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The roles of insulin and hyperglycemia in sepsis pathogenesis

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Abstract: Hyperglycemia is a risk marker of morbidity and mortality in acute critical illness, and insulin therapy seems to be beneficial in this patient group. Whether this is true for a population of sepsis patients, as such, has not been investigated in clinical trials, but evidence from in vitro studies and experimental sepsis suggests that this may be the case. The endocrinology of septic patients is characterized by a shift in the balance between insulin and its counter-regulatory hormones favoring the latter. This leads to prominent metabolic derangements composed of high release and low use of glucose, amino acids, and free fatty acids (FFA), resulting in increased blood levels of these substrates. Circulating, proinflammatory mediators further enhance this state of global catabolism. Increased levels of glucose and FFA have distinct effects on inflammatory signaling leading to additional release of proinflammatory mediators and endothelial and neutrophil dysfunction. Insulin has the inherent capability to counteract the metabolic changes observed in septic patients. Concomitantly, insulin therapy may act as a modulator of inflammatory pathways inhibiting the unspecific, inflammatory activation caused by metabolic substrates. Given these properties, insulin could conceivably be serving a dual purpose for the benefit of septic patients. *J. Leukoc. Biol.* 75: 413–421; 2004.

Key Words: metabolism · endocrinology · stress hyperglycemia · septic shock · immunology · inflammation

INTRODUCTION

Sepsis continues to cause significant morbidity and mortality despite advances in supportive treatments [1]. Clinical trials of agents intervening at specific points in inflammatory pathways or directly on effector molecules have not provided effective, new therapies of sepsis. As yet, no studies have appeared on specific effects of insulin in clinical sepsis, but wide attention has recently been given to insulin as an unspecific modulator of acute inflammation. Therefore, the aim of this review is to provide a "pro" argument in the ongoing discussion concerning beneficial effects of insulin therapy in sepsis. In doing so, we will give a short overview of the literature concerning insulin therapy in nondiabetic, clinical conditions characterized by local or systemic acute inflammation. We shall review the metabolic and endocrine derangements of sepsis in the attempt to clarify the role insulin may have in restoring homeostasis. Finally, we shall lay particular emphasis on the interaction between sepsis pathogenesis and the effects of insulin and hyperglycemia.

HYPERGLYCEMIA AND INSULIN TREATMENT IN CLINICAL STUDIES

There is growing interest in reducing hyperglycemia in patients with acute illness. This has been prompted by the fact that an association between hyperglycemia and mortality is described in several studies.

Umpierrez et al. [2] have shown that in-hospital hyperglycemia is a common finding, also in patients without known diabetes. Nondiabetics with hyperglycemia were more frequently admitted to the intensive care unit (ICU) and had increased mortality. This association was not found in diabetic patients with hyperglycemia [2].

Our results from a prospective study with 135 nondiabetic patients admitted to a multidisciplinary ICU suggest an increase in mortality with increasing blood glucose level. Organ dysfunction was more severe in patients with high blood glucose levels (unpublished results).

The work by Greet Van den Berghe and coworkers [3] has prompted a pronounced interest in the possible beneficial effects of insulin administration to sepsis patients. The study is a nonblinded, randomized, controlled trial involving 1548 patients requiring mechanical ventilation admitted to a surgical ICU. The patients were randomized to strict glycemic control (intensive treatment group, blood glucose level, 80–110 mg/dl) or conventional treatment (blood glucose level, 180–200 mg/dl) during their stay in the ICU. The strict glycemic control induced a 32% reduction in the overall mortality rate during intensive care. It is interesting that the greatest mortality reduction was found in a subgroup of patients with multiple organ failure and a proven septic focus. The insulin treatment also proved beneficial on various indices of morbidity; i.e., the intensive insulin treatment reduced the duration of intensive care, the duration of ventilatory support, and patients' transfusion requirements. Further, the occurrence of renal impair-

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ment, critical illness polyneuropathy, blood stream infections, and hyperbilirubinemia was reduced in the intensive treatment group. This study raises the imminent question of what governs the beneficial effects observed in the intensive treatment group. In this respect, it is interesting that 39.2% of the conventionally treated patients were given insulin albeit at a lower dose.

On the basis of multivariate regression analyses, Van den Berghe et al. [4] proposed that the beneficial effects on mortality and morbidity were determined by lower blood glucose rather than high insulin dose.

It has previously been described that continuous insulin infusion to maintain blood glucose level lower than 200 mg/dl after cardiac surgery in diabetic patients reduced the incidence of deep sternal wound infections [5]. Increased mortality in patients with hyperglycemia was also found in ischemic diseases such as myocardial infarction [6] and stroke [7], but the association could, at least partly, be explained by severity of injury and the cortisol level [8–10]. Glucose–insulin–potassium infusion lowered mortality in patients with myocardial infarction [11].

METABOLIC ALTERATIONS IN SEPSIS

The initial metabolic response to sepsis is closely regulated by specific endocrine changes, which inactivate anabolic pathways and increase anterior pituitary activity [12]. Publications from Van den Berghe [13] suggest that it is not only the amount of hormones but also the secretion pattern that are disturbed during sepsis.

Since the publication by Van den Berghe and coworkers [3], the glucometabolic actions of insulin have been in focus. Insulin is also known to have profound influence on blood levels of free fatty acids (FFA) and amino acids (AA). Both of these substances have been shown to affect the immune system.

Insulin resistance characterizes the septic patient, and it seems that the balance between insulin and its counter-regulatory hormones (cortisol, glucagon, growth hormone, and catecholamines) is perturbed in the metabolic response to sepsis.

In the healthy human body, there is a strictly regulated balance between anabolic and catabolic turnover of substrates in the tissues. Metabolically, there are three major substrates that supply energy, namely: FFA, glucose, and AA. Although glucose and FFA are stored in the body as stores of energy, AA primarily serve a functional purpose (including skeletal muscle, peptides, proteins). To what extent glucose, FFA, or AA are metabolized is regulated primarily by insulin and its counter-regulatory hormones, but also availability plays a significant role, at least in the normal physiological state. As described above, the overall endocrine reaction to sepsis turns the metabolism toward catabolism (**Fig. 1**). In the nonstressed, fasted or post-absorptive state, the level of glycemia is regulated by the glucose output from the liver, and the metabolic substrate is mainly FFA. It seems that one of the metabolic problems during sepsis is an inability to use FFA as a metabolic substrate. Normally, the glucose output from the liver arises from glycogen breakdown, resynthesis from recycled carbons (i.e., lactate and glycerol), and to a much lesser extent, from gluconeogenesis (GNG; AA such as alanine and glutamine). This finely regulated, interorgan substrate exchange is severely disrupted in sepsis. Impaired insulin sensitivity (insulin resistance) in the peripheral tissues results in increased availability of AA and FFA as a result of a shift toward lipolysis and proteolysis. The liver's function as a regulator of glycemia is also disrupted as a result of hepatic insulin resistance. This results in increased hepatic glucose output, initially as a result of glycogenolysis, but later on from GNG.

In the following, we shall discuss the individual actions of insulin and its counter-regulatory hormones on glucose, AA, and lipid metabolism in greater detail.

Insulin

In the early phase of sepsis, there are low circulating concentrations of insulin in serum, although this does not seem to be caused by decreased secretion but rather increased clearance [14, 15]. In the chronic phase, there seems to be a nonpulsatile and insufficient secretion of insulin, and there is a reduced biologic response peripherally and in the liver, a condition resembling type II diabetes. Insulin has a pivotal role in glucose metabolism, but also lipid and AA metabolism is affected by insulin. In 1999, Ferrando and coworkers [16] showed that insulin treatment promoted protein synthesis in burn patients, and in 2001, it was shown by Van den Berghe and coworkers [3] that insulin treatment to surgical intensive patients improved their survival.

Cortisol

The hypothalamus-pituitary-adrenal-axis response to acute illness is an increase in the release of adrenocorticotropin hormone (ACTH), probably secondary to a rise in corticotropin-releasing hormone, and in inflammatory mediators. ACTH and an activated renin-angiotensin system give rise to an increased secretion of aldosterone and cortisol [12]. Tumor necrosis factor-α (TNF-α) also directly increases the release of cortisol [17], which shifts the metabolism, steeply increasing the blood levels of glucose, FFA, and AA and ensuring availability of substrates to vital organs such as the brain by inducing insulin resistance [12]. In prolonged, critical illness serum ACTH is found to be low, and cortisol concentrations remain elevated, indicating that in this phase, cortisol release may be driven through an alternative pathway, possibly involving endothelin [18]. Why ACTH levels are low in prolonged, critical illness is unclear; a role for atrial natriuretic peptide or substance P has also been suggested [18]. In contrast to serum-cortisol levels, circulating levels of adrenal androgens such as dehydroepiandrosterone sulfate, which has immunostimulatory effects on T helper type 1 cells, are low during prolonged, critical illness [19–21].

Growth hormone (GH)

During acute, critical illness high baseline levels and more frequent peaks [22] are seen, and as is the case for insulin, the pulsatility is thought to be important for the biologic effects. GH carries out most of its anabolic effects through insulin-like growth factor 1 (IGF-1), and the levels are low in critical

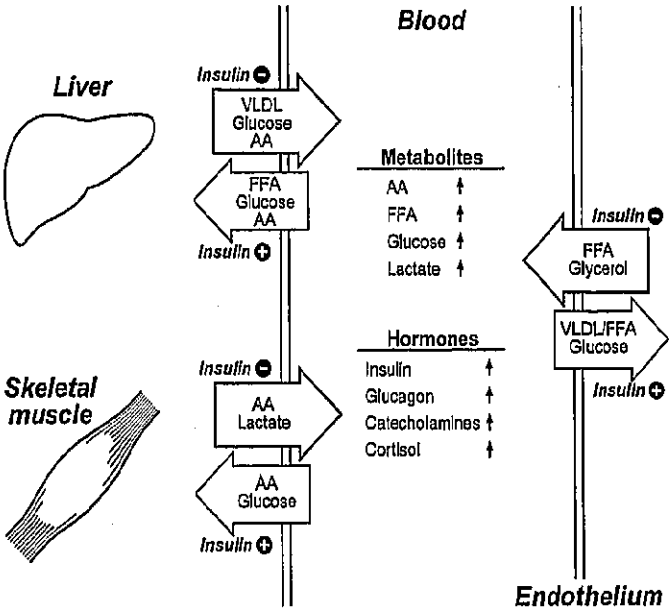

Fig. 1. The sepsis induced changes in circulating hormones and metabolites. The bold arrows across the endothelial barrier indicate the direction of net metabolite flux. VLDL, Very low-density lipoproteins.

illness. The alterations have been interpreted as peripheral resistance to GH and have been observed in human and animal models of acute stress [22, 23]. As acute, critical illness becomes chronic GH continues to be released in a pulsatile manner. The amount of GH released in each pulse is much smaller, and the level of circulating GH between pulses is higher. This response has been described in humans and was recently confirmed in an animal model of prolonged, critical illness [24–27].

Prolonged, critical illness is associated with significant "wasting", and different strategies have been attempted to overcome this problem. In 1992, it was suggested that recombinant GH to patients with sepsis reduced nitrogen excretion and improved nitrogen balance [28]. Therefore, it was investigated whether GH administration to ICU patients would be of any benefit. Unfortunately, the study showed a significant mortality increase in the treatment group. The reason for this is still being discussed [29].

Glucagon

As a classical counter-regulatory hormone glucagon possesses an important role in maintaining euglycemia by stimulating hepatic glucose output during fasting and acute illness. The levels during infection or stress are high [30]. Glucagon increases hepatic glucose output primarily by inducing glycogenolysis [31]. In addition, increased glucagon levels drastically increase urea synthesis in rats given exogenous glucagons [32]. The effect of glucagon on human urea synthesis seems more complex as administration only exerts a transient effect, and cortisol may play a permissive role through peripheral proteolysis or more directly on liver metabolism [33]. The effect may increase the release of AA from skeletal muscle in human sepsis, but this remains to be further investigated.

Catecholamines

The levels of endogenous catecholamines are generally high during sepsis. Furthermore, many patients are treated with exogenous vasopressors in pharmacological doses as a result of hypotension. It is interesting that the myocardium is relatively catecholamine-resistant during sepsis [34]. Whether the same is true for hepatic responsiveness is not well described.

Peripherally, epinephrine and β-adrenergic stimulation rapidly inhibit insulin-mediated glucose uptake (IMGU) by induction of insulin resistance, mainly in the skeletal muscle [35]. The insulin-signaling pathway may be altered by β-adrenergic stimulation by cyclic adenosine monophosphate (cAMP) and cAMP-independent mechanisms [36]. An inhibitory action at multiple sites is suggested, as the insulin signal is disturbed at receptor level [37] as well as through the tyrosine kinase [38], the glucose transporter (GLUT) protein [39] and the glycolytic pathway [40]. Moreover, induction of lipolysis by β-adrenergic stimuli leads to decreased oxidation of glucose through the action of the Randle cycle [41].

The splanchic (hepatic) reaction to catecholamines is an increase in hepatic glucose output primarily from GNG [42].

Glucose metabolism in sepsis

The concentration of glucose in the blood is normally regulated within narrow limits, but the rate of glucose uptake and oxidation varies greatly. Twelve GLUT isoforms have been identified, three of these (GLUT1, GLUT2, and GLUT4) play an important role in glucose uptake. GLUT1 is the GLUT responsible for non-IMGU (NIMGU) and is situated primarily in the central nervous system and erythrocytes. IMGU primarily occurs through mobilization of GLUT4 to the cell membrane and is situated predominantly in skeletal muscle. GLUT2 is a bidirectional GLUT located in the kidneys and the liver. In spite of pronounced insulin resistance in sepsis, it has been demonstrated that sepsis causes a marked increase in skeletal muscle glucose uptake [43]. The increased NIMGU is a result of up-regulation of GLUT1 [44, 45].

In stress-induced insulin resistance, impaired glycogen synthesis prevails, accompanied by an increased pyruvate synthesis [46, 47]. Whether this causes the increase in serum lactate

seen in sepsis or whether it is a result of impaired lactate clearance needs further investigation [48].

The counter-regulatory hormones glucagon, cortisol, catecholamine, and GH all tend to raise the glycemia level as a result of stimulation of hepatic GNG and glycogenolysis and through inhibition of IMGU.

AA metabolism in sepsis

The erosion of lean body mass (i.e., skeletal muscle) resulting from protracted, critical illness remains a significant risk factor for increased morbidity and mortality in patients with prolonged sepsis [49]. The catabolic response in skeletal muscle, in particular in sepsis, is characterized by inhibited protein synthesis [50, 51] and stimulated protein breakdown [52, 53]. AA released into the bloodstream as a consequence of net proteolysis in skeletal muscle are taken up by the liver and used for acute-phase protein synthesis and GNG [54, 55], but the enterocytes and polymorphnuclear neutrophils (PMNs) also use glutamine as an energy source [56–58]. The quantitatively significant AA released from skeletal muscle during sepsis are alanine and glutamine [59]. The catabolic response in skeletal muscle is mediated by a number of regulators, the most important being glucocorticoids. The role of cytokines seems to be more complex. The effect of TNF-α is suggested to be mediated through release of glucocorticoids. Administration of interleukin (IL)-1 to rats stimulated muscle protein breakdown in vivo [60] but not in vitro [61, 62]. Glucocorticoids may be the most important inducer of skeletal muscle proteolysis in sepsis as blocking glucocorticoids attenuates the proteolysis [63]. Acidosis is also known to promote proteolysis, although the mechanism is not entirely clear [64]. It has been suggested that the stimulatory effect of insulin on protein synthesis was retained while the muscles became resistant to the hormone's effect on protein degradation [65]. As the effect of insulin on protein synthesis was maintained, the resistance of protein breakdown most likely reflected a post-receptor defect. In more recent studies, it is suggested that protein breakdown in muscles from septic rats was resistant to the regulatory effects of IGF-1 as well [66]. Similar to insulin, IGF-1 stimulated protein synthesis in control and septic muscle, suggesting that the resistance to IGF-1 was at the post-receptor level.

Lipid metabolism in sepsis

FFA levels in sepsis are significantly increased, partly as a result of hepatic insulin resistance and partly as a result of insulin resistance in adipose tissue [67]. As FFA and glucose blood levels increase they interact, and FFA is suggested to impair glucose metabolism at various sites, one being inhibition of glucose oxidation [41] and another being stimulation of protein kinase C (PKC) [68].

During sepsis, the liver increases its uptake of FFA and glucose as a result of increased levels in plasma. The glucose is metabolized in the hepatocyte to malonyl-CoA, which is known to inhibit the action of Carnitin-palmitoyl transferase (CPT), the mitochondrial-membrane enzyme responsible for transport of long-chained FFA into the mitochondria for oxidation. The accumulation of malonyl-CoA also increases the hepatic FFA, triglycerides (TG), and VLDL synthesis, further increasing the plasma FFA, TG, and VLDL [69]. Recently, it was suggested that hyperinsulinemia and hyperglycemia increase malonyl-CoA, inhibit functional CPT-1 activity, and shunt FFA away from oxidation toward storage in healthy human muscle [70]. Whether this is also the case in sepsis remains to be elucidated.

Recently, FFA receptors (FFAR) [71] have been discovered on different cell surfaces, including surfaces on leukocytes [72]. The first described FFAR, now named FFA(1)R, is activated by medium- to long-chain FFA. It is expressed in skeletal muscle, heart, liver, and pancreatic β cells. The second FFAR, FFA(2)R, is predominantly expressed in peripheral blood leukocytes and to a lesser extent in spleen. FFA have long been known to affect the cells of the immune system [73], but what the actual physiological significance is and how FFA activation of FFA(2)R affects the immune system, primarily the neutrophils, remain to be further investigated.

ACUTE INFLAMMATION—EFFECTS OF HYPERGLYCEMIA AND INSULIN

The metabolic derangements of sepsis described above have multiple consequences on inflammatory signaling. In the following, we aim to describe these consequences and thereby identify several key mediators of inflammation and inflammatory pathways on which insulin therapy may have an effect.

Interaction between leukocytes and endothelium

Disturbed interaction between leukocytes and endothelium plays a pivotal role in sepsis pathogenesis. Functional interaction between leukocytes and endothelium, i.e., rolling, adhesion, and transmigration, is dependent on up-regulation of adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), P- and E-selectin. The circulating levels of these adhesion molecules are elevated in human sepsis [74, 75].

Hyperglycemia has been shown by intravital microscopy to increase leukocyte rolling, adhesion, and transmigration in rat mesenteric venules in vivo [76]. The effects were not dependent on changes in osmolarity. Immunohistochemistry revealed P-selectin expression in the mesenteric venules to be up-regulated by glucose within hours in a time-dependent manner. Insulin reverted the effect on all three functional capabilities as well as on P-selectin expression. These data are confirmed by two studies investigating leukocyte interaction with human umbilical cord endothelial cells. Puente Navazo et al. [77] found that high ambient glucose concentration increased monocyte binding and P-selectin expression—both were reversible by addition of insulin. Morigi et al. [78] found leukocyte adherence to be increased by glucose and argued that E-selectin, ICAM-1, and VCAM-1 played a role in the adherence. An elegant human in vivo study investigated circulating adhesion molecules in relation to hyperglycemia and hyperinsulinemia [79]. Hyperglycemia caused an elevation in the level of soluble (s)ICAM-1 in type 2 diabetics and healthy control subjects, an effect that was completely abolished by concurrent hyperglycemia and hyperinsulinemia. Moreover, overnight eu-

glycemic clamping of the type 2 diabetic patients brought their sICAM-1 levels down to that of controls.

From the above, it seems clear that hyperglycemia and insulin have well-established effects on molecules that are able to affect the interaction between leukocytes and endothelium in sepsis (**Fig. 2**), although these experiments were performed to study the early phases of atherogenesis.

Supporting this expectation is the fact that the signaling pathways are shared by other proinflammatory factors, e.g., TNF-α and endotoxin. eNO is a key modulator of leukocyte-endothelium interaction [80], acting by inhibiting cytokine-induced expression of ICAM-1 and VCAM-1 [81] and by suppression of P-selectin expression [82]. High glucose levels and FFA are thought to act by increasing intracellular levels of ROS, possibly through a PKC-dependent activation of nicotinamide adenine dinucleotide phosphate oxidase (NADPH) [83, 84]. Intracellular ROS intermediates may then react with NO to reduce its availability and may serve as activators of NF-κB [78], thereby increasing the expression of adhesion molecules.

Several groups have investigated the effects of insulin on these signaling pathways. Dandona and coworkers [85, 86] worked with cultured human aortic endothelial cells. They found that physiologically relevant concentrations of insulin suppressed NF-κB-binding activity and ICAM-1 expression, the latter dependent on stimulation of NO production by insulin, which stimulates eNO production within minutes through receptor-mediated activation of phosphatidylinositol-3 kinase (PI-3K) [87] but also stimulates de novo eNOS production [88]. Aside from these regulatory functions, insulin is known to cause vasodilatation. In healthy humans, hyperinsulinemia stimulates eNO production to an extent that significantly increases leg blood flow [89]. One might argue that systemic NO production is more than sufficiently enhanced in sepsis. However, animal studies of experimental endotoxemia show that eNOS may in fact be depressed in the lungs and the heart [90, 91], whereas eNOS activity is stimulated in other vascular beds along with a general stimulation of inducible NOS activity. We have found that lipopolysaccharide induces depression of eNOS mRNA levels in heart, liver, and lung from pigs [92]. The levels of eNOS mRNA were normalized in vivo by a euglycemic hyperinsulinemic clamp. In support of this, the clamp in endotoxemic and control animals increased the fraction of NO in expired air.

It follows from this discussion that insulin conceivably has an expedient effect on leukocyte-endothelial interaction in sepsis. This effect may serve to avert unwanted leukocyte sequestration and uphold microcirculatory homeostasis.

PMNs

Once the PMNs have transmigrated the endothelial barrier, their ability to deal with invading microorganisms is crucially dependent on chemotaxis, fagocytotic capability, and oxygen-dependent superoxide production (respiratory burst). It is well known that PMN functions are depressed in diabetic patients [93, 94]. As we shall discuss here, hyperglycemia and insulin resistance affect the basic functions of PMNs, and this could bear consequence on the PMN dysfunction observed during sepsis.

The chemotactic ability of neutrophils is reduced in diabetic patients [93], and elevated glucose concentrations seem to interfere with chemokinetic control of neutrophils from healthy humans in vitro [95]. At physiologic concentrations, insulin has the ability to increase chemotaxis of activated PMNs [96] mediated through signals involving receptor-stimulated activation of PI-3K [95]. Hyperglycemia induces insulin resistance in PMNs by stimulating PKC [97], which down-regulates the insulin receptor's tyrosine kinase activity and thus, ultimately, intracellular PI-3K activity [98].

In line with this, several studies find the respiratory burst of isolated PMNs dose-dependently reduced by glucose in vitro

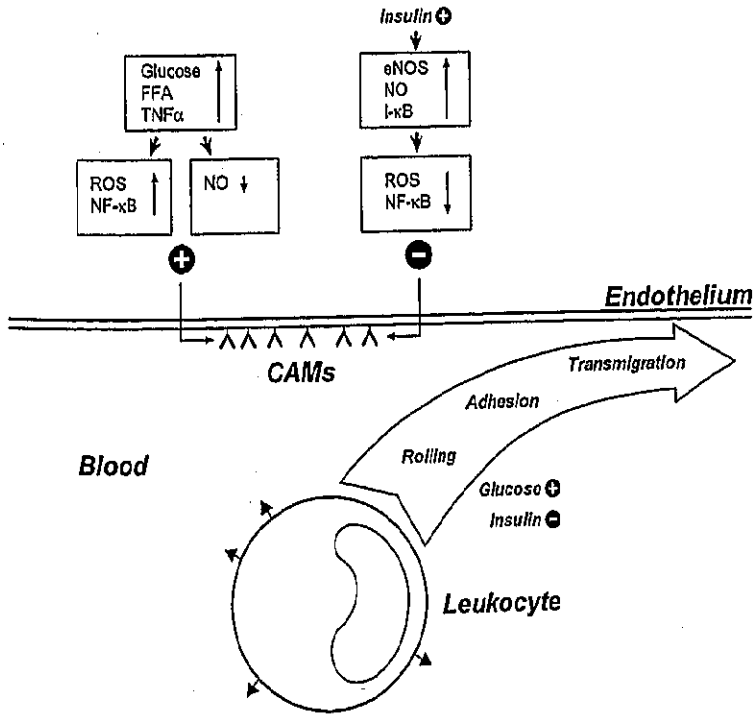

Fig. 2. The effects of insulin, glucose, and FFA on cell adhesion molecule (CAM) expression and leukocyte-endothelial interaction. ROS, reactive oxygen species; NF-κB, nuclear factor-κB; NO, nitric oxide; eNOS, endothelial NO synthase; I-κB, inhibitory κB.

[99–102]. Insulin does affect the production of hydrogen peroxide positively [103], whereas the superoxide ion generation seems more dependent on ambient glucose concentration.

The fagocytic capability of PMNs in response to insulin has been investigated in a human in vivo study of diabetic cardiac surgery patients. The post-operative (1 h) reduction in PMN phagocytic function was significantly less affected in the group randomized to aggressive insulin treatment versus standard treatment, and both groups returned to normal levels 24 h post-operatively [104].

Macrophage migration inhibitory factor (MIF)

MIF is known to be a regulatory cytokine with a stimulatory effect on macrophage function and counteracting the effects of glucocorticoids on these cells [105]. MIF is secreted constitutively by the anterior pituitary gland, by immune cells in response to proinflammatory stimuli, and by pancreatic β cells in response to glucose stimulation [106]. Further, MIF acts in an autocrine manner to stimulate insulin secretion. Thus, MIF and insulin are expected to act in concert to antagonize the anti-inflammatory effects and the catabolic effects of glucocorticoids during sepsis. Teleologically, one would expect insulin to have an effect on MIF secretion. One study addresses this issue. Sakaue and coworkers [107] did a study in cultured adipocytes in which they found that MIF mRNA and intracellular MIF levels were up-regulated by the costimulatory effect of glucose and insulin. They also found MIF secretion to increase in response to treatment with the insulin-sensitizing agent pioglitazone. This result suggests that an improvement in insulin resistance will lead to MIF release. Given this mechanism, one may speculate that insulin therapy during sepsis could result in increased MIF release, although as yet, no other data exist supporting this hypothesis.

Mannose-binding lectin (MBL)

Activating the lectin pathway of complement activation MBL plays an important role in innate immunity. Deficiency of MBL is associated with an increased susceptibility to infections [108]. The study on intensive insulin therapy in ICU patients by Van den Berghe et al. [3] recently measured MBL levels in a subgroup of patients [109]. Only patients who needed prolonged intensive care (>5 days) were included, as these were the ones benefiting from the intensive insulin therapy. In the group treated with the conventional insulin regimen, MBL levels were overall higher. Patients dying during ICU stay had lower MBL compared with ICU survivors in this group, but this was not the case for patients in the intensive insulin-treated group. The result suggests that insulin has an inhibitory effect on the systemic release of this marker of innate immunity and, at the same time, attenuates the adverse effects of low-serum MBL.

Cytokine production

Hyperglycemia has been found to influence the production of proinflammatory cytokines acutely and chronically [110]. In this study, subjects with impaired glucose tolerance (IGT) had higher baseline levels of TNF-α and IL-6 compared with normal controls. Moreover, the IGT subjects had a higher and more sustained cytokine release in response to acute pulses of hyperglycemia while the endogenous insulin release was clamped with a somatostatin analog. An in vitro study demonstrated that hyperglycemia dose-dependently stimulates TNF-α and IL-6 production, confirming the independent action of glucose [111]. Conversely, TNF-α and IL-1β are strongly implicated in the development of insulin resistance during experimental conditions [112] and in humans [113]. This mutually stimulatory property of glucose and proinflammatory cytokines could potentially aggravate inflammation in a physiologic setting characterized by cytokemia and hyperglycemia, such as sepsis.

In experimental sepsis, high doses of insulin clearly seem to reduce the production of proinflammatory cytokines. We investigated the effect of hyperinsulinemia during acute endotoxemia in pigs and found significant reductions in systemic TNF-α and IL-6 releases [114]. The inhibitory effect of insulin on leukocyte cytokine production in vitro supports this finding. A study of obese humans revealed that insulin, even at low doses (2–2.5 IU/h), was able to increase I-κB protein levels and reduce ROS generation and NF-κB-binding activity in isolated mononuclear cells [115]. Also, insulin has been shown to down-regulate the number of TNF-α receptors on human monocyte-derived macrophages as well as reduce their TNF-α-stimulated killing of bacteria [116], which indicates that insulin also attenuates the inflammatory consequences of TNF-α. Indeed, this is confirmed by a study in which rats were treated with recombinant human TNF-α. The katabolic, anorexic, and histopathologic changes observed after TNF-α treatment were all reversed when high doses of insulin and TNF-α were concurrently administered [117].

CONCLUSION

Given the limits of current knowledge, it is often difficult to predict the magnitude of change and even the direction of change in a certain mediator or pathway. Immunological treatment goals in sepsis may vary greatly, depending on whether a patient's condition is dominated by inflammation or characterized by a state of immunologic anergy. Therefore, the general aim should be to restore homeostasis rather than to affect any specific mediator in any specific direction.

Insulin may provide a means to restore metabolic homeostasis in sepsis through specific anabolic actions on glucose, AA, and FFA turnover. Given the effects on metabolic substrates and the independent actions on inflammatory signaling, insulin may indeed possess the properties of an unspecific, inflammatory modulator acting to prevent and possibly stop undesirable inflammatory activation. Thus, further trials on experimental and clinical sepsis are warranted to disclose the role of insulin in restoring inflammatory homeostasis.

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