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Insulin resistance in human sepsis: implications for the nutritional and metabolic care of the critically ill surgical patient

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Loss of the anabolic effect of insulin (insulin resistance) is a key component of the adverse metabolic consequences of sepsis and may contribute to the apparent lack of efficacy of feeding regimens in critically ill patients. The mechanisms which underlie the development of insulin resistance in stress remain unclear. In this series of studies, the locus of insulin resistance in the septic patient was shown to lie within the metabolic pathways of glucose storage (glycogen synthesis) within skeletal muscle, was noted to be unrelated to the actions of hormone mediators such as leptin and was shown not to be associated with altered nutrient-induced thermogenesis during total parenteral nutrition (TPN). Clinically applicable maximal rates of glucose-based TPN for septic patients were calculated. A technique was also developed in which insulin resistance could be induced and studied in healthy volunteers. These studies demonstrated that insulin resistance develops within 7 h of an inflammatory stimulus and, as in clinical sepsis, is characterised by selective impairment of glucose storage. Finally, a series of related studies indicated that the magnitude and nature of the inflammatory response *in vivo* could be enhanced by exogenous insulin infusion, indicating links between the hormone systems involved in intermediary metabolism and the inflammatory response. These findings have significant implications for the optimal design of feeding regimens for critically ill patients.

Key words: Infection – Total parenteral nutrition – Catabolism – Lipopolysaccharide – Endotoxin

Nutritional and metabolic support play a key role in the management of critically ill surgical patients. Despite aggressive nutritional support, however, preservation of lean body tissue in such patients remains problematic[1] and loss of lean body mass may contribute to delayed recovery by virtue of the resulting muscle weakness and deficiencies in immune responsiveness and wound healing. One of the principal metabolic alterations associated with the stress response of injury and/or infection is loss of end-organ sensitivity to insulin (insulin resistance).[2]

Insulin resistance has been defined[3] as 'the unresponsiveness of anabolic processes to the normal effects of insulin' and it typically presents with the biological features of insulin deficiency (Table 1), despite the presence of normal, or even elevated, plasma insulin concentrations.

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Table 1 Key metabolic effects of insulin

Carbohydrate metabolism
Increases uptake of glucose into skeletal muscle and adipose tissue cells
Increases storage of glucose as glycogen
Reduces rate of breakdown of glycogen
Reduces conversion of amino acids to glucose in liver (gluconeogenesis)
Lipid metabolism
Increases conversion of glucose into free fatty acids (FFAs) and triglycerides in liver and adipose tissue
Reduces breakdown of fat into FFAs in adipose tissue
Prevents production of ketone bodies by the liver
Protein metabolism
Increases uptake of amino acids by skeletal muscle and liver
Reduces rate of protein breakdown in skeletal muscle

Since insulin promotes an integrated anabolic response to feeding, it is apparent that loss of the anabolic effect of insulin is likely to result in intolerance of feeding (manifest as hyperglycaemia and a diabetic-like state) and impaired retention of muscle protein (leading to muscle wasting). Since the majority of metabolically active tissues in the body (and especially skeletal muscle, which is the major route of intravenous glucose disposal) require insulin for normal glucose uptake, it is hardly surprising that sepsis may lead to abnormalities of fuel substrate oxidation.

Early studies of fuel substrate oxidation in septic patients revealed both a significant increase of metabolic rate in sepsis (and hence fuel substrate requirements) and also an apparent impairment of glucose oxidation. As the severity of sepsis increases, an increased reliance on lipid (as opposed to glucose) as an oxidative fuel was observed, findings which have clear ramifications for the design of feeding regimens in such patients.[4]

Studies of glucose metabolism in human sepsis and injury have generally employed the glucose clamp technique, in which glucose is infused intravenously, with or without exogenous insulin.[5] A key feature of these techniques is that when plasma insulin concentration is raised to a predetermined level by exogenous infusion, the rate of simultaneous glucose infusion required for stable 'euglycaemia' (plasma glucose concentrations are usually maintained at 5 mmol/l), represents total glucose utilisation by the body, which in turn reflects whole body insulin sensitivity. By sampling across an individual tissue bed (for example, the forearm, where the principle metabolically active tissue is skeletal muscle), it is possible to examine the relative influence of key metabolically active tissues to whole-body insulin sensitivity. Further refinements to the technique have included simultaneous infusion of dideuterated glucose, enabling simultaneous estimation of hepatic endogenous glucose production rate.[6] Application of the glucose clamp methodology to injured and septic patients has demonstrated global decreases in whole body glucose utilisation in sepsis[7] and injury,[8] and also suggested that skeletal muscle is the principal locus of the defect in insulin-mediated glucose utilisation.[8]

The precise mechanisms underlying the development of insulin resistance in critically ill surgical patients remain unclear, however, both in relation to aetiology and also with respect to the molecular and cellular defect in glucose metabolism within insulin-resistant tissues. While sepsis is associated with significant elevations of plasma concentrations of counter-regulatory hormones[9] and excessive activation of the sympathetic nervous system,[10] both of which may impair insulin sensitivity, it is unclear whether they can account for the insulin resistance observed in human critical illness. Infusion of counter-regulatory hormones for several days, for example, has been shown to reproduce some of the metabolic effects of critical illness, including insulin resistance;[11,12] however, the plasma concentrations of counter-regulatory hormones achieved in such studies were significantly in excess of those encountered in the majority of septic or injured patients. In the postoperative setting, marked reductions in sensitivity to insulin occur with only minor and transient changes in counter-regulatory hormone or cytokine concentrations.[13] Similarly, although insulin resistance in obesity is associated with elevation of plasma leptin concentrations, leptin inhibits insulin signalling in cell culture[14] and increased plasma leptin concentrations and loss of the normal diurnal rhythm of plasma leptin[15] occur in sepsis, leptin was shown to be unlikely to account for the reduced insulin sensitivity.[16]

Preliminary studies under clinically relevant conditions, including infusion of glucose-based TPN[17] and glucose alone,[18] at rates of calorie administration which resemble those used in TPN, suggested that the total capacity of septic humans for glucose oxidation, the energetic cost of glycogen synthesis and the heat energy dissipated during TPN were not significantly altered.[19]

Insulin resistance in sepsis is specifically related to impairment of the glucose storage pathway

As indicated above, studies of insulin resistance in critical illness have chiefly focused on disordered whole body glucose disposal. Reduced glucose utilisation could, however, be the consequence of a variety of different and potentially unrelated defects in cellular glucose metabolism (Fig. 1). Defective activation of the insulin receptor,

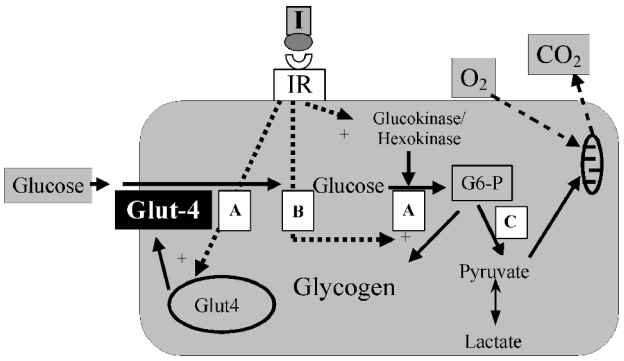

Figure 1 Major metabolic pathways regulating glucose entry into and oxidation and storage within the skeletal muscle cell, and the effect of insulin resistance on the metabolic fate of glucose. Blockade/impairment of pathways at 'A' would result in impairment of both glucose storage and oxidation, while pathway at 'B' would result in impairment of glucose storage alone, and blockade or impairment of pathway at 'C' would result in isolated impairment of glucose storage. IR, insulin receptor; I, insulin molecule; G6-P, glucose-6-phosphate; Glut-4, insulin-sensitive glucose transporter.

impairment of the signalling pathway between the insulin receptor and the insulin-sensitive glucose transporter (Glut-4), abnormalities of translocation of Glut-4 from the cytosol to the plasma membrane of insulin-sensitive tissues, and defective insulin-mediated activation of hexokinase would all lead to impairment of both glucose oxidation and storage (since glucose would be unable to enter the cell or enter the initial steps of phosphorylation required for either the metabolic pathways serving glucose oxidation or glycogenesis). In contrast, impairment of insulin-mediated activation of pyruvate dehydrogenase or phosphofructokinase (key control steps in the glycolytic pathway leading to glucose oxidation) would impair glucose oxidation but leave storage unaffected, whereas defective activation of glycogen synthase would impair storage but leave oxidation unaffected. Since the locus of the defect in glucose utilisation could thus be inferred from knowledge of the relative contributions of oxidation and non-oxidative disposal (storage) to glucose utilisation in critical illness, we examined total glucose utilisation, oxidation and storage in 24 patients with abdominal sepsis and 26 healthy age and sex-matched control subjects.[19] In comparison to earlier, potentially flawed studies in which the hyperglycaemic clamp technique had been used[20] and in which systematic differences between plasma insulin concentrations occurred between septic and healthy subjects, the euglycaemic hyperinsulinaemic clamp technique was employed. This ensured that the biological response in question (rates of total glucose utilisation, glucose oxidation and storage) could be compared in septic patients and healthy volunteers at the same plasma insulin concentration, thus indicating that any differences in glucose utilisation observed between the two groups could not be due to differences in insulin concentration. Studies were conducted using insulin infusion rates of 40 and 240 mU/m^2/min, which produce physiological (70 μU/ml) and supraphysiological (600 μU/ml) insulin concentrations, respectively, in order to determine whether any defect in glucose utilisation could be overcome, provided a sufficiently high plasma insulin concentration was reached. These studies (Fig. 2) demonstrated that glucose oxidation was, in fact, preserved in sepsis and reached a maximum, at the lower insulin infusion rate, of approximately 4 mg/kg FFM/min in both septic patients and healthy controls, a figure similar to that reported previously.[21]

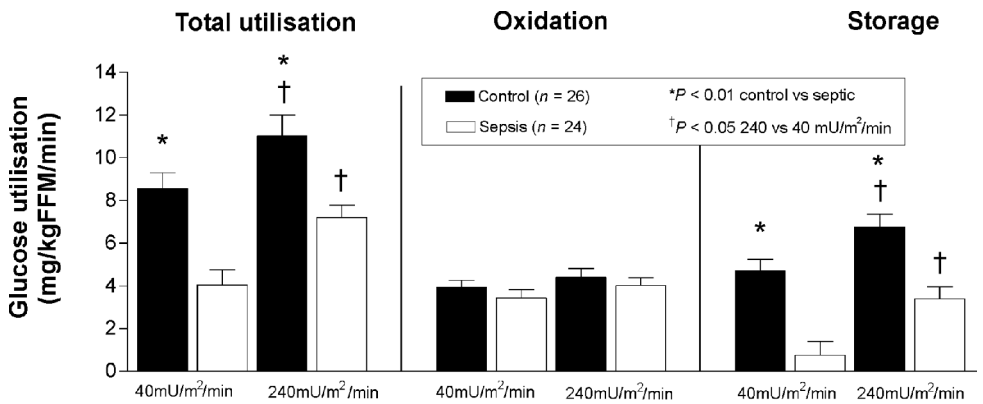

Figure 2 Total glucose utilisation, oxidation and storage in patients with abdominal sepsis (open squares; $n = 24$) and healthy controls (filled squares; $n = 26$). All subjects were studied during conditions of euglycaemic hyperinsulinaemia, at insulin infusion rates of 40 and 240 mU/m^2/min. All values are mean (SE). *$P < 0.01$, control versus septic; †$P < 0.05$, 40 versus 240 mU/m^2/min.

These findings imply that the locus of the defect in glucose metabolism in the insulin-resistant septic patient lies within the skeletal muscle cell and relates to defective insulin-mediated activation of the glycogen storage pathway. The specific molecular abnormality is unclear, but may relate either to the glycogen synthase enzyme itself or one of the many intracellular kinases which control its activation. The practical implications, however, are that significant hyperglycaemia might be avoided in the septic patient fed intravenously with glucose-based TPN regimens, provided that glucose is not administered at rates in excess of 4 mg/kg FFM/min (a rate of energy provision which can provide approximately 50% of non-protein calories[19]), and that exogenous insulin infusion is unlikely to provide satisfactory control of hyperglycaemia in the parenterally fed patient if these rates of glucose administration are substantially exceeded.

Insulin resistance is induced by endotoxaemia in man

One of the key limitations of studies in which septic or injured patients are compared with healthy volunteers, however well-matched, is that there are series of confounding factors which may directly or indirectly affect insulin sensitivity.[13] In particular, septic or injured patients are likely to suffer from chronic or acute nutrient depletion, immobility, cancer, and may be receiving treatment with inotropic drugs (usually catecholamines or related compounds), which may all independently reduce insulin sensitivity.[1] These factors are almost impossible to control for in clinical studies. In addition, the nature of sepsis makes it difficult to explore the time course of the resulting insulin resistance, since it is often unclear when the precise onset of sepsis occurred and, furthermore, the severity of sepsis may wax and wane during an individual septic episode. While animal studies have employed a variety of models of sepsis in order to clarify the pathophysiology of the metabolic responses,[22,23] it has, until recently, not been possible to replicate these studies in man. Therefore, to explore the development of acute human insulin resistance, we employed a model of acute infection in which intravenous lipopolysaccharide (LPS, *Escherichia coli* endotoxin) is administered to healthy volunteers.[24] This model had previously been shown to induce an acute systemic response with fever, tachycardia and acute changes in plasma concentrations of counter-regulatory hormones and pro-inflammatory cytokines.[25] The aims of these studies were, therefore to examine the time course of the effect on glucose metabolism, to study the development of insulin resistance, and to relate it to the associated changes in plasma concentrations of counter-regulatory hormones and cytokines. Specifically, the study was designed to test the hypothesis that the same locus of insulin resistance encountered in septic patients (defective glucose storage rather than oxidation) could be induced in healthy volunteers. Six healthy subjects underwent a 10-h euglycaemic clamp (insulin infusion rate 80 mU/m^2/min), with either

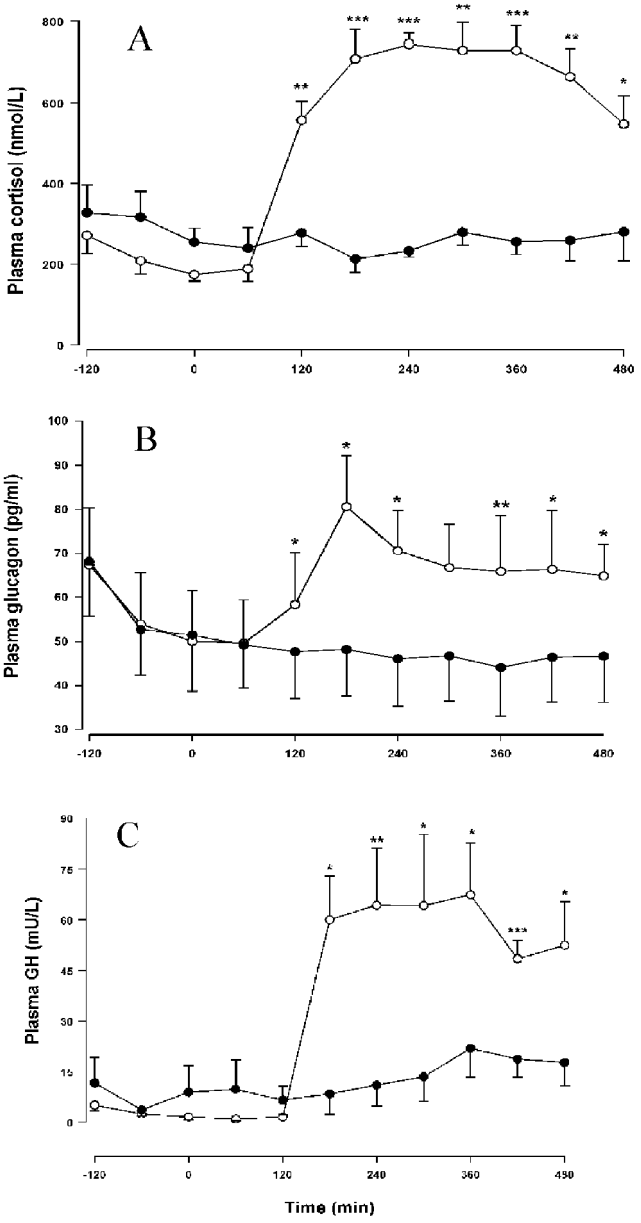

Figure 3 Plasma cortisol (A), glucagon (B) and growth hormone (C) concentrations in subjects receiving either 20 U/kg *E. coli* LPS i.v. (open circles; $n = 6$) or saline control (filled circles; $n = 6$), administered at 0 min, during euglycaemic hyperinsulinaemia. All values are mean (SE). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ LPS versus saline control.

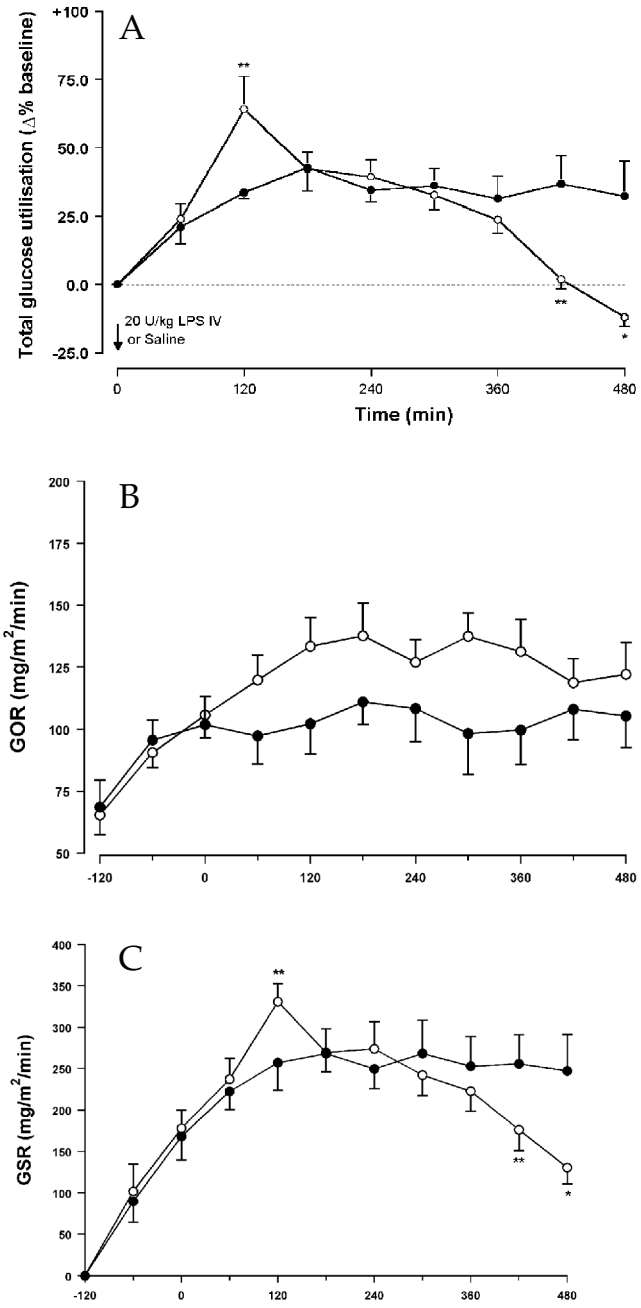

Figure 4 (A) Percentage change in total glucose utilisation rate during euglycaemic hyperinsulinaemia after either 20 U/kg *E. coli* LPS i.v. (open circles; $n = 6$) or saline control (filled circles; $n = 6$). All data are mean (SE), $^{*}P < 0.05$, $^{**}P < 0.01$ LPS versus control. (B) Glucose oxidation rate during euglycaemic hyperinsulinaemia in subjects given LPS, 20 U/kg i.v. (open circles; $n = 6$) or saline (filled circles; $n = 6$) at time 0. All data are mean (SE), $^{*}P < 0.05$, $^{**}P < 0.01$ LPS versus control. (C) Glucose storage rate during euglycaemic hyperinsulinaemia in subjects given LPS, 20 U/kg i.v. (open circles; $n = 6$) or saline (filled circles; $n = 6$) at time 0. All data are mean (SE), $^{*}P < 0.05$, $^{**}P < 0.01$ LPS versus control.

administration of LPS or saline (control) after 2 h, a time point at which steady- state conditions of glucose utilisation are achieved. The purpose of the euglycaemic clamp in the control group (receiving saline) was to control for the effects of a long-duration insulin infusion on glucose metabolism. Studies were undertaken in a paired manner and in random order and, as with studies on septic patients, glucose utilisation was measured by examining the rate of exogenous glucose infusion required to maintain plasma glucose at 5 mmol/l, while glucose oxidation rates were measured by collection and analysis of respiratory gases (indirect calorimetry). As anticipated, LPS administration induced a pyrexia, tachycardia and a counter-regulatory hormone (cortisol, glucagon and growth hormone, but not adrenaline) response in all subjects (Fig. 3). The effect on glucose metabolism was, however, complex. The onset of symptoms was associated with a brisk increase (+64.1 ± 12.0%) in total glucose utilisation (Fig. 4A) which was not observed in the control arm of the study, in which a more steady and progressive rise to a delayed plateau (+35.6 ± 3.2%) was observed. This early and transient increase in glucose utilisation occurred at the same time as clinical symptoms developed in the experimental subjects and was related to increased non-oxidative glucose disposal, rather than oxidation, implying either non-insulin mediated storage of glucose in muscle, increased anaerobic glucose utilisation (within the immune system) or a transient insulin-like effect of endotoxin.

In the late phase of the LPS arm of the study, a progressive reduction in glucose utilisation occurred (–12.0 ± 3.4%), indicative of the development of insulin resistance. This began approximately 7 h after LPS administration, at a time when counter-regulatory hormone responses were already maximal. In contrast, glucose oxidation (Fig. 4B) increased similarly in both arms of the study and appeared to be preserved entirely despite LPS administration. The changes in glucose utilisation associated with the metabolic response to LPS (Fig. 4C) could be accounted for almost entirely by changes in non-oxidative glucose disposal (*i.e.* glucose storage).

The mechanism underlying the development of insulin resistance in this model remains unclear, but the time course suggests a role for cortisol and/or growth hormone and additional studies using a selective growth hormone receptor antagonist are planned. Additionally, pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α) have been suggested to play a role in the insulin resistance of obesity and diabetes.[26] Radioactive *in situ* hybridisation studies of quadriceps muscle biopsies taken from human subjects in our laboratory 6 h after LPS administration have demonstrated that human endotoxaemia is associated with induction of mRNA for TNF-α in skeletal muscle (Fig. 5).

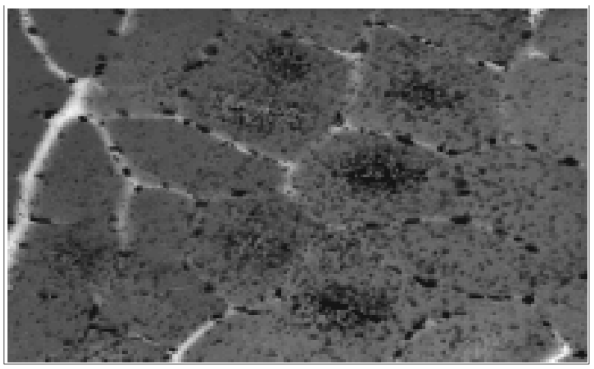

Figure 5 Photomicrograph of radioactive *in situ* hybridisation study of human quadriceps muscle biopsy, taken 6 h after LPS administration. Black particles represent mRNA for TNF-α and can be clearly seen within myocytes.

Hyperinsulinaemia augments the systemic inflammatory response to human endotoxaemia

While the haemodynamic state of the septic patient may affect plasma insulin concentrations, with adrenergic-mediated suppression of insulin secretion featuring prominently in shock states,[9] the stable, resuscitated intensive care or postoperative ward patient tends to exhibit normal, or even elevated, plasma insulin concentrations, despite evidence of insulin resistance. While it has been suggested that low-grade chronic inflammation may play a pathogenetic role in the insulin resistance of type II diabetes and obesity, on the basis of increased activity of pro-inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) at the tissue level,[27] *in vitro* studies have suggested that insulin and insulin-like growth factors may also regulate pro-inflammatory cytokine production by cells of the immune system[28] and *in vivo* animal studies have indicated that glucose and/or insulin can either up-regulate[29] or inhibit[30] the pro-inflammatory cytokine response to endotoxin, in an apparently species-specific manner.

Having validated the human endotoxaemia model in our own laboratory, we aimed to test the hypothesis that the systemic inflammatory response to LPS would be modulated according to the level of insulinaemia that prevailed when LPS was given.[31] Paired studies in random order were performed in 14 healthy adult subjects, who received either LPS or saline during euglycaemic clamp (insulin infusion rate 80 mU/m^2/min; n = 6) or non-clamp (saline infusion; n = 8) conditions. In each case, the LPS (20 U/kg) or saline (control) was given 2 h after the commencement of the clamp or saline infusion. Hourly measurement of temperature, pulse and blood pressure was undertaken for the next 6 h, together with sampling of arterialised venous blood for measurement of counter-regulatory hormones and pro-inflammatory cytokine concentrations.

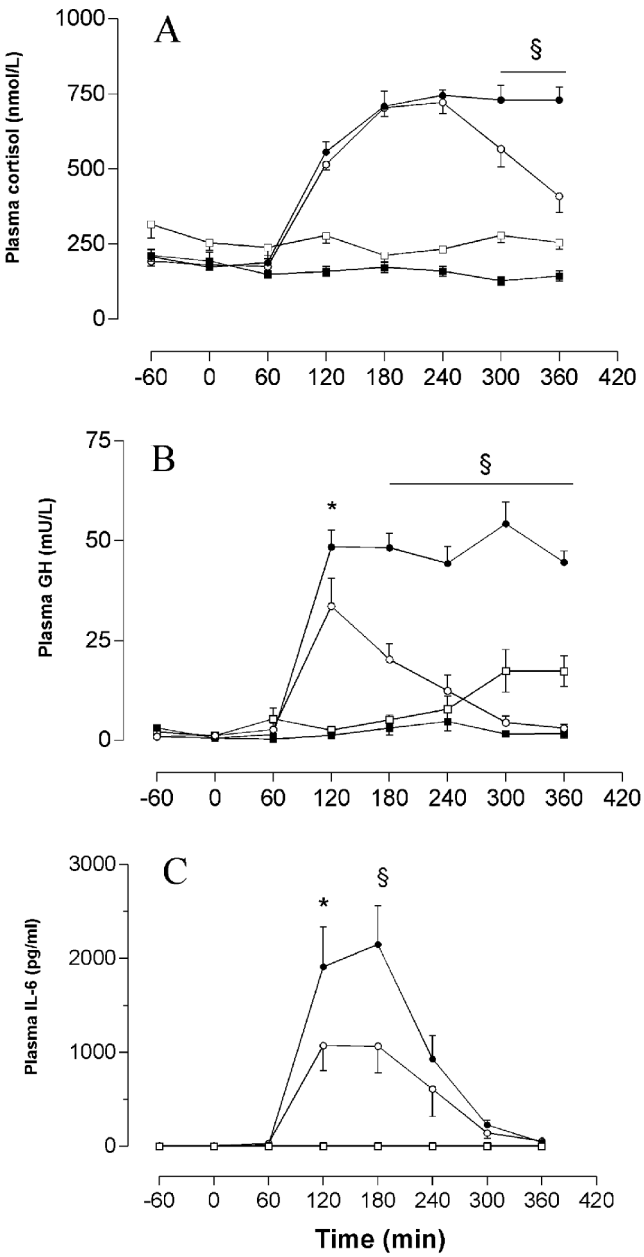

Figure 6 Effect of euglycaemic hyperinsulinaemia upon plasma cortisol (A), growth hormone (B) and IL-6 (C) concentrations following 20 U/kg *E. coli* LPS i.v. (at time 0 min). Filled circles, clamp/LPS (n = 6); open circles, saline/LPS (n = 8); open squares, clamp/Saline (n = 6); filled squares, saline/saline (n = 8). All data are mean (SE), $^*P < 0.05$, $^‡P < 0.01$, $^§P < 0.001$, clamp/LPS versus saline/LPS, respectively.

Surprisingly, raising plasma insulin levels acutely during euglycaemic hyperinsulinaemia led to a marked increase in the magnitude of the plasma IL-6, cortisol and growth hormone responses to LPS (Fig. 6), suggesting an integrated

up-regulation of stress response in the presence of hyperinsulinaemia, while the magnitude of the fever and the TNF-α response remained unaltered. *In vitro* studies of isolated immune and endocrine cells are currently being undertaken to determine the mechanism of this insulin-mediated up-regulation of the stress response. It is unclear whether these findings will be clinically applicable, given the short-term nature of the studies and the non-physiological conditions of euglycaemia and hyperinsulinaemia. If exogenous hyperinsulinaemia does up-regulate the systemic inflammatory response in man, however, this might have serious clinical implications for the outcome of the systemic inflammatory response syndrome in patients in whom insulin infusion is used as an adjunct to glucose-based TPN.

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