CRITICAL CARE

REVIEW

Bench-to-bedside review: Glucose and stress conditions in the intensive care unit

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Abstract

The physiological response to blood glucose elevation is the pancreatic release of insulin, which blocks hepatic glucose production and release, and stimulates glucose uptake and storage in insulin-dependent tissues. When this first regulatory level is overwhelmed (that is, by exogenous glucose supplementation), persistent hyperglycaemia occurs with intricate consequences related to the glucose acting as a metabolic substrate and as an intracellular mediator. It is thus very important to unravel the glucose metabolic pathways that come into play during stress as well as the consequences of these on cellular functions. During acute injuries, activation of serial hormonal and humoral responses inducing hyperglycaemia is called the 'stress response'. Central activation of the nervous system and of the neuroendocrine axes is involved, releasing hormones that in most cases act to worsen the hyperglycaemia. These hormones in turn induce profound modifications of the inflammatory response, such as cytokine and mediator profiles. The hallmarks of stress-induced hyperglycaemia include 'insulin resistance' associated with an increase in hepatic glucose output and insufficient release of insulin with regard to glycaemia. Although both acute and chronic hyperglycaemia may induce deleterious effects on cells and organs, the initial acute endogenous hyperglycaemia appears to be adaptive. This acute hyperglycaemia participates in the maintenance of an adequate inflammatory response and consequently should not be treated aggressively. Hyperglycaemia induced by an exogenous glucose supply may, in turn, amplify the inflammatory response such that it becomes a disproportionate response. Since chronic exposure to glucose metabolites, as encountered in diabetes, induces adverse effects, the proper roles of these metabolites during acute conditions need further elucidation.

Introduction

Acute life-threatening situations cause an intense stress response. These situations promote immuno-inflammatory and metabolic responses that are entangled in an intricate way, as the cells involved in these key events ontogenetically originate from a unique primordial organ combining both immune and metabolic functions, namely the 'fat body' [1]. Acute stress-induced hyperglycaemia [2] is observed in many conditions, such as myocardial infarct [3], and shock states, especially septic [4], but also traumatic [5], as well as stroke [6]. The observed concordance between elevated blood glucose and mortality raised the question of a causative relationship between hyperglycaemia and prognosis [7].

A landmark monocenter study published in 2001 suggested that hyperglycaemia has a deleterious impact on prognosis in mostly surgical ICU patients, since tight glucose control by intravenous insulin dramatically improved mortality [8]. The large debate following this publication questioned the population studied (mainly cardiovascular surgical patients), the respective roles of glycaemia control versus additional insulin, and the impact of the amount of exogenous carbohydrate [9]. In 2006, the same group published another study performed on medical ICU patients testing the same protocol used in the first study [10]. In this new study, global mortality did not improve with tight control of glycaemia and a worsening of the death rate in a subgroup of patients staying less than 3 days in the ICU was observed. The group treated with tight control of glycaemia for more than 3 days had a reduction in severity and number of organ failures, which surprisingly did not translate to outcome benefit. Subsequent ICU trials published recently [11-15] have failed to confirm a benefit of tight control of glycaemia on prognosis in critically ill patients while emphasizing the potential role of hypoglycaemia in explaining the divergent results.

The recently published meta-analysis by Marik and Preiser [9] showed that, overall, tight glycaemic control

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did not reduce 28-day mortality (odds ratio (OR) 0.95; 95% confidence interval (CI), 0.87 to 1.05), the incidence of blood stream infections (OR 1.04; 95% CI, 0.93 to 1.17), or the requirement for renal replacement therapy (OR 1.01; 95% CI, 0.89 to 1.13). The incidence of hypoglycaemia was significantly higher in patients randomized to tight glycaemic control (OR 7.7; 95% CI, 6.0 to 9.9; $P < 0.001$). Metaregression demonstrated a significant relationship between the 28-day mortality and the proportion of calories provided parenterally ($P = 0.005$), suggesting that the difference in outcome between the two Leuven Intensive Insulin Therapy Trials and the subsequent trials could be related to the use of parenteral nutrition. More importantly, when the two Leuven Intensive Insulin Therapy Trials were excluded from the meta-analysis, mortality was lower in the control patients (OR 0.90; 95% CI, 0.81 to 0.99; $P = 0.04$; $I(2) = 0\%$).

The focus of this review is an integrative description of the main pathways and mechanisms involved in the acute stress conditions responsible for hyperglycaemia, and the description of complex situations involving both the stimulation of systemic inflammation and changes in metabolic requirements [16] in an attempt to clarify apparent contradictory results.

Metabolic pathways using glucose during acute critical conditions

The normal response to a stress situation associates the activation of central nervous system and neuroendocrine axes with increased release of hormones such as cortisol, macrophage inhibiting factor (MIF) [17,18], epinephrine and norepinephrine, growth hormone, and glucagon. These hormones profoundly modify the inflammatory response, especially cytokine release. Stress hormones generate globally a systemic pro-inflammatory profile while anti-inflammation is predominant at the tissue level (for a review, see [19]). These hormones, except for MIF, also stimulate, among other mechanisms, gluconeogenesis and hepatic glucose production, thus aggravating hyperglycaemia [20].

The pancreatic insulin release in response to blood glucose elevation leads to the blocking of hepatic glucose production and the stimulation of glucose uptake and storage by the liver, muscle and adipose tissue. If this first line of regulation fails to control glucose levels, the microenvironment of cells will contain high levels of glucose. To enter the cell, glucose uses transporters that allow facilitated diffusion (via concentration gradients) through the cytoplasmic membrane. These transporters are part of the superfamily of glucose transporters encoded by the *GLUT* genes; there are several isoforms, such as GLUT4, and their expression on the cell surface is amplified by insulin [21].

After entering the cell, glucose may go through different metabolic pathways in addition to glycolysis, as summarized in Figure 1. During the early hours of stress, the metabolic stimulation of the cell corresponds to increased mitochondrial energy production (ATP) with increased O_2 and glucose consumption [22]. Similarly, during cell proliferation, glucose availability is necessary for the induction of glycolytic enzymes, such as hexokinase, pyruvate kinase or lactate dehydrogenase. This glycolysis favours lactate production despite O_2 availability [23], and regeneration of NAD^+, which is required for additional cycles of glycolysis [24].

Recognition and cellular mechanisms of acute conditions

Acute critical conditions cause cellular injuries that are known to initiate repair or cell death pathways (Figure 2). These integrative mechanisms tend to either contain the response at the local level or, on the contrary, spread it by recruiting circulating cells and factors for repair.

Damaged cells communicate with innate immune cells by releasing intracellular factors named damage-associated molecular pattern molecules (DAMPs), such as calgranulines [25] and alarmines [26,27] (Figure 2). Together with pathogen-associated molecular pattern molecules (PAMPs), they activate the cellular expression of Toll-like receptors (TLRs) [28]. Accumulation of abnormal proteins, which are processed by the proteasome S26 system in the endoplasmic reticulum [29], as well as fluctuations of nutrients or energy availability, hypoxia, viruses and toxins activate a complex transcriptional response called the endoplasmic reticulum stress response (Figure 2), or the unfolded protein response [30].

Receptors for recognition of inflammation appear on both target cells and inflammatory cells. The alteration of the extracellular milieu is transmitted into the cell, modifying its functions. In peripheral blood mononuclear cells, for instance [31], an increased energy demand associated with a simultaneous metabolic failure can occur [32,33]. The increased permeability of the injured mitochondria leads to energy loss and cell death, which by itself fuels the inflammatory process through the release of the cell contents.

Injuries due to cellular environment

Hypoxia

Hypoxia induces hypoxia-inducible factors (HIFs), O_2-sensing transcription factors that regulate the transcription of genes [34] encoding numerous molecules involved in vascular reactivity, recruitment of endothelial progenitors, and cytoprotection [35,36]. During hypoxia (Figure 3), liver and skeletal muscle glycogenolysis is stimulated, increasing glucose availability [37]. Increased expression of GLUTs on any cell type [38-40] is mediated by the activation of AMP kinase and p38

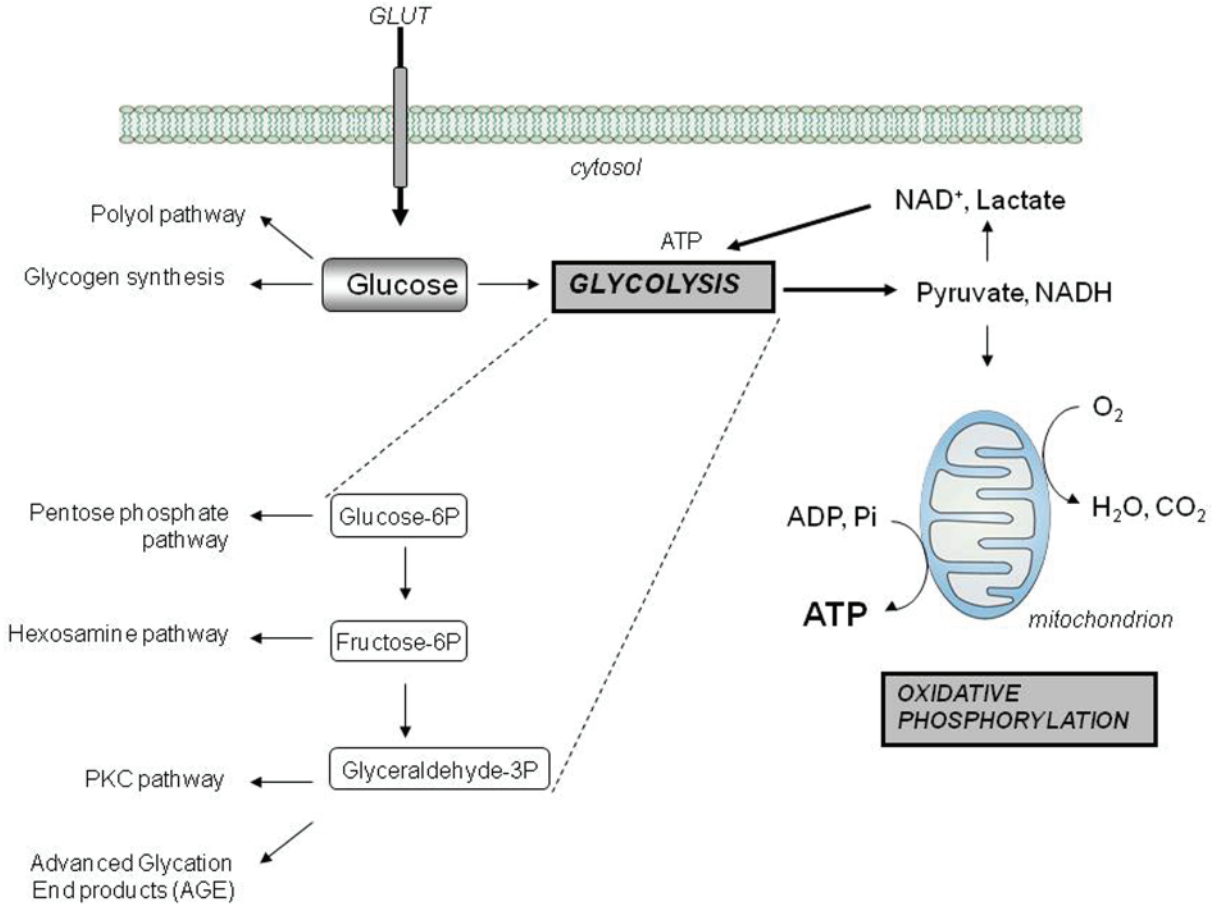

Figure 1. Overview of glucose metabolism in mammalian cells. Glucose is known to be oxidized through cytoplasmic glycolysis to produce pyruvate. Pyruvate may be reduced into lactate by lactate dehydrogenase or it may enter the mitochondria to participate in the citric acid cycle and the production of ATP by the mitochondrial respiratory chain and ATPase. However, glucose can be involved in other pathways. Glycogen synthesis is a major way to store glucose in muscle and liver. In the polyol pathway, aldose reductase reduces toxic aldehyde to inactive alcohol and glucose to sorbitol and fructose. In reducing NADPH to $NADP^+$, this enzyme may be deleterious by consuming the essential cofactor needed to regenerate reduced glutathione, an essential antioxidant factor in cells. The hexosamine pathway originates from glycolysis at the fructose-6-phosphate level. In this pathway, glutamine fructose-6-phosphate amidotransferase is involved in the synthesis of glucosamine-6-phosphate, which is ultimately converted to uridine diphosphate (UDP)-N-acetyl-glucosamine. This glucosamine is able to activate transcription factors such as Sp-1 and to induce the production of pro-inflammatory cytokines. Diacylglycerol, which activates isoforms of protein kinase C (PKC), may be produced from dihydroxyacetone phosphate. The PKC activation can induce several pro-inflammatory patterns, such as activation of the transcription factor NF-κB, and the production of NADPH oxidase or pro-inflammatory cytokines. The pentose phosphate pathway may use glucose-6-phosphate to produce pentoses for nucleic acid production. This pathway is also able to produce NADPH for use in lipid, nitric oxide and reduced glutathione production, and also the synthesis of reactive oxygen species by NADPH oxidase. Advanced glycation end product (AGE) synthesis is linked to high intracellular glucose concentrations. AGEs can induce cell dysfunction by modifying cell proteins, and extracellular matrix proteins, which changes signalling between the matrix and the cell, or by activating receptors for advanced glycation end products (RAGEs), which induce the production of the transcription factors NF-κB and TNF-α or other pro-inflammatory molecules. GLUT, glucose transporter.

mitogen-activated protein kinase [41,42], with an altered cellular redox status [41,43].

While glycolysis is activated by hypoxia, phosphofructokinase-1 and lactate dehydrogenase activity is stimulated by increased lactate production [44] associated with decreased mitochondrial oxygen consumption. This mechanism, described since 1910 in tumour cells as the 'Warburg effect' [45], seems to be adaptive to the lack of oxygen while maintaining cell redox status. A sufficient amount of energy is then produced but without an increase in reactive oxygen species (ROS) production by the mitochondria [46].

Adenosine

Adenosine production mainly results from ATP degradation during stress when it is released into the extracellular space. Adenosine regulates innate and adaptive immune functions by interacting with almost every immune cell

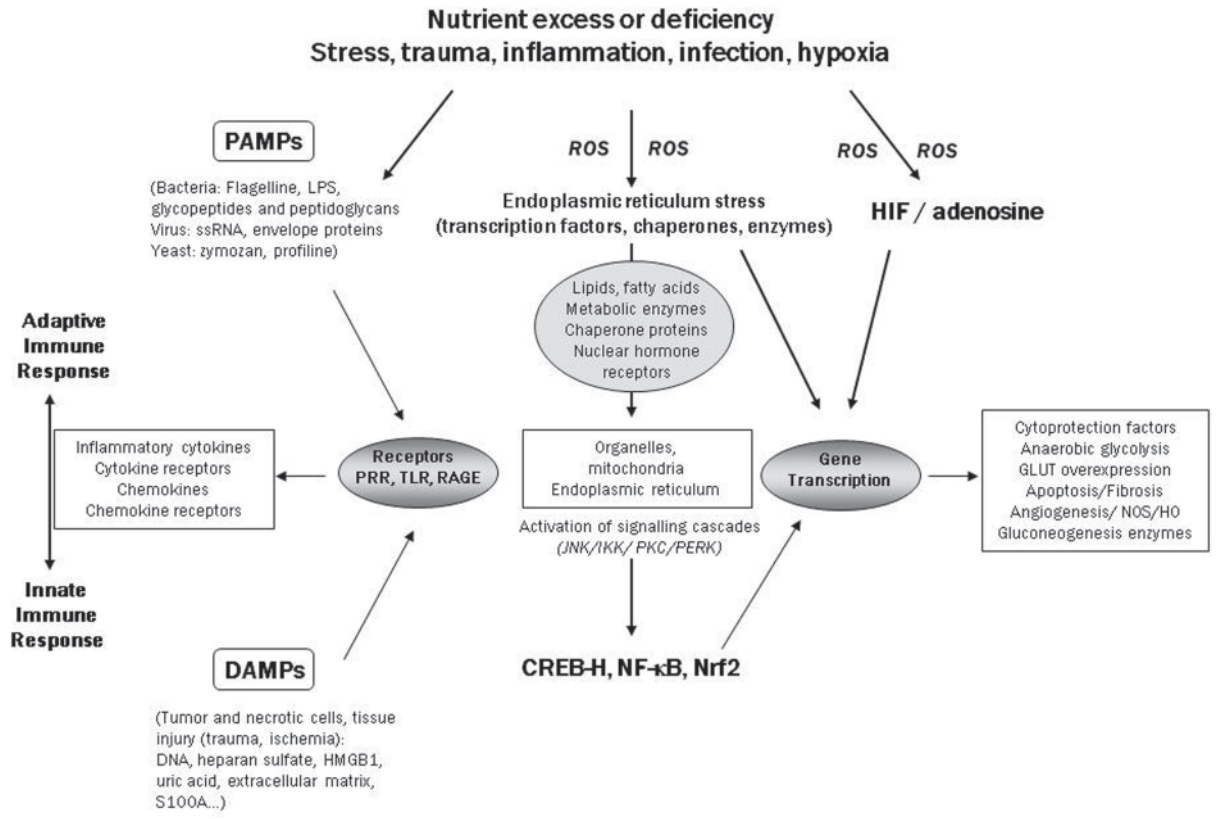

Figure 2. Integration of stress-signalling mechanisms. Damaged or dysfunctioning cells communicate with innate immune cells by releasing intracellular factors named damage-associated molecular pattern molecules (DAMPs). During cell death, these molecules, such as calgranulines from the protein S100 A superfamily or alarmines such as the nuclear protein high-mobility group box 1 (HMGB1), are released into the extracellular space to activate the immune system. These molecules associate with pathogen-associated molecular pattern molecules (PAMPs) from destroyed pathogens to activate cellular expression of Toll-like receptors (TLRs) of the pattern recognition receptor (PRR) superfamily. Some of these receptors, specifically TLR2, 4 and 9, recognize multiple DAMPS released during stress and cell death. Proteins with abnormal conformation are processed by the proteasome S26 system in the endoplasmic reticulum, where protein kinase R-like endoplasmic reticulum kinase (PERK)-type kinases are activated; these pathways depend on Ire1 (which requires inositol) and nuclear factors, such as NF-κB and Nrf2 (NF-E2 related factor). Nrf2 controls the expression of genes encoding enzymes that remove reactive oxygen species (ROS), including heme oxygenase 1 (HO-1) and glutathione S-transferase (GST). PERK-dependent phosphorylation of Nrf2 thus coordinates a transcriptional program connecting oxidative stress and endoplasmic reticulum stress. Activation of the transcription factor CREB-H can be achieved through this endoplasmic reticulum stress; CREB-H is responsible for the acute inflammatory response in the liver with acute phase protein synthesis. Adapted from [1]. GLUT, glucose transporter; HIF, hypoxia-inducible factor; HO, heme oxygenase; IKK, IκB kinase; JNK, c-Jun N-terminal kinase; LPS, lipopolysaccharide; NOS, nitric oxide synthase; PKC, protein kinase C; RAGE, receptors for advanced glycation end products; ssRNA, single-stranded RNA.

[47]. It inhibits antigen presentation, pro-inflammatory cytokine production and immune cell proliferation, and participates in tissue repair and remodelling. Adenosine induces increased intracellular cAMP, which stimulates protein kinase (PK)A, which in turn activates the transcription factor CREB (cAMP response element-binding), thus linking the inflammatory response to alterations of glucose metabolism [48].

Oxidative stress

Oxidative stress produces ROS, which alter normal cell function. ROS are permanently released at a low rate at the cytoplasmic membrane (NADPH oxidase, myeloperoxidase, cyclooxygenase) and in the cytoplasm (heme oxygenase, xanthine oxidase), and also within the mitochondria. When activated, phagocytic cells display a specific response called the 'respiratory burst', which is an acute overproduction of ROS by the activation of the NADPH oxidase Nox 2. Oxidative stress may indirectly modify glucose metabolism since it induces DNA alterations that activate the nuclear enzyme poly-ADP-ribose polymerase 1 (PARP-1). This activation consumes NAD^+ and depletes its intracellular stores, which in turn hampers glycolysis and ATP production, in parallel with altered cell functions [49]. A transient low level of oxidative stress with redox alterations stimulates glucose uptake via insulin-independent GLUT transporters mediated by the AMP kinase pathway [50,51].

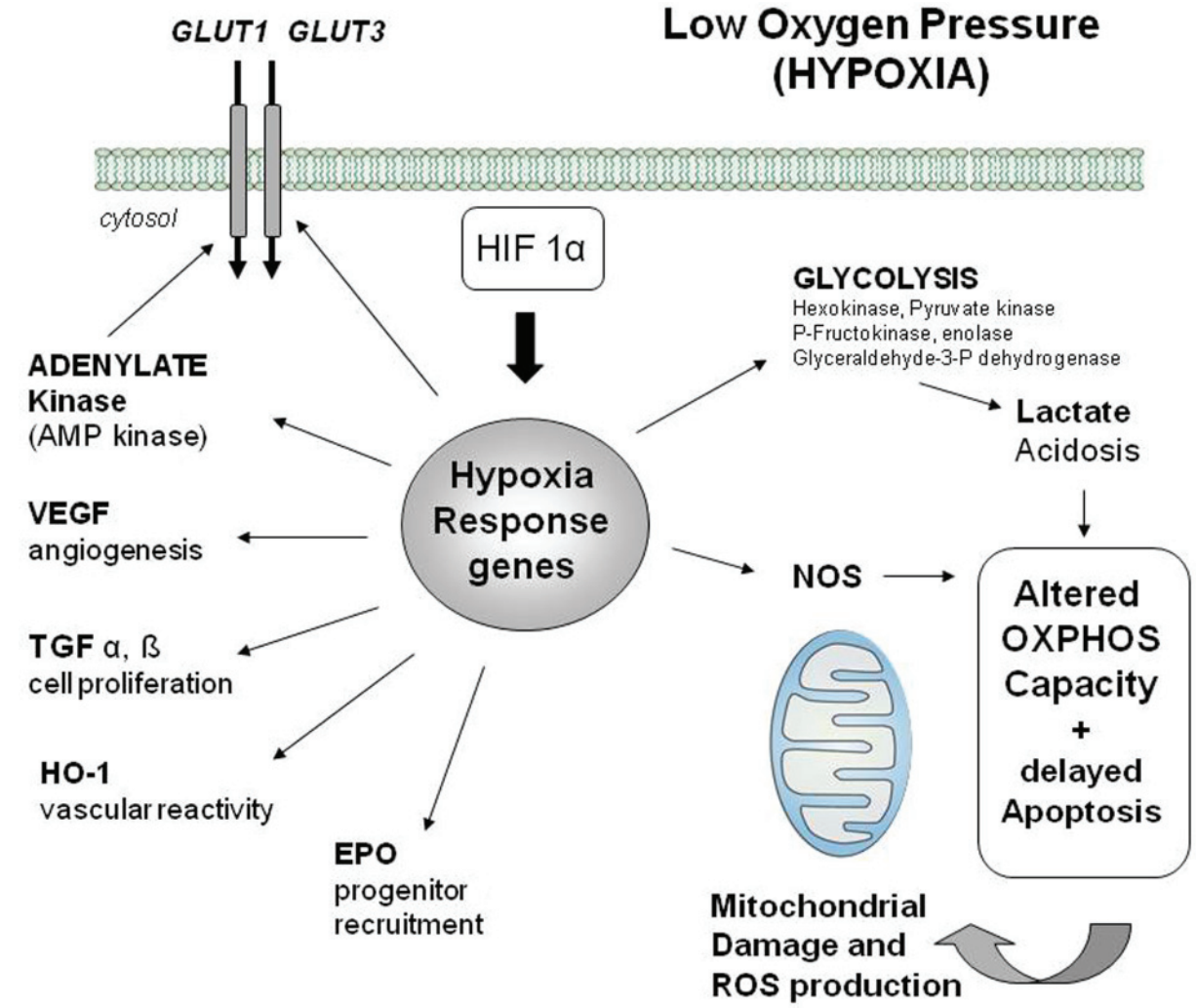

Figure 3. Role of hypoxia in cell metabolic reprogramming. Hypoxia-inducible factors (HIFs), O_2-sensing transcription factors, regulate the transcription of genes encoding Heme-oxygenase-1 (HO-1), erythropoietin (EPO), and numerous molecules involved in vascular reactivity (such as nitric oxide synthase (NOS)), recruitment of endothelial progenitors, and cytoprotection through angiogenic growth factors such as vascular endothelial growth factor (VEGF). During hypoxia, glycogenolysis is stimulated, increasing glucose availability. An increase in glucose transporter (GLUT) expression enables augmented glucose uptake. This overexpression of GLUTs is mediated by the activation of AMP kinase (AMPK) and p38 mitogen-activated kinase. Stimulation of AMPK results from a decreased cytoplasmic ATP/AMP ratio together with altered cellular redox status. Phosphofructokinase-1 and lactate dehydrogenase activity is stimulated by increased lactate production. HIF decreases mitochondrial oxygen consumption and induces the expression of pyruvate dehydrogenase kinase, the main inhibitor of pyruvate dehydrogenase and of the entry of acetylCoA into mitochondria. Adapted from [36]. OXPHOS, oxidative phosphorylation; TGF, transforming growth factor.

Sepsis, an integrative condition

Sepsis corresponds to a systemic inflammation related to the abnormal presence of bacterial antigens and involves different mechanisms such as hypoxia and oxidative stress. At the early phase, inhibition of glycogen synthesis results in increased global glucose availability and increased cellular uptake [52-54]. Glucose uptake appears to be most increased in organs containing a vast population of phagocytic cells (liver, spleen, gut, lung) [55-57]. In rats injected with endotoxin or TNF-α, insulin-independent glucose uptake is increased in liver non-parenchymal cells (Küpffer cells, endothelial cells) [58], as observed in circulating immune cells, including polymorphonuclear leukocytes [59,60], lymphocytes, monocytes and macrophages [61-63]. Skeletal muscle displays only a limited increase in glucose uptake, probably because of the development of insulin resistance.

Sepsis also modifies cytoplasmic glycolysis at the transcriptional level. In healthy volunteers receiving intravenous endotoxin, there was an early under-expression of genes encoding metabolic enzymes [64]. In particular, the key enzymes of glycolysis and those of the

mitochondrial respiratory chain (MRC) were transiently under-expressed. In the diaphragm of septic rats, transcription, synthesis and activity of the constituents of the MRC, as well as of phosphofructokinase-1, a key-enzyme of glycolysis, are reduced [65]. In muscle of septic rats, the activity of pyruvate dehydrogenase is reduced, with a simultaneous increase in the activity of its inhibitor, pyruvate dehydrogenase kinase. The net result of these modifications is a reduction in pyruvate entering the mitochondria while the conversion of pyruvate to lactate is promoted [66].

In septic shock patients, increased use of glucose and increased lactate production was observed under aerobic conditions [67]. A microdialysis study of quadriceps muscles showed lactate overproduction during septic shock resulting form exaggerated aerobic glycolysis through Na/K-ATPase stimulation. To maintain cell functions, stimulation of glycolysis was shown to adaptively compensate for the metabolic rate increase [68]. Elevated circulating epinephrine stimulates Na/K-ATPase, which promotes lactate hyperproduction without any oxygen debt [69].

Mitochondrial dysfunction during sepsis [70] involves alterations in the structure [71] and function of the MRC, including impairment of key enzymes of electron transport and ATP synthesis [72,73] and mitochondrial biogenesis [74]. These results were also found with monocytes [75] and skeletal muscle [76] harvested from septic shock patients. ATP levels in skeletal muscle cells were maintained despite mitochondrial ultrastructural alterations [76]. This mitochondrial dysfunction results from plasmatic factors that promote uncoupled MRC oxygen consumption [77] that correlates with sepsis-induced modifications of the immune phenotype and is associated with increased mitochondrial permeability [78].

In summary, glucose metabolism alterations in acute critical conditions can be viewed as a 'redistribution of glucose consumption away from mitochondrial oxidative phosphorylation' towards other metabolic pathways, such as lactate production. This re-channelling does not seem to affect energy supply to the cells. This may result from decreased ATP consumption by the cells, which in turn lose some of their characteristics, indicating metabolic failure [79].

Why does glycaemia finally increase during acute injury?

Stress-induced hyperglycaemia results from the combined effects of increased counter-regulatory hormones that stimulate glucose production and reduced uptake associated with insulin resistance, that is, decreased insulin activity. There is also inadequate pancreatic insulin release with regard to glycaemia (or adaptive 'pancreas tolerance'). Insulin release during stress is decreased mainly through the stimulation of α-adrenergic pancreatic receptors [20]. Pro-inflammatory cytokines may directly inhibit insulin release by β pancreatic cells [80]. A new glucose balance results, allowing a higher blood 'glucose pressure', which affects tissues differently depending on whether they are insulin-dependent or not.

Glucose availability also relies on delivery to cells, analogous to oxygen diffusion. For glucose to arrive at a cell with reduced blood flow (ischemia, sepsis), it must move from the blood stream across the interstitial space. Glucose movement is dependent entirely on a concentration gradient, and for adequate delivery to occur across an increased distance, the concentration at the origin (blood) must be greater. Therefore, in the face of reduced or redistributed blood flow, hyperglycaemia is adaptive.

Development of insulin resistance

Insulin resistance (IR) is a reduction in the direct effect of insulin on its signalling process leading to metabolic consequences [81], very similar to type 2 diabetes, and is commonly observed during sepsis [82].

Insulin acts mainly on the liver, muscle and fat (metabolic effects), but it also targets many cellular subtypes to stimulate essentially protein and DNA synthesis as well as apoptosis (mitogenic effects). Hepatic IR involves increased hepatic glucose production (gluconeogenesis) together with decreased glycogen synthesis. During sepsis, however, gluconeogenesis can be limited by inhibition of important enzymes [83,84]. Muscle IR corresponds to decreased glycogen deposition and glucose uptake linked to decreased expression of GLUT4, while a transient defect in insulin signalling has also been described [85]. IR in adipocytes leads to inhibition of lipogenesis and activation of lipolysis.

The main mediators

Pro-inflammatory cytokines (IL-6, TNF-α), as well as endotoxins via TLR4, participate in the development of IR by stimulating hepatic glucose production [86] and altering insulin signalling [87]. These cytokines activate numerous kinases that inhibit insulin signal transduction [88-91]. TNF-α has been shown to induce the expression of SOCS-3 (Suppressor of cytokine signalling-3), which specifically inhibits insulin receptor phosphorylation [92].

MIF is not only produced by various immune cells [93] and the anterior pituitary gland, but also by islet β cells, where it positively regulates insulin secretion [94]. During inflammation in skeletal muscle, locally produced MIF stimulates glucose use and lactate production [95]. In endotoxemic mice genetically deficient in MIF, glucose metabolism is almost normalized when compared to wild-type mice [96]. Increased circulating cortisol participates in the maintenance of blood glucose not only by

increasing its production or decreasing its utilization, but also by directly inhibiting insulin secretion by ß cells [97].

Endogenous catecholamines are also involved in the alteration of glucose metabolism during endotoxaemia [98], especially in the liver [99]. Exogenous epinephrine metabolic effects on glucose turnover were, however, attenuated in endotoxic rats when compared to controls [100].

Role of exogenous glucose supply and induced hyperglycaemia

Glucose acts not only as an energetic substrate but also as a signalling molecule of the cellular environment, as shown in diabetes with chronic hyperglycaemia. Stress-induced acute hyperglycaemia has been less studied up to now as it has been considered an adaptive response. Some concepts from chronic hyperglycaemia may, however, be used in acute conditions. Intravenous administration of exogenous glucose yielded similar glycaemia in control and septic animals despite higher insulin levels in the septic group [101]. Hepatic glycogen deposition was observed only when glucose was infused via the portal vein [31,102].

Glucose-controlled genomic modifications

In fasted animals, increased circulating glucagon induces a gluconeogenic program by activating the nuclear transcription factor CREB through a molecule named Crtc2 (CREB regulated transcription coactivator 2) or TORC 2 (Transducer of regulated CREB activity 2) [103,104]. The expression rate of gluconeogenic enzymes is thus increased, especially for glucose-6-phosphatase.

Re-feeding in turn increases insulin levels, which inhibits hepatic glucose production partly by ubiquitin-dependent destruction of Crtc2 [105]. During sustained hyperglycaemia, the hexosamine pathway can be activated [106]. In hepatocytes, Crtc2 is then O-glycosylated on a serine residue instead of being phosphorylated. It can thus migrate into the nucleus to activate CREB and the gluconeogenic program, contributing to maintain hyperglycaemia [107]. This has been described as the 'sweet conundrum' [105]. Regulation of this pathway during acute injury remains to be proven.

Hyperglycaemia and the inflammatory response

In diabetics, glucose channelling through alternative glycolytic pathways seems to depend on MRC activity [106,108]. The accumulation of energy substrates induced by isolated hyperglycaemia without a concomitant increase in energy demand may enhance the flux of carbon hydrates to the mitochondria with increased activity of the MRC and proton driving force. Once the activity of ATPase is saturated, intermediate radicals from the MRC will accumulate and may react with the surrounding available O_2 to produce ROS [109], as shown in bovine endothelial cells. When inhibiting this radical production, the activity of alternative glycolytic pathways is decreased as well as the expression of transcription factor NF-κB [110]. Inhibition of glyceraldehyde-3-phosphate dehydrogenase, an enzyme involved in cytoplasmic glycolysis, has also been observed. Metabolites accumulate upstream of this enzyme and are funnelled towards alternative pathways (Figure 1). Polymers of ADP-ribose, produced by nuclear PARP to repair DNA altered by mitochondrial ROS, may be involved in this inhibition. PARP, by migrating into the cytosol, may be a key to glucose toxicity [111]. There is still a lack of evidence to fully extrapolate these theories to explain mitochondrial dysfunction and organ failure observed during stress-induced hyperglycaemia.

Glucose also acts as a pro-inflammatory molecule [81,112]. Glucose ingestion in healthy volunteers rapidly increases the activity of NF-κB [113] and the production of mRNA for TNF-α [114]. Under the same conditions, acute hyperglycaemia increased the activity of the transcription factors AP-1 (Activator protein-1) and EGR-1 (Early growth response-1), which in turn activate the production of matrix metalloproteinase-2 (MMP-2) by monocytes, an enzyme that facilitates the diffusion of inflammation by hydrolysing extracellular matrix. Production of tissue factor, a prothrombotic and proaggregant molecule [115], is increased, as is production of cellular adhesion molecules [116]. Acute hyperglycaemia induced in healthy volunteers by octreotid, an inhibitor of insulin release, leads to a rapid and transient secretion of proinflammatory cytokines (IL-6, TNFα, IL-8). This effect is amplified in insulin-resistant subjects and blunted with antiradical treatment [117].

Glucose-cytokine interactions

In vitro, an increased release of IL-1ß has been measured in the culture medium of human monocytes exposed to hyperglycaemic conditions after endotoxin stimulation [118]. In our model of endotoxaemia [102], glucose supply interfered with haemodynamic, metabolic and inflammatory responses, with a dramatic increase in circulating TNF-α when intraportal glucose was administered. Fasting on the other hand seemed to attenuate the response to endotoxin.

In liver transplant patients, glucose feeding during the early postoperative period induced major haemodynamic modifications within the graft, where the immuno-inflammatory insult occurs [119], including almost halted arterial hepatic inflow. This vasoconstriction was specifically related to glucose since fructose, amino acids and fatty acids did not provoke this effect. One tempting hypothesis for this effect involves increased production of ROS, which are well known to vasoconstrict arteries.

Glucose and ROS production

Nutrients, and especially glucose, are able to stimulate oxidative stress and inflammatory responses [106]. The body thus needs to regulate nutrient excesses in order to maintain metabolic homeostasis. STAMP2 (Six-transmembrane protein of prostate 2) has recently been detected in adipose tissue, a key organ in the management of nutrient excesses, and is also expressed in the heart, liver, lung and platelets [120]. In STAMP2 genetically deficient mice, the effects of insulin on liver, muscle and adipose tissue are altered, all three being essential organs for glucose homeostasis. STAMP2 is a metalloreductase involved in iron handling, which may influence ROS production [121]. Ingestion of glucose in healthy volunteers led to increased production of ROS in circulating monocytes and polymorphonuclear leukocytes. This was associated with the rapidly increased synthesis of NADPH oxidase subunits [122].

These data suggest that glucose induces profound modifications of the monocyte pro-inflammatory response. In peripheral blood mononuclear cells harvested from healthy volunteers and septic patients [77,123], increasing extracellular glucose increased glucose uptake. Subsequent stimulation of these cells by various agonists increased ROS production via NADPH oxidase in both the healthy volunteers and the septic patients. The link between ROS and intracellular glucose levels could be the increased production of NADPH via the pentose phosphate cycle [123] (Figure 4). More studies are needed to confirm these multifaceted effects and to confirm that such a coordinated regulation between nutrient availability and the intensity of the inflammatory response is also at play during acute insults. To cite Leverve, 'it appears that glucose obviously plays a very subtle role in oxidant cellular signaling. It can either increase or decrease ROS production and can either increase or decrease the antioxidant defense […]. Therefore it is not surprising that any change in blood glucose must be considered as a complex event, and taking care of glycemia and redox homeostasis will be probably central in the management of ICU patients in the next years' [124].

Recent *in vitro* data suggest that giving glucose boluses after hypoglycaemia may trigger neuronal death due to ROS overproduction [125]. In healthy volunteers, hyperglycaemic spikes induced increased pro-inflammatory cytokine levels that were blunted by antioxidant pretreatment [117]. This introduces the concept of glucose variability, which by itself seems to be deleterious with regard to outcome in critically ill patients [126,127].

Future prospects

Many questions regarding glycaemia remain to be solved for daily critical care practice. How should we achieve glycaemic control: should we take into account nutritional support, especially parenteral nutrition [9]? Should we control the physiological response to an induced hyperglycaemia or should we control the endogenous stress-induced hyperglycaemia that may be adaptive in the absence of exogenous glucose intake? Is there a place for new therapeutics such as incretins [128]? Does endogenous hyperglycaemia have a similar impact as hyperglycaemia induced by nutritional support? These questions in turn prompt investigation of the role of glucose deprivation induced by fasting with regard to normoglycemia achieved by insulin therapy. Similarly, the consequences of spontaneous versus insulin-induced hypoglycaemia remain to be investigated. Answers to these questions will probably help to solve the conflict between supporters and opponents of tight glycaemia control in the ICU. This discussion is in accordance with the concerns raised by several authors about early initiation of parenteral nutrition in acute critical patients [129,130], as supported by the results of two large multicentre studies, Nice-Sugar [14] and Glucontrol [15].

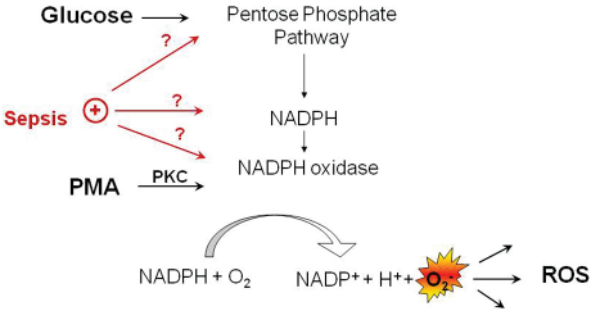

Figure 4. Glucose and reactive oxygen species production during sepsis: hypothesis. In peripheral blood mononuclear cells harvested from healthy volunteers and septic patients, increasing extracellular glucose increased glucose uptake. Subsequent stimulation of these cells by various agonists, such as PMA (phorbol 12-myristate 13-acetate), a protein kinase C (PKC) activator, increased reactive oxygen species (ROS) production via NADPH oxidase in both the healthy volunteers and septic patients. The link between ROS and intracellular glucose levels could be increased production of NADPH via the pentose phosphate pathway.

Conclusion

Glucose metabolism is profoundly altered during acute conditions, from its uptake to the induction of complex programs of gene expression [14]. The increased glucose availability in cells is not necessarily used to produce ATP by mitochondria. Glucose seems able to activate pro-inflammatory metabolic pathways. While chronic exposure to these end products seems deleterious (diabetes), their actual roles during acute conditions need to be further elucidated. Early stress-induced hyperglycaemia has been described as an adaptive response that could in turn sustain an adaptive inflammatory response (host

defence, wound healing, and so on). Glucose intake-induced hyperglycaemia may, however, lead to maladjusted and disproportionate inflammation that should be avoided. How then should this subsequent hyperglycaemia be prevented: should we limit glucose supply at the early phase of inflammation?

Si quis febricitanti cibum det, convalescenti quidem, robur : ægrotanti verò, morbus fit
Hippocrates [131]

(*Food given to those who are convalescent from fever, increases strength; but if there be still disease, increases the disease*)

Abbreviations
CI = confidence interval; CREB = cAMP response element-binding; Crtc = CREB regulated transcription coactivator; GLUT = glucose transporter; HIF = hypoxia-inducible factor; IL = interleukin; IR = insulin resistance; MIF = macrophage inhibiting factor; MRC = mitochondrial respiratory chain; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells; OR = odds ratio; PARP-1 = poly-ADP-ribose polymerase 1; PK = protein kinase; ROS = reactive oxygen species; TLR = toll-like receptor; TNF = tumour necrosis factor.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MRL, CD, and DP participated in the analysis of references and writing of this review.

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