Insulin sensitivity of glucose and fat metabolism in severe sepsis

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ABSTRACT

In order to quantify the changes in insulin sensitivity, particularly of endogenous glucose production and fat metabolism, in patients with severe sepsis, a prospective study was conducted in five normal subjects and in five patients with severe sepsis hospitalized in an intensive care unit. The responses of endogenous glucose production, glucose utilization, plasma fatty acids and ketone body concentrations to progressive increase in plasma insulin levels (exogenous insulin infusion rates of 0, 0.5, 1 and 2 m-units min⁻¹ kg⁻¹) were measured using the isoglycaemic clamp technique. Total glucose turnover was determined with D-[6,6⁻²H₂]glucose. In each group, plasma glucose was maintained at basal levels (control subjects, 4.32 ± 0.22 mmol l⁻¹; patients with sepsis, 7.10 ± 2.29 mmol l⁻¹; P < 0.05). Plasma insulin concentrations were comparable in the two groups at an insulin infusion rate of 0.4 m-unit min⁻¹ kg⁻¹ for controls and 0.5 m-unit min⁻¹ kg⁻¹ for patients with sepsis, but differed following infusion at 2 m-unit min⁻¹ kg⁻¹ (control subjects, 102 ± 13.4 m-units l⁻¹; patients with sepsis, 124.8 ± 19.7 m-units l⁻¹; P < 0.05). Endogenous glucose production was completely suppressed in control subjects by the first insulin infusion (0.4 m-unit min⁻¹ kg⁻¹), but was only suppressed during infusion at 1 m-unit min⁻¹ kg⁻¹ insulin in patients with sepsis. The glucose utilization rate increased significantly with exogenous insulin infusion in control subjects, but did not increase in patients with sepsis. Plasma non-esterified (free) fatty acid and ketone body levels were significantly decreased in both groups by the infusion of exogenous insulin, but the sensitivity of lipolysis was impaired in patients with sepsis. In conclusion, sepsis impaired to a varying extent the action of insulin on endogenous glucose production, glucose utilization, lipolysis and ketogenesis. Whole-body glucose uptake was the most affected, with a total lack of response to the elevated insulin levels obtained in this study. Suppression of endogenous glucose production and lipolysis could only be achieved with higher doses of insulin than those required in normal subjects.

INTRODUCTION

Stress, such as injury or sepsis, has long been known to induce abnormalities in glucose metabolism [1]. The metabolic response to stress, including impaired carbohydrate metabolism and increased use of lipids as oxidative fuel, is mainly associated with ‘insulin resistance’, and is to a large extent mediated by an overproduction of counter-regulatory hormones and cytokines [2,3]. Most studies in injured patients have centred on describing the alterations in glucose utilization and oxidation [4–13]. Few studies have investigated abnormalities in endogenous glucose production and fat metabolism in sepsis. These studies have shown that...
endogenous glucose production (EGP) was elevated, and was resistant to the usual suppression by hyperglycaemia and hyperinsulinaemia [4,6,8,11]. Only pharmacological plasma insulin levels suppressed EGP [10]. Conversely, glucose utilization was greater than in healthy volunteers under basal conditions [10], but was not stimulated by glucose or insulin infusion. However, the validity of these studies is limited, since the response to insulin was usually evaluated in a few subjects at different points in different patients, and not completely in the same subjects [7,12]. Moreover, insulin sensitivity was often measured during hyperglycaemic clamp. The plasma glucose level, in itself, changes glucose utilization and production [14]. To our knowledge, no study has investigated the response to insulin of glucose and fat metabolism without modification of the plasma glucose level.

The aim of the present study was to quantify the changes in the insulin sensitivity of EGP and fat metabolism in patients with severe sepsis. In order to achieve this goal, we established in normal subjects and in patients with severe sepsis dose–response curves of changes in glucose production and plasma fatty acid and ketone body concentrations in response to progressive increases in plasma insulin concentration, while glucose levels were maintained at the respective basal level of each group.

**MATERIALS AND METHODS**

**Subjects**

This study was performed in accordance with the principles of the Declaration of Helsinki. After approval by the local ethical committee on human investigation, informed consent was obtained from five normal volunteers and from the families of five patients with sepsis hospitalized in an intensive care unit.

All normal subjects (five males; 25–38 years old) were within 10% of their ideal body weight (71.8 ± 2.4 kg). No subject was taking any medication or had a personal or family history of diabetes mellitus. All patients had stable body weight and had followed their usual diet before the study.

The individual characteristics of the patients with sepsis are shown in Table 1. All were in good health before their acute illness and were within 20% of their ideal body weight (Metropolitan Life Insurance Co.). None had a personal history of diabetes. Sepsis was established by the presence of three of the following criteria: increased body temperature (38.5 °C), leucocyte count of > 8 x 10^9 cells/l, bacteraemia, and the presence of abdominal suppuration. The sepsis score [15] and severity of illness score (IGS1) [16] were established on the day the study was performed. All patients were intubated and mechanically ventilated with positive end-expiration pressure (< 8 cmH₂O). They were haemodynamically stable throughout the entire study period and had not received dopamine or any other vasoactive drug for 6.7 ± 2.7 days (5–10 days) (Table 1). All patients demonstrated normal renal (creatininaemia < 200 μmol·l⁻¹) and liver (prothrombin time, 69.8 ± 5.5%; total bilirubin, 14 ± 3 mol·l⁻¹) function (Table 1). The study was performed 12.4 ± 8.9 days (5–30 days) after admission to the intensive care unit.

**Materials**

D-[6,6-²H]Glucose (99% atom % excess ²H) was obtained from CEA (Gif sur Yvette, France). Chemical and isotopic purity was confirmed by GC-MS. D-[6,6-²H]Glucose was diluted with sterile isotonic NaCl and tested for pyrogens before administration. Aliquots of tracer were collected at the end of each test to check the concentration and to calculate the actual infusion rate. Insulin (Actrapid HM; Novo, Copenhagen, Denmark) was dissolved in sterile isotonic NaCl containing 2% (w/v) human serum albumin.

**Procedures**

**General procedures**

All tests were initiated between 08.00 and 09.00 hours after a 12-h fast in healthy subjects and an 8-h fast in
patients with sepsis. They were performed over a 500-
min period, and isotopes were infused throughout.
During the first 140 min (T0; basal period), isotopes
alone were infused. D-[6,6-3H]Glucose was infused at a
rate of 0.22 μmol min⁻¹·kg⁻¹ after a priming dose of
17.8 μmol·kg⁻¹ in the basal state (T0) and during the first
dose of insulin (T1), and at a rate of 0.56 μmol·min⁻¹·
kg⁻¹ after a priming dose of 26.6 μmol·kg⁻¹ during the
last two doses of insulin (T2 and T3). Throughout the
final 360 min, insulin was infused at three different rates,
for 120 min each (T1, 140–260 min; T2, 260–380 min;
T3, 380–500 min), following a priming intravenous bolus
dose calculated using the method of Rizza et al. [17].
Insulin was infused using a Precidor pump (Bioblock
Scientific, Strasbourg, France). During insulin infusion,
the plasma glucose concentration was clamped at the
basal level for each patient by variable glucose infusion
[20 % (w/v) glucose; Aguettant, Lyon, France] delivered
by an artificial pancreas (Biostator GCIIS II; Miles
Laboratory, Frankfurt, Germany) and an additional
peristaltic pump (Dubernard Hospital, Bordeaux,
France). KH₂PO₄ (40 mmol K⁻¹ glucose) was added to
prevent hypokalaemia and hypophosphataemia. Blood
was collected before initiating the test and during each
insulin infusion period for various determinations. The
amount of glucose infused was calculated every 10 min,
and the results from the final 30 min of each insulin
infusion period were used for the calculations of glucose
kinetics.

Healthy subjects
Tests were performed in the post-absorptive period.
Three Teflon IV catheters were inserted: two into the
veins of one forearm for blood glucose analysis by an
artificial pancreas and for the different infusions, and one
into a vein of the contralateral hand for intermittent
sampling of arterialized blood. This hand was kept in a
hot blanket (60°C) to collect arterialized blood. Insulin
was infused at rates of 0.4 (T1), 1 (T2) and 2 (T3)
m-units·min⁻¹·kg⁻¹.

Patients with sepsis
Tests were also initiated between 08.00 and 09.00 hours,
8 h after replacement of parenteral nutrition by an
intravenous infusion of isotonic saline. All patients had
been on total parenteral nutrition before the study, and
during the preceding 24 h they had received total par-
enteral nutrition providing 130 % of basal energy re-
quirements (carbohydrates 60 %, lipid 40 % and a
caloric/nitrogen ratio of 150). A Teflon IV catheter was
inserted into a vein of one forearm for blood glucose
analysis by an artificial pancreas. Insulin, glucose, pot-
assium and isotopes were infused throughout a central
venous catheter. Blood samples were withdrawn via an
arterial catheter. Insulin was infused at rates of 0.5 (T1),
1 (T2) and 2 (T3) m-units·min⁻¹·kg⁻¹.

Analytical methods
Plasma glucose, lactate, acetoacetate and D-β-hydroxy-
butyrate concentrations were determined in neutralized
 perchloric acid extracts of plasma by enzymic methods,
as described previously [18]. ‘Ketone bodies’ refers to
the sum of acetoacetate and D-β-hydroxybutyrate.
Plasma non-esterified (‘free’) fatty acids (NEFA) were
measured by an enzymic method [19], and plasma levels
of immunoreactive insulin [20], glucagon [21], C-peptide
[22] and cortisol [23] were measured by RIA. Plasma
noradrenaline, adrenaline and dopamine levels were
measured by HPLC [24]. The isotopic enrichment of
plasma glucose was determined using the bisbutyl-
borate acetate derivative of the glucose and GC-MS
techniques [25]. Glucose appearance (Rₕ) and disap-
pearance (Rₚ) rates at the end (the last 30 min) of the basal
and each insulin infusion period were calculated using
steady-state equations (Figure 1). EGP was calculated by
subtracting the rate of infusion of exogenous glucose
from the isotopically determined rate of glucose ap-
pearance. The rate of glucose clearance was calculated by
dividing its rate of uptake (rate of disappearance) by its
corresponding plasma concentration.

Statistical analysis
Results are expressed as means ± S.D. Both inter-group
and intra-group differences were analysed by two-way
ANOVA followed by Newman–Keul’s procedure to
identify the differences. Inter-group comparisons were
performed by unpaired Student’s t test. A P value of
< 0.05 was considered significant.

RESULTS

Baseline data
Hormone and metabolite concentrations in the basal
state for the control subjects and the patients with sepsis
are shown in Tables 2 and 3. Plasma glucose and lactate
levels were significantly higher in patients with sepsis
than in control subjects. Plasma NEFA and ketone body

![Figure 1 Changes in plasma isotopic enrichment in patients
with sepsis](image)
levels were not different. In patients with sepsis, all hormone values were higher than normal reference values, except for insulin (Table 3). In control subjects, we only measured plasma insulin and glucagon levels (Table 2). EGP was increased in patients with sepsis, but this did not reach the level of significance (Table 2; Figure 2). There were no significant differences in glucose utilization or glucose clearance rate between the groups (Table 2; Figure 3).

**Isoglycaemic/hyperinsulinaemic clamp**

During the infusion of graded doses of insulin, plasma glucose was maintained at a level similar to the basal value both in control subjects (4.32 ± 0.22 mmol·l⁻¹) and in patients with sepsis (7.10 ± 2.29 mmol·l⁻¹). Plasma glucose levels during the clamp were different between groups (P < 0.05) (Figure 2). When insulin was infused at an increasing rate, steady-state plasma insulin concentrations were comparable in the two groups during T1 (control subjects, 28.3 ± 6.7 m-units·l⁻¹; patients with sepsis, 39.2 ± 12.1 m-units·l⁻¹) and T2 (60 ± 11.1 and 69.9 ± 11.1 m-units·l⁻¹ respectively), but they differed (P < 0.05) during T3 (102 ± 13.4 and 124.8 ± 19.7 m-units·l⁻¹ respectively) (Figure 2). In both groups, plasma glucagon concentrations remained at levels similar to basal values (within the range of normal values in healthy subjects) throughout the hyperinsulinaemic clamp. The rate of exogenous glucose infusion required for the maintenance of plasma glucose at the basal level during these sequential insulin infusions was significantly different between groups (P < 0.001) and between periods (P < 0.0001) (Figure 2).

During the first infusion period, EGP was completely suppressed in control subjects, while it remained at 40% of basal EGP in patients with sepsis (P < 0.05), despite a higher insulin infusion rate (0.5 compared with 0.4 m-unit·min⁻¹·kg⁻¹) (Figure 2). In patients with sepsis, EGP was suppressed during the second insulin infusion period (1 m-unit·min⁻¹·kg⁻¹), but reappeared during the last period (2 m-units·min⁻¹·kg⁻¹). In patients with sepsis, the insulin level that totally suppressed EGP was 105 m-units·l⁻¹ [calculated from the linear relationship (y = 3.204 − 0.030x)], and half-suppression of the initial value measured was obtained with a plasma insulin concentration of 47.4 m-units·l⁻¹.

In control subjects, glucose utilization increased significantly (P < 0.001) with each increase in the infusion rate of exogenous insulin. In contrast, in patients with sepsis, glucose utilization did not increase during the infusion of exogenous insulin, even at a rate of 2 m-units·min⁻¹·kg⁻¹ (Figure 3). Accordingly, the glucose clearance rate increased significantly in control subjects (P < 0.01), while it did not increase in patients with sepsis.

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**Table 2** Basal hormone and metabolite concentrations in control subjects and in patients with sepsis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control subjects</th>
<th>Septic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (mmol·l⁻¹)</td>
<td>3.80 ± 0.23</td>
<td>6.89 ± 2.27**</td>
</tr>
<tr>
<td>Plasma lactate (µmol·l⁻¹)</td>
<td>372 ± 54</td>
<td>1833 ± 1401*</td>
</tr>
<tr>
<td>Plasma NEFA (µmol·l⁻¹)</td>
<td>225 ± 51</td>
<td>397 ± 213</td>
</tr>
<tr>
<td>Plasma ketone bodies (µmol·l⁻¹)</td>
<td>82 ± 47</td>
<td>146 ± 64</td>
</tr>
<tr>
<td>Plasma insulin (m-units·l⁻¹)</td>
<td>12.0 ± 6.7</td>
<td>14.6 ± 5.0</td>
</tr>
<tr>
<td>Plasma glucagon (ng·l⁻¹)</td>
<td>374 ± 255</td>
<td>129 ± 24*</td>
</tr>
<tr>
<td>EGP (µmol·min⁻¹·kg⁻¹)</td>
<td>12.71 ± 1.67</td>
<td>19.51 ± 8.67</td>
</tr>
<tr>
<td>Glucose clearance rate (ml·min⁻¹·kg⁻¹)</td>
<td>3.30 ± 0.49</td>
<td>2.89 ± 1.01</td>
</tr>
</tbody>
</table>

**Table 3** Plasma hormone concentrations during the four test periods in patients with sepsis

<table>
<thead>
<tr>
<th>Hormone</th>
<th>110–140 min (T0)</th>
<th>230–260 min (T1)</th>
<th>350–380 min (T2)</th>
<th>470–500 min (T3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucagon (ng·l⁻¹)</td>
<td>343 ± 213</td>
<td>353 ± 222</td>
<td>310 ± 254</td>
<td>273 ± 222</td>
</tr>
<tr>
<td>Cortisol (nmol·l⁻¹)</td>
<td>1751 ± 1730</td>
<td>1682 ± 1930</td>
<td>1647 ± 2007</td>
<td>1780 ± 2431</td>
</tr>
<tr>
<td>Noradrenaline (ng·l⁻¹)</td>
<td>1327 ± 1129</td>
<td>1458 ± 1466</td>
<td>1364 ± 1461</td>
<td>1810 ± 1999</td>
</tr>
<tr>
<td>Adrenaline (ng·l⁻¹)</td>
<td>190 ± 200</td>
<td>184 ± 320</td>
<td>174 ± 206</td>
<td>343 ± 505</td>
</tr>
<tr>
<td>Dopamine (ng·l⁻¹)</td>
<td>168 ± 231</td>
<td>221 ± 371</td>
<td>206 ± 355</td>
<td>335 ± 589</td>
</tr>
</tbody>
</table>
Insulin sensitivity in patients with sepsis

Figure 2  Changes in plasma insulin concentration, plasma glucose levels, exogenous glucose infusion and EGP

Values are given for control subjects (empty bars) and for patients with sepsis (shaded bars) during the basal period (T0) and the three insulin infusion periods (T1, T2 and T3). Values are means ± S.D. Differences between groups are indicated by: *P < 0.05, **P < 0.01, ***P < 0.001. The plasma insulin level differed between infusion rates (P < 0.001) in both groups; at T3 the plasma insulin concentration in patients with sepsis was higher than that in control subjects (P < 0.05). Plasma glucose levels were not different from basal values in either group, but differed between groups (P < 0.05). The rate of infusion of exogenous glucose differed between the groups, increased significantly in the control group (P < 0.001), and did not rise in the septic group. EGP decreased significantly in both groups (P < 0.001), and was different between groups at T1 (P < 0.05).

(Figure 3). Plasma lactate levels did not increase during the test period in septic patients (Figure 3), whereas they rose significantly in control subjects (from 372 ± 54 to 738 ± 59 μmol·l⁻¹) (P < 0.0001).

Figure 4 shows the changes in plasma NEFA and ketone body concentrations during the test period in control subjects and in patients with sepsis. All of these metabolites decreased significantly in both groups as the rate of infusion of exogenous insulin increased (NEFA, P < 0.01; ketone bodies, P < 0.003). In control subjects, plasma NEFA and ketone bodies were at their minimum concentrations during the first insulin infusion period, whereas in patients with sepsis the lowest values were not obtained until the second (ketone bodies) or the third (NEFA) periods. In patients with sepsis, the insulin level totally suppressing NEFA release was 120 m-units·l⁻¹, [calculated from the linear relationship (y = 441.803 −3.683x)], and half-suppression of the initial value measured was obtained at a plasma insulin concentration of 66 m-units·l⁻¹. For ketone bodies, suppression of release occurred at a plasma insulin concentration of 136 m-units·l⁻¹, and half-suppression at 64 m-units insulin·l⁻¹ (y = 137.140 −1.007x).

Figure 3  Changes in glucose utilization, glucose clearance rate and plasma lactate levels

Values are given for control subjects (empty bars) and for patients with sepsis (shaded bars) during the basal period (T0) and the three insulin infusion periods (T1, T2 and T3). Values are means ± S.D. Differences between groups are indicated by: *P < 0.05, **P < 0.01, ***P < 0.001. Glucose utilization and plasma lactate levels increased significantly in control subjects (P < 0.001), but did not increase in septic subjects. The glucose clearance rate rose significantly in control subjects (P < 0.01), but did not increase in patients with sepsis.
DISCUSSION

In the present study, we investigated the effects of increased plasma insulin levels on EGP, glucose utilization and lipolysis in patients with severe sepsis. The sensitivity of EGP and lipolysis to insulin was diminished in patients with sepsis, as EGP and lipolysis could only be suppressed by high doses of insulin. Glucose utilization and the glucose clearance rate were not stimulated by exogenous insulin even at the highest infusion rate.

EGP

In our patients with sepsis, in spite of hyperglycaemia, basal EGP was higher (+53.7%) than in normal subjects. The difference did not reach statistical significance, probably owing to large standard deviations. This elevation was probably due to the sepsis, because these results are similar to those observed in other studies in septic or injured subjects [4,5,8,10,11,13] showing an increase in EGP of approx. 50–200%. However, in the present study, since the patients with sepsis were older than the healthy subjects (44–65 compared with 25–38 years), we cannot eliminate the effect of aging, which could exaggerate glucose intolerance following stress. However, whatever the age of the subjects, the effect of stress on EGP is always found [26,27].

The sensitivity of EGP to insulin was decreased in septic patients. EGP could be totally suppressed in both groups, but the plasma insulin concentration required for a half-maximal effect was higher in patients with sepsis (47.4 m-units l⁻¹). To our knowledge, the insulin sensitivity of EGP in septic or injured patients had not been measured previously. However, Shangraw et al. [10,13] showed that EGP could be suppressed by pharmacological doses of insulin (plasma insulin concentrations of 736 and 1298 m-units l⁻¹). The sensitivity of EGP to insulin in normal subjects could not be calculated in the present study, because it was totally suppressed by the first rate of exogenous insulin infusion (plasma insulin concentration of 28.3 m-units l⁻¹). In a previous study, we found that the insulin level for half-suppression of EGP was 10.9 m-units l⁻¹ when glucagon secretion was suppressed by somatostatin, and 15.2 m-units l⁻¹ in a test when glucagon was replaced at normal levels [28]. This latter value is similar to the values found by Nurjhan et al. [29]. In the study of Rizza et al. [17], the concentration of insulin causing half-maximal suppression of glucose production was 29 m-units l⁻¹, and that for complete suppression of EGP was approx. 60 m-units l⁻¹. This suggests a shift of EGP to higher values for any insulin concentration in patients with sepsis.

During sepsis, the suppressive effect of insulin on EGP requires 1.5–3 times higher plasma insulin levels compared with the situation in normal subjects. Lastly, in all patients with sepsis, a sudden recovery of EGP was observed with the highest insulin infusion rate, as though EGP became insensitive to insulin. This rise is unexplained. The experimental artefact commonly obtained with use of the hyperinsulinaemic/euglycaemic clamp and tracer is the inverse phenomenon, with a negative EGP [28]. Moreover, in our study, plasma isotopic enrichment during the last two periods was greater than 1.5%, and the variations in plasma isotopic enrichment at the end of each period were minor. In clinical practice with patients with sepsis, one might be interested in the suppression of EGP with the aim of reducing gluconeogenesis and the use of amino acids, and therefore decreasing muscle catabolism. Only a pharmacological dose of insulin can achieve this goal [30,31], and studies should be conducted to demonstrate an improvement in patient outcome.

Glucose utilization

Basal values for glucose utilization were similar in the two groups, but glucose utilization and glucose clearance rate were not increased in patients with sepsis by the rise in insulin levels. Furthermore, plasma lactate levels did not increase during the test period in patients with sepsis. In our patients, we observed both a mild hyperlactataemia in the basal state and a lack of increase in lactate levels during the test period. Concerning the basal mild hyperlactataemia, this observation is common during sepsis in haemodynamically stable patients [32]. This could be interpreted as evidence of lactate overproduction due to the presence of occult cell hypoxia during sepsis. However, several observations refute this hypothesis and suggest lactate overproduction (increased
glycolysis or muscle catabolism) or a decrease in blood lactate clearance [32]. We suggest that the absence of an increase in the plasma lactate level following the increase in insulin concentration was due to the absence of an increase in glucose utilization during hyperinsulinaemic clamp.

In the presence of physiological plasma insulin concentrations, peripheral glucose uptake appears to have been insensitive to insulin, and remained near to basal levels. Our results differ from the findings of previous studies [4,6,7,9,10,12]: glucose uptake was impaired but glucose utilization still increased with glucose or insulin infusion, although it remained at lower levels than in normal subjects. However, in those studies the insulin concentration was higher than the highest plasma insulin level in our study (124.8 m-units l⁻¹·min⁻¹). The same was also true for EGP. The impairment of the action of insulin on lipolysis in patients with sepsis mainly by decreasing lipolysis and NEFA availability.

Plasma NEFA and ketone body concentrations change in line with the rates of lipolysis and ketogenesis respectively. Plasma NEFA and ketone body levels were not totally suppressed in patients with sepsis, as they were in normal subjects. Moreover, the insulin levels required to obtain significant decreases in NEFA and ketone body levels were higher in septic than in normal subjects. The half-suppression of NEFA release and ketogenesis in patients with severe sepsis was as sensitive to insulin as the half-suppression of EGP (half-maximal response at plasma insulin levels of 66 m-units l⁻¹·min⁻¹ for NEFA and 64 m-units l⁻¹·min⁻¹ for ketone bodies). To our knowledge, similar results have never been published previously. In control subjects, as for EGP sensitivity, we could not calculate the half-maximal and maximal insulin levels for the suppression of lipolysis or ketogenesis, since both were totally suppressed at the first rate of exogenous insulin infusion. However, it is well known that lipolysis is more sensitive to insulin than is EGP in normal subjects. Nurjhan et al. [29] showed that the plasma insulin concentration causing half-suppression of lipolysis was 13.4 m-units l⁻¹·min⁻¹, which was approx. 50% of the concentration that caused half-suppression of EGP. Therefore, as the insulin sensitivities for EGP and lipolysis were similar in patients with sepsis, sepsis would appear to impair the sensitivity of lipolysis to insulin more than that of EPG. The impairment of the action of insulin on lipolysis in patients with sepsis induces an increase in plasma NEFA levels. Such an increase is known to contribute to the overproduction of glucose in normal and obese subjects with Type II (non-insulin-dependent) diabetes [28,34] and to muscle insulin resistance in obese patients with Type II diabetes. Part of the maintained EGP in patients with sepsis, despite high plasma insulin levels, could be due to the elevation in NEFA in these patients. In such patients, EGP could be enhanced or maintained by the rise in plasma lactate levels. Indeed, lactate is a neoglucogenic precursor; however, Tappy et al. [35] found that the infusion of lactate failed to increase EGP in patients with sepsis, in contrast with its effect in healthy subjects. Lastly, as is well known [36], the increases in cortisol and catecholamine levels observed in our patients with sepsis and the inflammatory response to stress (cytokines) [37,38] may also contribute to the increased inhibition of insulin action.

With respect to ketogenesis in patients with sepsis, plasma ketone body concentrations were strongly positively correlated to plasma NEFA levels (r² = 0.783; P < 0.0001). As in normal subjects [39], insulin inhibited ketogenesis in patients with sepsis mainly by decreasing lipolysis and NEFA availability.

**Conclusions**

From the present study, we conclude that sepsis impairs the action of insulin on EGP, glucose utilization, lipolysis and ketogenesis. This impairment of insulin sensitivity differs depending on the tissue or metabolic pathway. Whole-body glucose uptake is the most affected, with decreases in both sensitivity and responsiveness to insulin. Maximal responses could be achieved for EGP and lipolysis in patients with sepsis, but the plasma insulin concentrations necessary to obtain half-maximal effects were higher. The insulin sensitivities of these two metabolic processes were similar in patients with sepsis, in contrast with the situation in normal subjects. This discrepancy between effects on different metabolic pathways has been noted previously during surgery [40], but not during sepsis or injury.

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