steer neural glucoregulation. Hyperglycaemia releases the inhibitory sympathetic tone on the pancreas, triggering insulin secretion through increased activity in the ventromedial hypothalamic nucleus. Hypoglycaemia provokes firing of the nucleus tractus solitarius and lateral hypothalamic glucosensors, increasing splanchnic sympathetic and decreasing parasympathetic activity, which results in glycogenolysis and reduced insulin release. Decreased firing of peripheral glucose sensors in the portal vein, the small intestine and liver in response to a rise in glucose concentration is communicated to the medullar nucleus solitarius and to the hypothalamus. This signal inhibits adrenal nerve activity and activates vagal pancreatic efferents suppressing catecholamine release and increasing insulin secretion, respectively. Accordingly, the CNS receives input regarding elevated portal vein glycaemia and responds by promoting hepatic glucose uptake.

Hepatic autoregulation allows the liver to respond directly and autonomously to an increase in circulating glucose by decreasing hepatic glucose production. The interconversion of glucose and glucose-6-phosphate (derived from GNG, glycogenolysis or plasma glucose) is regulated by the enzymes glucokinase (also called hexokinase-IV) and glucose-6-phosphatase (Fig. 1). This glucose cycle embodies a crucial adaptation mechanism for hepatic glucose output and glucokinase controls the final common pathway for glucose release into the circulation, underscoring its central role in hepatic autoregulation of glucose production. Inhibition of glycogenolysis explains the decline in hepatic glucose output brought about by hyperglycaemia. Apparently, high intra-hepatic glucose-6-phosphate levels from enhanced flux of plasma glucose through glucokinase stimulate glycogen synthase, inhibit glycogen phosphorylase and more than double glucose–glucose-6-phosphate cycling.
Fig. 1. Simplified model of insulin signalling and intra-cellular glucose processing. Insulin binding to the extracellular domain of the insulin receptor elicits receptor auto-phosphorylation (P) and tyrosine phosphorylation of intracellular Insulin Receptor Substrate (IRS). The IRS pathway leads to activation of kinases dependent upon phosphatidylinositol (PI) 3-kinase, such as Akt. Akt modulates enzyme activities that besides affecting NO generation and apoptosis, control lipid, protein and glucose metabolism. An overview of different aspects of glucose metabolism is shown on the right side: glucose uptake; glucose cycling; glycogen synthesis/glycogenolysis; gluconeogenesis; Cori and glucose-alanine (G-Ala) cycle; glucose oxidation. LDH: lactate dehydrogenase, PDH: pyruvate dehydrogenase.
rate, whereas GNG remains unaffected. Second, hepatic autoregulation averts increased hepatic glucose output secondary to an increase in gluconeogenic precursors, such as lactate or glycerol. In fact, hyperglycaemia with substantial hepatic glycogen stores (overnight fast) merely inhibits hepatic glucose output by decreased glycogenolysis or enhanced glucose cycling. By contrast, hyperglycaemia with depleted glycogen stores (prolonged fast) autoregulates hepatic glucose production through suppression of GNG or decreased gluconeogenic substrate uptake.

**Alterations of carbohydrate metabolism during critical illness**

The stress response interplay between hormones, cytokines and the CNS.

The stress response following trauma has been characterised by a hypometabolic ebb and a subsequent, hypermetabolic flow phase. The response to sepsis and burns seems limited to a flow phase. The ebb phase begins immediately after trauma and lasts 12–24 h. The flow phase peaks at around 3–5 days, abates by 7–10 days and merges into the anabolic phase. Severity of injury and complications determine flow phase duration.

The ebb phase is characterised by reduced energy expenditure with decreased cardiac output, peripheral vasoconstriction and high sympatho-adrenal activity. Typically, systemic catecholamine release and direct sympathetic stimulation elicit hepatic glycogenolysis, promoting hyperglycaemia. Following trauma, the degree of hyperglycaemia parallels the severity of injury and is proportional to plasma epinephrine concentrations. Hyperglycaemia immediately following trauma is independent of glucagon levels, which are generally normal. Insulin levels following injury seem normal, which is to be considered low relative to the degree of hyperglycaemia. Presumably, reduced insulin release results from pancreatic α-adrenergic receptor activation. Primary beta-cell dysfunction was also described in hyperglycaemic critically ill children with respiratory and cardiovascular failure.

At the onset of the flow phase, oxygen delivery and metabolic substrate are restored. This period comprises elevated energy expenditure, increased cardiac output, systemic vasodilatation, protein catabolism and systemic inflammation. Hyperglycaemia persists as a result of GNG and insulin resistance. Catecholamine effects on carbohydrate metabolism subside. Hepatic GNG is predominantly activated by significantly increased glucagon levels. However, the induction of GNG by exogenously infused glucagon is transient, but persists in combination with epinephrine and cortisol. Plasma cortisol is moderately elevated and merely potentiates glucagon and epinephrine action on hepatic glucose production. Growth hormone promotes hyperglycaemia through enhanced GNG and impaired peripheral IMGU. The rise in insulin concentration observed during this hypermetabolic stress phase is less pronounced than the increase in the counter-regulatory glucagon levels.

Cytokines affect glucose metabolism through the glucoregulatory hormones, in addition to a direct effect on glucose metabolism. Several rat models revealed that high levels of tumour necrosis factor (TNF) reproduced stress-related changes in glucose metabolism: hyperglycaemia, increased GNG, hepatic and peripheral insulin resistance. TNF stimulates glucagon secretion, enhancing GNG. Interferon-α (INF-α) administration to healthy volunteers raises glucagon, cortisol and growth hormone levels, as well as insulin clearance. Hyperglycaemia following intraventricular interleukin-1α (IL-1α) injection was associated with glucagon and corticosterone secretion and prevented by pre-administration of α- and β-antagonists, indicative for adrenergic mediation. Finally, cytokines seem to inhibit insulin secretion in a concentration-dependent manner.

Alteration in intravascular volume, acidosis, hypoxia or pain not only prompt hormone and cytokine release, but also trigger the CNS directly. The main central stress loci are the hypothalamus, secreting corticotropin-releasing hormone (CRH) and locus coeruleus norepinephrinergic neurons of the brainstem. These loci control the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, respectively. CRH promotes adrenocorticotropic hormone (ACTH) release from the anterior pituitary, stimulating cortisol production by the adrenal cortex. Cortisol exerts a negative feedback on the synthesis of CRH and ACTH. The term immune–HPA axis underscores the regulatory role of cytokines on the HPA. TNF, IL-1 and IL-6 synergistically stimulate CRH and ACTH secretion. IL-1, IL-2, IL-6 and IFN-α increase glucocorticoid synthesis in the adrenal cortex directly. Interestingly,
preoperative exposure to post-stress corticosterone concentrations attenuated the inflammatory neuroendocrine response in rats, with reduced surgery-induced adrenaline release, lower IL-6 levels and lower plasma glucose levels.43

Increased glucose production

Most forms of critical illness are characterised by an increased rate of glucose production.31 Glucose production during stress seems refractory to exogenous glucose administration44 or is significantly higher than in healthy controls infused with a comparable caloric load, despite high endogenous insulin levels.45

Lactate and alanine are the main substrates for stress-related hepatic GNG. Lactate originates from neutrophils and macrophages in the lungs of patients with acute lung injury, in intestines and in wounds or from hepatocytes of patients with liver dysfunction.15,46,47 Infection or injury stimulate the phagocytic respiratory burst, inducing the production of oxygen radicals, which is associated with an increased flux of glucose through the glycolytic pathways.48 Glycolysis and the Krebs cycle are uncoupled in phagocytes; hence, less than 1% of the glucose is oxidised. Lactate is converted to glucose in the hepatic Cori cycle (Fig. 1). In hypermetabolic sepsis, net hepatic extraction of lactate is almost tripled.49

Alanine undergoes hepatic recycling to glucose in the glucose–alanine cycle (Fig. 1). Circulating alanine is mainly derived from de novo synthesis and only 30% from muscle breakdown.50 New alanine is formed by glucose-derived pyruvate and deamination of branched-chain amino acids providing the carbon skeleton and the ammonia moiety, respectively. Increased alanine uptake and glucose production was noticed in vitro in hepatocytes derived from IL-1-treated rats, while these alternations could not be reproduced by in vitro incubation of normal hepatocytes with IL-1, suggestive for hormonal mediation of the IL-1 effect.51

During normal fast, glycerol plays a negligible role in hepatic GNG. However, during stress, glycerol, derived from fat mobilisation, may account for about 20% of glucose production, being the major source of new carbons since it is not recycled, unlike lactate or alanine.52 Interestingly, while GNG is acutely increased following infusion of glycerol or lactate to hyperglycaemic trauma patients, the net hepatic glucose output is unaffected.25 Precursor autoregulation of hepatic glucose production seems preserved during critical illness, though at a higher level of glucose production.

Data regarding renal glucose production during critical illness are scarce. Chronic infusion of stress hormones led to significantly increased renal glucose output.53 Glutamine, being the main substrate for renal GNG, adds new carbons to the glucose carbon pool similar to glycerol.54

Pathophysiology of insulin resistance

Insulin resistance is present in the majority of stress syndromes, but is most pronounced during sepsis.31,55

The interaction between the pro-inflammatory cascade or counter-regulatory hormones and insulin-signalling pathway is not entirely understood. Nonetheless, injury seems to inhibit insulin-induced tyrosine phosphorylation of IRS-1 and PI3-kinase activation, which causes defective GLUT4 translocation.1,56

TNF-α appears to play an essential role in the pathogenesis of insulin resistance. In endothelial cells, TNF-α reduces tyrosine phosphorylation and expression of the insulin receptor (IR).57 In hepatocytes, adipocytes and muscle cells, TNF-α blunts insulin-induced IRS-1 tyrosine phosphorylation and PI3-kinase activation.56,58 In fact, TNF-α may induce IRS-1 serine phosphorylation, which prevents IRS-1 interaction with IR as well as subsequent IRS-1 tyrosine phosphorylation by IR and binding to PI3-kinase.56

Furthermore, TNF-α, IL-1 and the endotoxin-Toll-like-receptor-4 pathway activate inhibitor κB kinase (IKK) complex, which is associated with IRS-1 serine phosphorylation.56,59 IKK is a serine kinase that controls activation of nuclear factor-kappa B (NF-κB), a ubiquitous nuclear transcription factor controlling multiple pro-inflammatory genes.50 Before activation, NF-κB is localised in the cytosol, bound to inhibitor κB (IκB). Serine phosphorylation by the IKK complex breaks up IκB, permitting
nuclear translocation of NF-κB, triggering the pro-inflammatory cascade, while serine phosphorylation of IRS-1 provokes insulin resistance.

Catecholamines presumably induce insulin resistance by the inhibition of insulin binding to IR and subsequent GLUT4 translocation.\textsuperscript{15,61,62} During sepsis, adrenergic β2-receptor activation affects skeletal muscle IMGU. The underlying downstream mechanisms remain elusive, but GLUT4 protein levels seem normal.\textsuperscript{63} The inhibition of insulin-induced tyrosine autophosphorylation of the IRβ kinase may explain how catecholamines reduce adipocytes IMGU.\textsuperscript{15,62} Glucocorticoids impair skeletal muscle GLUT4 translocation.\textsuperscript{64} Growth-hormone-treated rats and growth-hormone-overexpressing transgenic mice revealed insulin resistance, related to reduced IR abundance, reduced IR and IRS-1 tyrosine phosphorylation and abolished insulin-induced PI3-kinase activation.\textsuperscript{65,66}

**Altered glucose uptake and use in the setting of peripheral insulin resistance**

Peripheral insulin resistance develops primarily because skeletal muscle becomes refractory to insulin action during stress.\textsuperscript{10} Apparently, the metabolic pathways involved in insulin-mediated glycogen synthesis are more sensitive to the inhibitory effects of mediators (such as cytokines (TNF, IL-1 and IL-6) and counter-regulatory hormones) than the more proximal molecules of the insulin signalling pathway regulating glucose uptake through GLUT4.

As discussed above, injury decreases insulin-induced GLUT4 translocation to the plasma membrane unequivocally. Notwithstanding, it seems unlikely that glucose transport is rate limiting for glucose processing by skeletal muscle during stress. In fact, severe injury raises whole-body glucose uptake significantly, solely by non-insulin-mediated mechanisms. Enhanced NIMGU is most prominent in lung, liver, spleen and wounds–organs involved in the immune response.\textsuperscript{37,56,67} This process seems modulated by TNF and IL-1 stimulation of GLUT1 synthesis, plasma membrane concentration and activity.\textsuperscript{68,69} Similarly, sepsis almost doubles muscle glucose uptake by enhanced NIMGU.\textsuperscript{56,70}

Following cellular uptake, glucose is phosphorylated and directed into either glycolysis or glycogen formation (Fig. 1). Stress-induced enhanced NIMGU leads to a mass effect of intracellular glucose that promotes glycolytic flux with increased pyruvate and lactate formation. Due to lack of a hypoxic stimulus for glycolysis during resuscitated stress, this process has been termed aerobic glycolysis.\textsuperscript{72} Older data suggested that defective oxidative use of glucose resulting from a down-regulation of pyruvate dehydrogenase (PDH) activity was involved in stress hyperglycaemia.\textsuperscript{73} However, more recent studies reported significantly increased (tripled) oxidative glucose metabolism in burned and septic patients.\textsuperscript{71,74}

Finally, several data support the contention that peripheral insulin resistance is related to reduced non-oxidative glucose use. Cytokine- or hormone-induced modifications of the insulin-signalling pathway seem to reduce glycogen synthase activity.\textsuperscript{55,75} While phosphorylation of mitogen-activated protein kinase (MAPK) normally stimulates glycogen synthase activity, TNF and endotoxin are recognised MAPK inhibitors and so affect glycogen synthase activity.\textsuperscript{76,77} Increased circulating free fatty acids may also impair glycogen synthesis.\textsuperscript{78}

**Central insulin resistance**

Insulin represses the transcription of insulin-like growth factor binding protein-1 (IGFBP-1), an important regulator of IGF bioavailability and a potential marker of hepatic insulin sensitivity as it is almost exclusively expressed in hepatocytes.\textsuperscript{79} High IGFBP-1 levels were confirmed in prolonged critically ill patients of the Leuven SICU study.\textsuperscript{80} Central insulin resistance is characterised by the inability of physiological insulin concentrations to suppress elevated hepatic glucose production.\textsuperscript{81}

The chronic exposure of rats to endotoxin provokes severe hepatic insulin resistance, indicated by decreased abundance, tyrosine phosphorylation and interactions of IR and the early steps of the post-receptor signalling pathways (IR/IRS-1/PI3-kinase; IRS–2).\textsuperscript{82}

Further investigations are warranted to explore the hypothesis that acquired defects in glucokinase expression or translocation may clarify hepatic insulin resistance.\textsuperscript{15,83} Still, there is evidence that TNF-α may be an important mediator. As described, TNF-α promotes IRS serine phosphorylation, preventing insulin-stimulated IRS tyrosine phosphorylation.\textsuperscript{56} The main TNF-α signalling pathways are driven by
c-Jun N-terminal kinase 1 (JNK1) and JNK2, which are ubiquitously expressed, and conceivably mediate TNF-induced IRS-1 serine phosphorylation. Recently, a rat model of trauma and haemorrhage showed that an increasing extent of blood loss was paralleled with increases in serum TNF-α, liver IRS-1 serine phosphorylation and liver JNK activation. TNF-α infusion mimicked these findings and blunted insulin signalling in the liver. Impaired insulin signalling was reversed by anti-TNF-α-antibody treatment, but not by anti-IL-6-antibodies. Obviously, TNF-α activation of JNK results in IRS-1 serine phosphorylation interfering with the hepatic insulin/IRS/PI3K/Akt pathway, provided that trauma is associated with haemorrhage.

Other causes of hyperglycaemia during stress

Total parenteral nutrition (TPN) administration to critically ill patients often promotes hyperglycaemia, especially when dextrose delivery exceeds 5 mg kg⁻¹ min⁻¹. In healthy circumstances, up to 40% of an ingested glucose load may be removed by the liver for storage as glycogen, while parenteral infusion of the same glucose load does not generate a similar increase in hepatic glucose uptake. Glucose concentration in the portal is considered to be the gut factor modulating this divergence.

Several conditions will aggravate stress hyperglycaemia: occult or pre-existing diabetes mellitus, cirrhosis (liver fibrosis impairs glycogen storage), pancreatitis, drugs (corticosteroids, thiazide diuretics, HIV protease inhibitors and phenytoin), hypokalaemia (inhibiting insulin secretion), bed rest and advanced age.

Mechanisms by which intensive insulin therapy achieves blood glucose control in critical illness

The administration of a sufficiently high dose of exogenous insulin has proven to be effective in overcoming hyperglycaemia in critical illness. The mechanism behind the glucose-controlling effect of insulin in stress has still not been resolved.

Analysis of a subset of prolonged critically ill patients from the Leuven SICU study delineated peripheral IMGU as the major glucoregulatory target for exogenous insulin in these patients. Post-mortem skeletal muscle biopsies of IIT patients contained significantly higher GLUT4 and hexokinase-II (the rate-limiting enzyme in muscular intracellular insulin-stimulated glucose metabolism) mRNA expression levels compared with conventional therapy (CIT). By contrast, post-mortem liver biopsies of these patients did not reveal altered glucokinase nor PECK transcript levels when IIT was compared with CIT. Likewise, IIT did not repress increased mRNA or circulating protein levels of IGFB-1. The increased metabolic insulin signal by IIT in these post-mortem skeletal muscle biopsies was corroborated by an increased IRS-1–PI3-kinase association and increased Akt phosphorylation. Since such effects could not be withheld on liver specimens, these results suggest that hepatic insulin resistance was actually not overcome by IIT in prolonged critical illness. Nonetheless, prevention of stress hyperglycaemia showed to be protective to the hepatocytic mitochondrial compartment, the site of oxidative glucose metabolism. Severe ultrastructural abnormalities and impaired activity of respiratory chain complex I and IV seen in the hepatocytes of the CIT group were virtually normalised in post-mortem liver biopsies of patients with tight glycaemic control. Contrary to studies of the liver, skeletal muscle biopsies showed identical morphological or functional findings in both study arms. These findings underscore the concept of avoiding glucose toxicity on the hepatocytic mitochondrial compartment by strict blood glucose control rather than a protective influence of insulinisation.

According to a study in severely traumatised patients at the onset of critical illness, normalisation of glycaemia during TPN infusion requires high insulin infusion rates and is accounted for by a reduction in endogenous glucose production, whereas whole-body glucose disposal is not increased by IIT. These results suggest that IIT could overcome hepatic insulin resistance in acute critical illness. The discrepancies with the data obtained in the Leuven studies are obvious. First, the Leuven patients were studied after prolonged critical care, whereas the trauma patients were evaluated within the first 48 h after injury. The relation between insulin sensitivity in liver and periphery may change with time, just as peripheral insulin resistance immediately post-surgery switches towards pronounced hepatic insulin resistance after 3 days. Second, the patients selected for subgroup analysis of the Leuven studies were non-survivors, which may have resulted in a selection of the most severely affected cases.
Third, a different methodology was applied: on the one hand, biopsies retrieved post-mortem after end-stage critical illness versus in vivo kinetic data. As already discussed, TNF-α may play a key role in the pathogenesis of central and peripheral insulin resistance. On the other hand, insulin may exhibit potent acute, anti-inflammatory effects. Sub-analysis of prolonged critically ill patients from the Leuven SICU and MICU study revealed no significant effect of IIT on TNF-α levels. In the prolonged critically ill SICU patients, IIT had only a mild influence on both the pro-inflammatory IL-6 and the anti-inflammatory IL-10. As far as counter-regulatory stress hormones are concerned, IIT lowered serum cortisol levels, irrespective of cortisol-binding capacity, in prolonged critically ill Leuven SICU patients. This reduction proved to be statistically related to improved outcome of IIT.

Conclusion

Hyperglycaemia develops rapidly and persists throughout critical illness, regardless of the type of injury. Evidence suggests that an elevated rate of glucose production is central to the disruption of normal glucoregulation characteristic of critical illness. Increased gluconeogenesis from substrates such as lactate, alanine and glycerol originates mainly in the liver. The liver, being refractory to the suppressive effect of abundant endogenous insulin levels, represents a major site of stress-induced insulin resistance. In addition, overall glucose uptake is increased during stress primarily through insulin-independent mechanisms in organs involved in the immune response. Reduced IMGU is noticed in skeletal muscle and heart, pointing to peripheral insulin resistance. Since glucose transport into skeletal muscle is guaranteed through markedly increased non-insulin-mediated glucose uptake, peripheral insulin resistance is rather driven by defective skeletal muscle glycogen synthesis.

Exogenous insulin therapy achieves tight glycaemic control, presumably by overcoming hepatic insulin resistance in acute critical illness and by stimulating peripheral IMGU and glucose use during prolonged critical illness.

Additional research is warranted to complement the present insights into the mechanisms and pathophysiology of insulin resistance, as well as in the action of exogenous insulin treatment. This knowledge may prove indispensable to refine future therapeutic strategies for stress hyperglycaemia and to assess the prognostic impact of preventing stress hyperglycaemia.

Practice points

- Although the underlying mechanism is different, stress hyperglycaemia is present during acute and prolonged critical illness despite elevated endogenous insulin levels.
- Increased gluconeogenesis is characteristic for hepatic insulin resistance and seems refractory to exogenous glucose administration.
- Peripheral insulin resistance seems caused by defective skeletal muscle glycogen synthesis.
- Exogenous insulin therapy normalises blood glucose levels in acute and prolonged critically ill patients.

Research agenda

- Further research is required to determine the role of alterations in glucokinase activity in the pathogenesis of central insulin resistance.
- The exact defects in skeletal muscle post-binding insulin signalling pathways resulting in impaired glycogen synthesis need to be unravelled.
- How exogenous insulin treatment overcomes insulin resistance during acute and prolonged critical illness warrants further investigation.
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Conflict of interest

The author reports having no conflict of interest.

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