Adiponectin in glucose metabolism

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Early endotoxemia increases peripheral and hepatic insulin sensitivity in healthy humans

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Submitted
Abstract

Objective:
Sepsis-induced hypoglycemia is a well known, but rare event of unknown origin. In the present study we examined the mechanism of sepsis-induced hypoglycemia, focusing on hepatic and peripheral insulin sensitivity by using the model of human endotoxemia.

Methods:
Glucose metabolism was measured in 18 healthy male volunteers during two hyperinsulinemic (insulin levels of 100 and 400 pmol/L) euglycemic (5 mmol/L) clamps on two occasions: with or without LPS.

Results:
Hepatic insulin sensitivity, defined as a decrease in endogenous glucose production during hyperinsulinemia (100 pmol/L), was higher in the LPS group compared to the control group (P = 0.010). Peripheral glucose uptake was higher in both clamps after LPS compared to the control setting (P = 0.006 and 0.010). In the LPS group, during both clamps, there was a significant increase in the plasma concentrations of norepinephrine and cytokines.

Conclusions:
These data indicate that shortly (two hours) after administration of LPS, peripheral and hepatic insulin sensitivity increase. This may contribute to the hypoglycemia occurring in some patients with critical illness, especially in the setting of intensive insulin therapy.
Introduction

Sepsis and critical illness are associated with an acute and reversible state of insulin resistance, characterized by hyperglycemia. Hypoglycemia is also seen in critical illness, as an infrequent feature of early sepsis. In animal studies it is known that hypoglycemia is the consequence of a decreased glucose production combined with a relative stimulation of glucose disposal by selective macrophage-rich tissues, mostly by an insulin-independent mechanism. In humans, the pathophysiology of hypoglycemia during sepsis is unexplored. As hypoglycemia is a rare and suddenly occurring event, requiring immediate glucose infusion, controlled studies with stable isotopes are not possible. However, intravenous administration of Gram-negative bacterial lipopolysaccharide (LPS) induces a systemic inflammatory response mimicking many of the clinical features associated with sepsis and can be administered safely in a well-defined manner to produce well-controlled effects. Until now only few studies have actually measured aspects of whole body glucose metabolism in humans after administration of LPS. The study by Bloesch et al. showed a significant decrease in plasma glucose concentration, two hours after LPS injection, followed by hyperglycemia. The decrease in glucose concentrations was ascribed to both a decrease in endogenous glucose production rate (rate of appearance of glucose/Ra) as well as an increase in peripheral glucose uptake (rate of disappearance/Rd) although the changes in Ra and Rd of glucose did not match in time with the short lasting drop in plasma glucose concentrations. Agwunobi et al. reported a significant increase in glucose infusion rate during a hyperinsulinemic euglycemic clamp two hours after a LPS bolus which they ascribed to an increase in peripheral glucose disposal. However since they did not use isotopes to measure glucose fluxes, this explanation for their findings remains an assumption. Critical illness is characterized by insulin resistance, influencing the normal balance between glucose production and uptake. An aspect of the pathophysiology of hypoglycaemia in early sepsis could be increased insulin sensitivity. This is especially relevant because it is more or less daily practice that severely ill patients, admitted to the ICU, receive intensive insulin therapy to achieve euglycemia and start almost immediately with feeding, resulting in exogenous and endogenous hyperinsulinemia respectively.

As no data on insulin sensitivity in early sepsis in humans exist we studied glucose metabolism, with the use of stable isotopes, during a hyperinsulinemic (100 pmol/L and 400 pmol/L) euglycemic (5 mmol/L) clamp, in healthy male volunteers, after LPS administration and in a control setting.
Subjects and Methods

Subjects
18 healthy, non-smoking, male volunteers were included (Table 1). None of them used medication, had an infection in the preceding three months, was obese (defined as a BMI > 25 kg/m²) or had a positive family history of diabetes. All volunteers had normal plasma values of fasting glucose, erythrocyte sedimentation rate, complete blood count, lipid profile, creatinine and liver enzymes and all had a normal oral glucose tolerance test according to the American Diabetes Association criteria 10. The study was approved by the Medical Ethical Committee of the Academic Medical Center in Amsterdam and all subjects gave written informed consent.

Protocol (Figure 1)
Volunteers (n= 18) were studied during euglycemia (5 mmol/L) either during a plasma insulin level of 100 pmol/L or an insulin level of 400 pmol/L. We chose a lower and higher insulin level to study hepatic and peripheral insulin sensitivity respectively. In the control group volunteers (n=6) were studied twice, i.e. during both clamps. Since we considered it not feasible to administer LPS twice to the same subjects, six volunteers underwent the clamp aimed at an insulin level of 100 pmol/L and six other volunteers underwent the clamp aimed at an insulin level of 400 pmol/L.

For 3 days prior to the study, all volunteers consumed approximately 250 g of carbohydrates and were asked to refrain from vigorous exercise. The present study was part of a study on the differential effects of plasma glucose and insulin concentrations on several parameters relevant for critical ill patients 11-13. The data on glucose metabolism in the present study have not been published earlier.

At 0745 h in the LPS group and at 0845 h in the control group a catheter was inserted into an antecubital vein for infusion of [6,6-2H₂]glucose, insulin, somatostatin, glucagon, glucose and LPS. (The difference in time was due to a slight difference in study protocol). Another catheter was inserted retrogradely into a contralateral hand vein kept in a thermoregulated (60 °C) plexiglas box for sampling of arterialized venous blood. At T = 0:00 h (15 minutes after insertion of the catheters) a blood sample was drawn for determination of background enrichment of plasma glucose. Thereafter a primed-continuous infusion of [6,6-2H₂]glucose (prime 8.0 μmol/kg; continuous 0.11 μmol•kg⁻¹•min⁻¹; >98 % pure and >99 % enriched, ARC Laboratories BV, Apeldoorn, The Netherlands) together with somatostatin (250 μg/h; Somatostatine-ucb, UCB Pharma BV, Breda, the Netherlands), glucagon (1 ng·kg⁻¹·min⁻¹; GlucaGen, Novo Nordisk, Alphen a/d Rijn, the Netherlands),
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insulin (Actrapid, Novo Nordisk, Alphen a/d Rijn, the Netherlands) at a rate of 10 or 40 mU/m² body surface area (BSA)•min⁻¹ (aimed for plasma insulin concentration of 100 pmol/L or 400 pmol/L respectively) and glucose (10 or 20 %) at a variable rate to maintain euglycemia (5 mmol/L), were started and continued for 6 hours in the control group and for 8 hours in the LPS group. [6,6-²H₂]glucose was added to the variable glucose to minimize changes in the achieved plasma isotopic enrichment of ~1 %.

At T = 3:00 h (after three hours of clamping) purified, lyophilized, LPS (Escherichia coli lipopolysaccharide, lot G, United States Pharmacopeial Convention, Rockville, MD) was administered to the LPS group by IV bolus (4 ng/kg) after reconstitution in sterile water for injection.

Analytical procedures
Plasma glucose was measured every five minutes at bedside from T = 0:00 until T = 6:00 in the control and until T = 5:00 in the LPS group. From T = 2:20 until T = 3:00 and from T = 5:20 until T = 6:00 in the control group and from T = 2:20 until T = 3:00 and T = 4:20 until T = 5:00 in the LPS group five samples were drawn for measurement of glucose

Figure 1. Experimental design for the clamp studies in the control and the LPS group. T = 0:00 h is 0800 h in the LPS group and 0900 h in the control group. gray arrow = control and LPS group; white arrow = LPS group; black arrow = control group

Figure 1. Experimental design for the clamp studies in the control and the LPS group. T = 0:00 h is 0800 h in the LPS group and 0900 h in the control group. gray arrow = control and LPS group; white arrow = LPS group; black arrow = control group
enrichment. The results of the glucose enrichments will be presented as mean of the five samples at T = 3:00 and at T = 5:00 (in the LPS group) or T = 6:00 (in the control group).

Glucagon, insulin, cortisol, (nor)epinephrine, FFA and total adiponectin were measured at T = 3:00 and T = 6:00 in the control group and at T = 3:00 and T = 5:00 in the LPS group.

Interleukin (IL)-6, IL-8, IL-10 and Tumor necrosis factor (TNF)-α were measured at T = 6:00 in the control group and at T = 5:00 in the LPS group.

Plasma glucose concentrations were measured with the glucose oxidase method using a Beckman Glucose Analyzer 2 (Beckman, Palo Alto, CA) with intra-assay variation of 2-3%. Insulin and cortisol were determined on an Immulite 2000 system (Diagnostic Products Corporation, Los Angeles, CA). Insulin was determined with a chemiluminiscent immunometric assay, intra-assay variation 47 pmol/L 6%, 609 pmol/L 3%; inter-assay variation 91 pmol/L 4%, 120 pmol/L 6%. The detection limit was 15 pmol/L. Cortisol was determined with a chemiluminiscent immunoassay, intra-assay variation 89 nmol/L 8%, 500 nmol/L 7%; inter-assay variation 136 nmol/L 8%, 1092 nmol/L 7%; detection limit 50 nmol/L. Glucagon and adiponectin were determined by RIA (Linco Research, St. Charles, MO). Glucagon: intra-assay variation 71 ng/L 10%, 147 ng/L 9%, inter-assay variation 84 ng/L 5%, 192 ng/L 7%, detection limit 15 ng/L. Adiponectin: intra-assay variation 3.0 μg/mL 2%, 8.5 μg/mL 7%; inter-assay variation 3.4 μg/mL 16%, 10.1 μg/mL 17%; detection limit 1 μg/mL. Norepinephrine and epinephrine were determined by an in-house HPLC method. Norepinephrine: intra-assay variation 3.54 nmol/L 2%; inter-assay variation 0.52 nmol/L 10%, 4.97 nmol/L 10%; Epinephrine: intra-assay variation 0.36 nmol/L 9% inter-assay variation 0.31 nmol/L 18%, 2.51 nmol/L 14%, detection limit 0.05 nmol/L. FFA were measured by an enzymatic method (NEFAC; Wako chemicals GmbH, Neuss, Germany), intra-assay variation 0.22 mmol/L 1%, 0.93 mmol/L 1%, inter-assay variation 0.10 mmol/L 15%, 0.48 mmol/L 4%, detection limit 0.01 mmol/L.

TNF-α, IL-6, IL-8 and IL-10 were measured by cytometric beads array (CBA) multiplex assay (BD Biosciences, San Jose, CA): detection limit 2.5 pg/mL.

[6,6-2H2]glucose enrichment was measured as described before 14. For the enrichment the intra- and inter assay variation was below 1 % at all levels.

Calculation and statistics
Ra and Rd of glucose were calculated using the modified form of the Steele equations for non-steady state measurements as described previously 15. Endogenous glucose production (EGP) was calculated as the difference between Ra glucose and glucose


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infusion rate. The change of EGP, Rd and glucoregulatory hormones during the 100 pmol/L and the 400 pmol/L clamp (T= 6.00 compared to T=3.00 in the control group and T = 5:00 compared to T = 3:00 in the LPS group) were calculated and expressed as the relative (%) difference.

Volunteer characteristics were compared using a Kruskal-Wallis test. For cytokines single values, measured during the 100 pmol/L and the 400 pmol/L clamp (T= 6.00 in the control group and T = 5:00 in the LPS group), were compared. All results were compared between the LPS and the control group using the Mann-Whitney U test. Data are presented as median [range]. Probability values of < 0.05 were considered statistically significant. SPSS statistical software version 12.0.1 (SPSS Inc, Chicago, IL) was used to analyze the data.

Results

Subjects characteristics (Table 1)
There were no differences between the groups.

Table 1. Volunteer characteristics

<table>
<thead>
<tr>
<th></th>
<th>control group</th>
<th>LPS group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 and 400 pmol/L (n=6)</td>
<td>100 pmol/L (n=6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>22 [22 - 23]</td>
<td>23 [20 -25]</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.7 [64 - 77.3]</td>
<td>70.1 [66.7 - 74.2]</td>
</tr>
<tr>
<td>Length (cm)</td>
<td>186 [172 - 190]</td>
<td>180 [168 - 186]</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>21.7 [21 - 23.4]</td>
<td>22.0 [19.9 - 23.6]</td>
</tr>
</tbody>
</table>

Data are expressed as median [range]

Glucose kinetics during the 100 pmol/L clamp in the control and the LPS group (Figure 2)
Euglycemia was obtained during all clamps. At T = 3:00 (just before LPS administration) glucose concentrations, EGP and Rd in the control and the LPS group were similar (P = 0.805, 0.749 and 0.262 respectively). In the control subjects between T=3:00 and T=6:00 EGP decreased with 55% [38 – 65 %] from 10.0 μmol•kg⁻¹min⁻¹ [6.0 – 16.3] to 4.2 μmol•kg⁻¹min⁻¹ [2.9 – 7.3] (P = 0.028) and Rd increased with 5 % [-2 – 39 %] from 28.2 μmol•kg⁻¹min⁻¹ [18.1 – 33.5] to 31.0 μmol•kg⁻¹min⁻¹ [25.0 – 34.5] (P = 0.046).

In the LPS treated subjects between T=3:00 and T=5:00 EGP decreased with 82 % [62 – 89 %] from 8.9 μmol•kg⁻¹min⁻¹ [4.9 – 17.8] before LPS administration to 1.5 μmol•kg⁻¹min⁻¹ [0.9 – 2.4] (P = 0.003) and Rd increased with 9 % [-10 – 44 %] from 25.3 μmol•kg⁻¹min⁻¹ [12.2 – 38.5] to 28.1 μmol•kg⁻¹min⁻¹ [16.0 – 44.5] (P = 0.008).
two hours after LPS and Rd increased with 75 % [35 – 95 %] from 21.4 μmol•kg^{-1}min^{-1} before LPS [14.9 – 36.9] to 35.4 μmol•kg^{-1}min^{-1} after LPS [20.2 – 64.8] (both \(P = 0.028\)).

In the LPS group the relative decrease in EGP and the relative increase in peripheral glucose disposal were significantly higher compared to those values in the control group (\(P = 0.010\) and 0.006, respectively).

Glucose kinetics during the 400 pmol/L clamp in the control and the LPS group (Figure 2)

Euglycemia was obtained in all clamps. At \(T = 3:00\) glucose concentration, EGP and Rd in the control and the LPS group were similar (\(P = 0.572, 0.102\) and 1.000 respectively). In the control group EGP and Rd remained similar between \(T = 3:00\) and \(T = 6:00\) (0.3 μmol•kg^{-1}min^{-1} [0.0 – 3.4] vs. 0.3 μmol•kg^{-1}min^{-1} [0.0 – 3.8] and 54.1 μmol•kg^{-1}min^{-1} [44.0 – 67.2] vs. 58.4 μmol•kg^{-1}min^{-1} [51.9 – 66.5] (\(P = 0.593\) and 0.248 respectively)).

In the LPS group between \(T = 3:00\) and \(T = 5:00\) EGP was unaffected: 2.9 μmol•kg^{-1}min^{-1} [0.0 – 5.3] before vs. 2.0 μmol•kg^{-1}min^{-1} [0.0 – 5.0] two hours after LPS (\(P = 0.593\) and 0.248 respectively))

Figure 2. Endogenous glucose production (EGP) and peripheral glucose uptake (Rd) during either a 100 pmol/L or a 400 pmol/L euglycemic (5 mmol/L) clamp. Results are expressed as relative changes in EGP and Rd from \(T = 3:00\) to \(T = 6:00\) in the control (= black blocks) and to \(T = 5:00\) in the LPS (= white blocks) group, - signifies the median. * \(P < 0.05\)
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0.500). Rd increased significantly from 55.1 μmol•kg⁻¹min⁻¹ [40.0 – 71.3] before vs. 80.2 μmol•kg⁻¹min⁻¹ [66.9 – 115.4] two hours after LPS (P = 0.028). This change was significantly higher compared to that in the control group: + 53 % [16 – 108 %] vs. + 12 % [-11 – 35 %] (P = 0.010).

Glucoregulatory hormones during the 100 pmol/L and 400 pmol/L clamp in the control and the LPS group (Table 2)

During the 100 pmol/L clamp at T = 3:00 there was no difference (P values not shown) between the control and the LPS group in plasma concentrations of respectively: insulin (pmol/L): 93 [80 – 123] versus 96 [62 – 122]; total adiponectin (μg/mL): 4.8 [4.2 -7.7] versus 7.2 [4.6 – 11.5]; FFA (mmol/L): 0.02 [0.02 – 0.03] versus 0.02 [0.02 – 0.09]; norepinephrine (nmol/L): 1.14 [0.46 – 10.2] versus 0.73 [0.49 – 1.07]; epinephrine (nmol/L): 0.06 [0.05 – 0.21] versus 0.08 [0.05 – 0.09]; glucagon (ng/L): 63 [42 – 102] versus 50 [21 –81] and cortisol (nmol/L): 199 [73 – 355] versus 170 [54 – 295].

During the 100 pmol/L clamp, after administration of LPS, there was a significant increase in norepinephrine compared to the control group (Table 2).

During the 400 pmol/L clamp at T = 3:00 there was no difference (P values not shown) between the control and the LPS group in plasma concentrations of respectively: insulin (pmol/L): 436 [332 – 463] versus 307 [277 – 483]; total adiponectin (μg/mL): 5.6 [2.9 -8.0] versus 6.6 [6.1 – 11.8]; FFA (mmol/L): 0.02 [0.02 – 0.05] versus 0.02 [0.02 – 0.03]; norepinephrine (nmol/L): 0.77 [0.42 – 1.76] versus 0.69 [0.41 – 0.82]; epinephrine

Table 2. Relative (%) changes of the glucoregulatory hormones during the 100 pmol/L and the 400 pmol/L euglycemic (5 mmol/L) clamps from T = 6.00 compared to T = 3.00 in the control group and T = 5.00 compared to T = 3.00 in the LPS group

<table>
<thead>
<tr>
<th></th>
<th>100 pmol/L control</th>
<th>100 pmol/L LPS</th>
<th>P</th>
<th>400 pmol/L control</th>
<th>400 pmol/L LPS</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (pmol/L)</td>
<td>3 [-28 - 16]</td>
<td>-35 [-100 - 35]</td>
<td>0.078</td>
<td>-1 [-3 - 14]</td>
<td>-19 [-27 - 15]</td>
<td>0.004</td>
</tr>
<tr>
<td>Total adiponectin (μg/mL)</td>
<td>-6 [-16 - 2]</td>
<td>-2 [-9 - 9]</td>
<td>0.145</td>
<td>-5 [-10 - 0]</td>
<td>-1 [-10 - 3]</td>
<td>0.171</td>
</tr>
<tr>
<td>FFA (mmol/L)</td>
<td>0 [33 - 0]</td>
<td>0 [0 - 50]</td>
<td>0.056</td>
<td>0 [33 - 0]</td>
<td>0 [0 - 50]</td>
<td>0.176</td>
</tr>
<tr>
<td>Norepinephrine (nmol/L)</td>
<td>-16 [-63 - 54]</td>
<td>295 [21 - 607]</td>
<td>0.006</td>
<td>2 [-44 - 73]</td>
<td>241 [117 - 1407]</td>
<td>0.004</td>
</tr>
<tr>
<td>Epinephrine (nmol/L)</td>
<td>0 [-17 - 17]</td>
<td>181 [35 - 638]</td>
<td>0.053</td>
<td>0 [-44 - 133]</td>
<td>98 [0 - 720]</td>
<td>0.107</td>
</tr>
<tr>
<td>Glucagon (ng/L)</td>
<td>-7 [-21 - 29]</td>
<td>-21 [-36 - 24]</td>
<td>0.150</td>
<td>-11 [-23 - 3]</td>
<td>-7 [-62 - 10]</td>
<td>0.784</td>
</tr>
<tr>
<td>Cortisol (nmol/L)</td>
<td>21 [31 - 221]</td>
<td>229 [100 - 780]</td>
<td>0.150</td>
<td>34 [50 - 106]</td>
<td>126 [76 - 283]</td>
<td>0.144</td>
</tr>
</tbody>
</table>

Data are expressed as median [range], n=6 per group.
(nmol/L): 0.08 [0.05 – 0.14] versus 0.07 [0.05 – 0.14]; glucagon (ng/L): 59 [52 – 92] versus 52 [32 - 71]; cortisol (nmol/L): 163 [115 – 287] versus 252 [142 – 306].

During the 400 pmol/L clamp, in the LPS group, there was a significant decrease in plasma insulin concentration and a significant increase in plasma norepinephrine concentration compared to the control group (Table 2).

Cytokines during the 100 pmol/L and the 400 pmol/L clamp in the control and the LPS group (Table 3)

During the 100 pmol/L and the 400 pmol/L clamp all cytokines were significantly higher in the LPS group compared to the control group.

### Table 3. Plasma cytokines concentrations during the 100 pmol/L and the 400 pmol/L euglycemic (5 mmol/L) clamps in the control (T = 6:00 h) and the LPS (T = 5:00 h) group

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>100 pmol/L Control</th>
<th>100 pmol/L LPS</th>
<th>p</th>
<th>400 pmol/L Control</th>
<th>400 pmol/L LPS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF-α (pg/ml)</td>
<td>3 [3 - 302]</td>
<td>10002 [4055 - 38158]</td>
<td>0.003</td>
<td>3 [3 - 173]</td>
<td>10610 [6266 - 19583]</td>
<td>0.003</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>3 [3 - 498]</td>
<td>2556 [1962 - 10555]</td>
<td>0.003</td>
<td>5 [3 - 34]</td>
<td>2948 [1809 - 4868]</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-8 (pg/ml)</td>
<td>13 [9 - 755]</td>
<td>3278 [2162 - 4378]</td>
<td>0.004</td>
<td>10 [7 - 460]</td>
<td>3143 [2181 - 4304]</td>
<td>0.004</td>
</tr>
<tr>
<td>IL-10 (pg/ml)</td>
<td>3 [3 - 28]</td>
<td>53 [37 - 76]</td>
<td>0.003</td>
<td>3 [3 - 15]</td>
<td>69 [24 - 300]</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are expressed as median [range], n=6 per group.

### Discussion

In early sepsis hypoglycemia is an infrequent feature followed by hyperglycemia in the later stages. The pathophysiological mechanism, especially underlying the hypoglycemia, is still unknown and can not be investigated in clinical sepsis since it has to be corrected instantaneously. In the present study, we show that administration of LPS, which serves as a validated model to mimic the clinical presentation of bacterial sepsis, results in an increase of peripheral and hepatic insulin sensitivity. Our data on EGP and Rd during insulin clamps extend prior assumptions that the decrease in plasma glucose concentration two hours after LPS is due to an increased Rd as well as a decrease in EGP.

The decrease in EGP is a phenomenon found previously in animal studies. Theoretically this decrease could be caused by either a depletion of glycogen or a decrease in gluconeogenesis and/or glycogenolysis. The explanation may be either due to a lack of substrate (such as alanine), a change in activity of glucose transporters in hepatocytes or an acute inhibition of enzymes involved in these processes. Although decreased
expression of genes encoding for important gluconeogenetic enzymes, such as PEPCK and G6Pase, has been reported after long term exposure to LPS this seems less likely in our acute experiments 18, 19.

The increased Rd can be the result of an increase in insulin and/or non-insulin mediated glucose uptake. In rodents it has been shown that LPS directly induces an increased non-insulin mediated glucose uptake by macrophage-rich tissue. However, indirect stimulation of glucose uptake via an increase in LPS-induced circulating factors with insulin like properties, such as cytokines can not be ruled out 3. As expected, in our study, after the administration of LPS, all plasma cytokines were significantly higher compared to the control group. The role of these inflammatory mediators is still controversial. On the one hand TNF-α, IL-6, IL-8 and IL-10 are associated with insulin resistance, which hampers peripheral glucose uptake 20-22. On the other hand infusion of TNF-α and IL-6 is known to enhance Rd of glucose, indicating that a possible role for these mediators can not be ruled out 23-26. However, since the infusion of IL-6 has previously shown to increase EGP, whereas TNF-α did not affect EGP, these factors can not fully explain the increased insulin sensitivity found in our study 25, 26.

Although adiponectin is known as a hormone with insulin-like properties 23, this adipocytokine unlikely plays a role in the enhanced insulin sensitivity found in the present study, as the change in plasma adiponectin levels did not differ between the LPS and the control group. The increased norepinephrine lead to insulin resistance and therefore can not explain the increased Rd nor the decreased EGP in the LPS group 27, 28.

A potential confounding factor in our study might be the one hour difference in insulin exposure between the LPS and the control group. It is known that prolongation of insulin infusion results in a decreased EGP and an increased Rd 29. The results of our study, however, show the opposite: in the group with the longest duration of insulin infusion (the control group), during both clamps, suppression of EGP was less and Rd was lower compared to the group with the shorter duration of insulin infusion (the LPS group).

Another distorting factor might be the lower plasma insulin concentrations during the 400 pmol/L clamp in the LPS group. However, this does not contradict our conclusion, as if the insulin concentrations in the LPS group would have been similar to the control group, the differences in Rd and EGP between groups would probably have been even more pronounced.

In conclusion, in extension to earlier studies, the results of our study show that, two hours after administration of LPS, peripheral and hepatic insulin sensitivity increase. This is of particular importance because, nowadays, most severely ill patients admitted to the ICU receive intensive insulin therapy to achieve euglycemia and start on feeding very early
on, resulting in exogenous and endogenous hyperinsulinemia respectively. This clinical setting in combination with the increased biological effects of insulin during LPS induced sepsis may put the patients at risk for developing hypoglycaemia and in fact may explain the incidence of hypoglycaemia seen in septic patients during intensive insulin treatment \(^8\). Unravelling the mechanism through which LPS establishes this effect seems helpful in treating patients by stabilizing glucose metabolism in sepsis.

Acknowledgments
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Reference List


