Epidural blockade improves substrate utilization after surgery

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Schricker, Thomas, Linda Wykes, and Franco Carli. Epidural blockade improves substrate utilization after surgery. Am J Physiol Endocrinol Metab 279: E646–E653, 2000.—The purpose of this study was to test the hypothesis that epidural blockade with local anesthetics improves the antitacatabolic effects of glucose after colorectal surgery. Sixteen patients were randomly assigned to undergo a 6-h stable isotope infusion study (3 h fasted, 3 h glucose infusion at 4 mg·kg⁻¹·min⁻¹) on the second postoperative day with or without perioperative epidural blockade. Protein synthesis, breakdown and oxidation, and glucose production and clearance were assessed by L-[1-¹³C]leucine and [6,6-²H₂]glucose. Epidural blockade did not affect protein and glucose metabolism in the fasted state. Glucose infusion increased glucose clearance (P < 0.05), accompanied by an increase in the respiratory quotient (P < 0.05) and a decrease in leucine oxidation (P < 0.05) only in the presence of epidural blockade. An inverse correlation (r = −0.74, P < 0.05) between changes in glucose clearance and leucine oxidation was observed. In conclusion, epidural blockade facilitates whole body glucose uptake and inhibits endogenous protein oxidation after abdominal surgery, indicating a shift from a protein to a more glucose-dominated substrate utilization.

Glucose administration at a higher rate fails to further inhibit glucose production in surgical patients but results in an increase in glucose oxidation and a more pronounced decrease of urea synthesis, an indirect parameter of protein catabolism (31). It has therefore been postulated that once enough glucose is given to achieve the maximal inhibition of gluconeogenesis the justification of administering higher doses resides in the ability of the body to oxidize the infused glucose. Hence, provision of energy and thereby minimizing the amount of amino acids oxidized for energy production has been regarded as a second mechanism responsible for the protein-preserving effect of glucose in critically ill patients.

Although provision of adequate quantities of glucose, either alone or as part of total parenteral nutrition, attenuates the protein losses via an increase in whole body protein synthesis, the elevated rate of protein catabolism continues unaltered (32). This limited effectiveness of nutritional support has been attributed to the nonsuppressibility of gluconeogenesis by glucose administration and to the impaired capacity of stressed patients to oxidize glucose, which is given in excess of the amount required for most efficient suppression of gluconeogenesis. Only one-half of the glucose infused at 4 mg·kg⁻¹·min⁻¹ is directly oxidized after surgical or accidental trauma, and this percentage even fell when glucose was administered in higher doses (32, 36).

The fact that even vigorous nutritional support fails to entirely curtail protein catabolism after trauma and during sepsis has led to the investigation of various pharmacological approaches. Infusion of insulin, the body’s key endocrine regulatory factor to promote protein anabolism, ameliorates protein losses in critically ill patients (2, 26). To overcome perioperative insulin resistance, however, insulin has to be administered in high doses (26). At the same time, provision of excessive amounts of glucose is required to maintain normoglycemia. This issue raises potential metabolic concerns because high carbohydrate intake causes fatty infiltration of the liver (12) and stimulates carbon dioxide production (1).
Because pain has been regarded as a potent trigger for the catabolic response to surgery, manipulation of the stress response by different analgesic techniques represents a more direct pharmacologic approach to modify protein catabolism. It is well established that blockade of nociceptive and nonnociceptive pathways, such as the sympathetic nervous system, by epidural local anesthetics improves nitrogen balance (34), attenuates the rise in whole body protein breakdown (7), and prevents the decrease of muscle protein synthesis after surgery (4). These results, however, were exclusively obtained in patients receiving perioperative parental feeding with impact on all aspects of protein and glucose economy.

The aim of this project was to test the hypothesis that the anticyclic effects of parenteral administration of glucose can be enhanced by epidural blockade with local anesthetics, initiated before and maintained after colorectal surgery. To gain an integrated insight into protein and glucose metabolism, dynamic changes in protein breakdown, amino acid oxidation, protein synthesis, glucose production, and glucose clearance were assessed by using stable isotope tracer kinetics in the fasted and fed state.

**METHODS**

**Patients**

The study was approved by the Ethics Committee of the hospital, and informed consent was obtained from all patients. Sixteen patients with localized nonmetastatic adenocarcinoma of the rectosigmoid colon scheduled for elective colorectal surgery were admitted to the study (Table 1). None of the patients suffered from cardiac, hepatic, renal, or metabolic disease. No subject had developed recent weight loss or had a plasma albumin concentration <35 g/l. The patients were allocated according to a computer-generated randomization schedule to an epidural group (EDA group) receiving perioperative epidural blockade with bupivacaine and fentanyl (n = 8) or a control group receiving postoperative patient-controlled analgesia (PCA) with intravenous morphine (n = 8).

**Anesthesia and Surgical Care**

At arrival in the anesthetic room, the patients in the EDA group assumed a sitting position, and an epidural catheter was inserted at one of the thoracic vertebral levels between T10 and T12. Neural blockade was initiated with 0.5% bupivacaine to achieve a bilateral sensory block to ice and pin prick from thoracic dermatome level four (T4) to sacral dermatome level five (S5). The block was maintained during the operation with boluses of 0.25% bupivacaine. General anesthesia in both groups was induced with intravenous thiopentone and was maintained with 35% nitrous oxide in oxygen and isoflurane. Fentanyl (3 μg/kg) was administered in the control group before surgical incision. All operations were carried out by the same surgeon and at the same time of the day (from 1100 to 1400). Patients in both groups received hypocaloric nutritional supplementation with glucose from 0800 to 2000 on the first postoperative day (100 ml/h 5% glucose equivalent to ~250 kcal) followed by infusion of 0.9% NaCl (100 ml/h) until the study period.

Sensory blockade from T4 to L5 covering the 10- to 15-cm paramedian subumbilical incision was postoperatively maintained in the EDA group by continuous epidural infusion of 0.1% bupivacaine supplemented with 2 μg/ml fentanyl. In the control group, pain relief was achieved by PCA with intravenous morphine. The incremental dose of morphine was 1–2 mg, lockout was 8 min, and dose duration was 30 s. Postoperative pain intensity was estimated using a 10-cm visual analog scale (VAS from 0 = no pain to 10 = worst pain imaginable). Pain treatment in both groups was adjusted to obtain a VAS score at rest below four. Patients in both groups were asked by the ward nurse to rise in bed, sit on the bed, and stretch the lower limbs.

**Glucose Infusion**

After a 3-h period of fasting, a solution of crystallized beet sugar (10% dextrose anhydrous; Avebe, Foxhol, Holland) was infused at 4 mg·kg<sup>-1</sup>·min<sup>-1</sup> for 3 h. The solution was prepared by the local pharmacy under sterile conditions and was tested for sterility, stability, and absence of pyrogens before intravenous infusion. The beet dextrose solution was chosen because of its low 13C content and therefore the lack of significant perturbation of 13CO<sub>2</sub> enrichment in expired air (6).

**Experimental Protocol**

Plasma kinetics of leucine and glucose were determined by a primed constant infusion of tracer quantities of 1-[1-<sup>13</sup>C]leucine (99% 13C) and [6,6-<sup>2</sup>H<sub>2</sub>]glucose (99% <sup>2</sup>H) obtained from Cambridge Isotope Laboratories (Cambridge, MA). Before each infusion study, sterile solutions of isotopes were prepared in the hospital pharmacy and were kept at 4°C until administration.

All tests were performed in the fasted state beginning at 0800 on the second postoperative day. The patients were studied in a temperature- and humidity-controlled environment (24°C, 35–42% relative humidity). A superficial vein in the dorsum of the hand was cannulated, and the cannula was kept patent with 2 ml·kg<sup>-1</sup>·h<sup>-1</sup> saline. A second superficial vein in the contralateral arm was cannulated to provide access for the infusion of the stable isotopes. Blood and expired air samples were collected before the infusion to determine baseline enrichments. Priming doses of 1 μmol/kg NaH<sub>13</sub>CO<sub>3</sub>, 4 μmol/kg 1-[1-<sup>13</sup>C]leucine, and 22 μmol/kg [6,6-<sup>2</sup>H<sub>2</sub>]glucose were administered and followed immediately by continuous infusions of 0.06 μmol·kg<sup>-1</sup>·min<sup>-1</sup> 1-[1-<sup>13</sup>C]leucine and 0.8 μmol·kg<sup>-1</sup>·min<sup>-1</sup> [6,6-<sup>2</sup>H<sub>2</sub>]glucose.

<table>
<thead>
<tr>
<th>Table 1. Biometric and clinical data of patients</th>
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<tr>
<td>Control</td>
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<tr>
<td>Sex (male/female)</td>
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<td>Age, yr</td>
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<td>Height, cm</td>
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<td>Weight, kg</td>
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<td>ASA (I/II)</td>
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<td>Preoperative fasting, min</td>
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<td>Surgery (n)</td>
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<td>Duration of surgery, min</td>
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Values are means ± SD; n, no. of patients. ASA: American Society of Anesthesiology.
13C]leucine lasting 6 h. [6,6-2H2]glucose was infused at a rate of 0.22 μmol · kg⁻¹ · min⁻¹ during the first 3 h (fasted period) and then was changed to 0.44 μmol · kg⁻¹ · min⁻¹ during the 3 h of glucose administration. Toward the end of each 3-h study period, four blood and expired breath samples were collected at 10-min intervals. Each blood sample was transferred immediately to a heparinized tube, centrifuged at 4°C (3,000 g, 15 min), and stored at −70°C. Breath samples were collected in a 2-l latex bag and transferred immediately to 20-ml vacutainers. A schematic representation of the protocol is shown in Fig. 1.

Gaseous Exchange

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed in the last hour of the fasted and fed state. The subjects were lying in a semirecumbent position (20°), breathing room air in the ventilated hood, for 20 min on each occasion. Oxygen consumption (V̇O₂) and carbon dioxide production (VCO₂) were measured, and the respiratory quotient (RQ) was calculated. An average value of V̇O₂, VCO₂, and RQ was taken, with a coefficient of variation <10%.

Analytical Methods

Isotopic enrichments. Plasma α-[1-13C]ketoisocaproate (α-KIC) enrichment was determined by electron-impact-select-ion-ion monitoring gas chromatography-mass spectrometry using the method previously described by Mamer and Montgomery (21), except that t-butyldimethylsilyl rather than trimethylsilyl derivatives were prepared. Expired 13CO₂ enrichment was determined by isotope ratio-mass spectrometry (Analytical Precision AP2003, Manchester, UK; see Ref. 28). Plasma glucose was derivatized to its penta-acetate compound, and the [6,6-2H₂]glucose enrichment was determined by gas chromatography-mass spectrometry using electron-impact ionization (27). In each analysis run, duplicate injections were always performed, and their means were taken to represent enrichment.

Plasma metabolites and hormones. Plasma glucose was measured by a glucose oxidase method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Plasma lactate assay was based on lactate oxidase and was performed using the synchron CX 7 system (Beckman Instruments). Circulating concentrations of cortisol, insulin, and glucagon were measured by sensitive and specific double-antibody RIAs (Amersham International, Amersham, Bucks, UK).

Calculations

When a physiological and isotopic steady state exists, the rate of appearance (Rₐ) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (APE or atom percentage excess) calculated by

$$R_a = \left( \frac{APE_{inf}}{APE_{pl}} - 1 \right) \times F$$

where F is the infusion rate of the labeled tracer (μmol · kg⁻¹ · min⁻¹), APEₐ is the tracer enrichment in the infused state, and APEₚ is the tracer enrichment in plasma. The APE used in this calculation was the mean of the four APE determined during steady-state conditions obtained at each phase of the studies. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of values above their mean, expressed as coefficient of variation. A coefficient of variation <5% was used as a confirmation of a valid plateau.

Under steady-state conditions, leucine flux (Q) is defined by the formula

$$Q = S + O = B + I$$

where S is the rate at which leucine is incorporated into body protein, O is the rate of oxidation of leucine, B is the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown, and I is the rate of leucine intake, including tracer and diet. In the postabsorptive state, the sole source of the essential amino acid leucine for protein synthesis and oxidation is that derived from the breakdown of endogenous proteins. Inspection of Eq. 2 indicates that, when studies are conducted after absorption, leucine flux is equal to leucine breakdown (22). Plasma enrichment of α-[1-13C]KIC during infusion of 1-[1-13C]leucine has been used as the basis for calculating both flux and oxidation of leucine (29). This steady-state reciprocal-pool model is considered to provide a more precise representation of intracellular precursor pool enrichment than leucine itself (29). In the calculation of oxidation, factors of 0.76 for the fasting state and 0.81 for the fed state were applied to account for the fraction of 13CO₂ released from leucine but retained within slow turnover rate pools of the body (22).

In the fasted state, the glucose Rₐ was equal to the endogenous production of glucose. During glucose infusion, endogenous glucose production was calculated by subtracting the glucose infusion rate from the total glucose Rₐ. In the physiological steady state, whole body glucose uptake equals the rate of endogenous glucose production. Because glucose uptake increases proportionally as blood glucose concentrations rise, changes in whole body glucose uptake do not necessarily reflect corresponding changes in the tissue's ability to take up glucose. This may be because most glucose uptake occurs in non-insulin-sensitive tissues, and the rate of uptake is to a large extent determined by the diffusion gradient for glucose. Thus the rate of glucose uptake has to be corrected for the prevailing plasma glucose concentration. The resulting value, the glucose clearance rate, represents an index of the ability of tissues to take up glucose. The plasma clearance rate of glucose was calculated as glucose Rₐ divided by the corresponding plasma glucose concentration.

Statistics

All data are presented as means ± SD. Comparisons for each dependent variable were performed using two-factorial ANOVA with the factors epidural blockade and glucose infusion. ANOVA for repeated measurements was applied to...
analyze any significant change in the plasma concentrations of metabolic substrates (glucose, lactate) and hormones (cortisol, insulin, glucagon) during glucose administration. If no significant change was detected between the two measurements obtained in the fasted state and after 120 and 180 min of glucose infusion, the two average values were compared. The relationships between leucine Ra and glucose Ra in the postabsorptive state and between changes in glucose clearance and leucine oxidation during glucose administrations were evaluated by the correlation coefficient. Statistical significance was accepted at P < 0.05.

RESULTS

Patients

There were no differences between the two groups regarding sex, age, height, and weight of patients. Preoperative fasting time and duration of surgery were also similar in both groups. Estimated blood loss never exceeded 400 ml, and no patient received blood transfusion. The average VAS at rest obtained 12 and 24 h after surgery and at the beginning of the infusion study on the second postoperative day was similar in the two groups (PCA group: 1.4 ± 0.8 cm; EDA group: 1.1 ± 0.6 cm). On the first postoperative day, patients in both groups were able to sit on the bed, but none of the patients could leave the bed for a walk.

Stable Isotope Kinetics

In all experiments, a plateau in the enrichments of plasma α-[1-13C]KIC, [6,6-2H2]glucose, and expired 13CO2 was achieved in the fasted and fed state (coefficient of variation <5%), permitting the use of the steady-state equation.

Epidural blockade had no significant effect on whole body protein synthesis, breakdown, leucine oxidation, glucose production, and glucose clearance in the fasted state (Table 2). A weak but significant correlation between leucine Ra and glucose Ra could be observed (r = 0.59, P < 0.05; Fig. 2).

Administration of glucose suppressed endogenous glucose production to a similar extent in both groups (P < 0.001) but did not significantly affect leucine Ra or protein synthesis. Glucose infusion decreased leucine oxidation in the EDA group (P < 0.05) without significant influence in the control patients. Glucose clearance did not change significantly in the control group but increased in patients with epidural blockade (P < 0.05), indicating improved insulin sensitivity. There was a significant inverse correlation between the changes in leucine oxidation and glucose clearance (r = −0.74, P < 0.05; Fig. 3).

Metabolites and Hormones

Epidural blockade had no significant influence on circulating concentrations of metabolic substrates and hormones in the fasted state (Table 3). Plasma concentrations of metabolites and hormones obtained after 150 and 180 min of glucose infusion were not significantly different. Glucose administration increased the plasma glucose and insulin concentration (P < 0.001), whereas plasma concentrations of lactate, glucagon, and cortisol remained unchanged.

Gaseous Exchange

V02, VCO2, and RQ were not significantly affected by epidural blockade in the fasted state (Table 4). Glucose infusion increased the RQ in the EDA group (P < 0.05) without exerting any significant effect on V02 and VCO2, V02, VCO2, and RQ did not change significantly in the control group.

DISCUSSION

The results of the present study indicate that epidural blockade with local anesthetics facilitates whole

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**Table 2. Kinetics of leucine and glucose metabolism in the fasted state and fed state**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Epidural</th>
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<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td>Leucine Ra, μmol·kg⁻¹·h⁻¹</td>
<td>120.6 ± 28.1</td>
<td>113.9 ± 29.2</td>
</tr>
<tr>
<td>Leucine oxidation, μmol·kg⁻¹·h⁻¹</td>
<td>17.2 ± 3.6</td>
<td>19.9 ± 4.1</td>
</tr>
<tr>
<td>Protein synthesis, μmol·kg⁻¹·h⁻¹</td>
<td>103.5 ± 27.1</td>
<td>94.0 ± 26.8</td>
</tr>
<tr>
<td>Glucose Ra, μmol·kg⁻¹·min⁻¹</td>
<td>11.35 ± 1.36</td>
<td>23.06 ± 1.53†</td>
</tr>
<tr>
<td>Endogenous glucose Ra, μmol·kg⁻¹·min⁻¹</td>
<td>11.35 ± 1.36</td>
<td>1.15 ± 2.25†</td>
</tr>
<tr>
<td>Glucose clearance, ml·kg⁻¹·min⁻¹</td>
<td>2.20 ± 0.44</td>
<td>2.94 ± 0.38</td>
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Values are presented as means ± SD. Ra, rate of appearance. Endogenous glucose Ra was calculated by subtracting the rate of exogenous glucose infusion from total glucose Ra. *P < 0.05 and †P < 0.001 compared with fasted state.

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Fig. 2. Correlation between leucine rate of appearance (Ra) and glucose Ra in the fasted state [leucine Ra = 4.975 + (0.051 × glucose Ra)], r = 0.59, P < 0.05]. ●, Control group; ○, epidural group.
Glucose, mmol/l 5.2

metabolites and hormones in the fasted and fed state

Table 3. Plasma concentrations of circulating metabolites and hormones in the fasted and fed state

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
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<th>Epidual</th>
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<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>5.2 ± 0.7</td>
<td>10.1 ± 1.9*</td>
<td>5.2 ± 0.5</td>
<td>9.8 ± 0.9*</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>0.9 ± 0.2</td>
<td>1.1 ± 0.4</td>
<td>1.2 ± 0.6</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Cortisol, pg/ml</td>
<td>254 ± 80</td>
<td>295 ± 81</td>
<td>282 ± 149</td>
<td>328 ± 186</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>115 ± 60</td>
<td>392 ± 185*</td>
<td>99 ± 18</td>
<td>268 ± 133*</td>
</tr>
<tr>
<td>Glucagon, pmol/l</td>
<td>25 ± 9</td>
<td>19 ± 16</td>
<td>27 ± 6</td>
<td>17 ± 5</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD. *P < 0.001 compared with fasted state.

Fig. 3. Correlation between changes in glucose clearance and leucine oxidation during glucose infusion [change in glucose clearance = 3.98 - (11.35 x change in leucine oxidation), r = −0.74, P < 0.05]. •, Control group; ◆, epidural group.

Body glucose uptake and decreases endogenous protein oxidation after abdominal surgery, indicating a shift from a protein to a more glucose-dominated substrate utilization. Epidural blockade, however, does not significantly alter endogenous glucose production and whole body protein catabolism in the fasted state. This finding appears to be in contrast to the widely held notion of beneficial effects of nociceptive blockade with local anesthetics upon postoperative protein and glucose metabolism such as improvement of nitrogen balance (34), blunting the fall in muscle fractional synthetic rate (4), and attenuation of the rise in whole body protein breakdown and oxidation after lower abdominal surgery (7). In addition, epidural local anesthetics have been shown to decrease glucose and urea production in patients after various surgical procedures (30). These studies, however, being exclusively conducted in patients receiving isocaloric and isonitrogenous parenteral nutrition, did not consider the hormonal and metabolic changes associated with fasting and feeding (33). Therefore, the impact of surgery and neural blockade might have been masked by greater changes resulting from nutritional factors. In an attempt to control for the potential metabolic impact of the patients’ nutritional status, the present study was undertaken in both postabsorptive and fed states. This study design also has been chosen because it has been demonstrated that epidural blockade does not influence protein economy after surgery when perioperative calorie intake is low (14) or absent (3). Thus the failure of epidural blockade to affect protein catabolism in the current study may well be explained by the minimal amount of calories administered on the first postoperative day and the absence of nitrogen in the diet, lending further support to the contention that the protein-sparing effect of epidural blockade requires adequate energy and nitrogen supply.

It has to be noted that mean postoperative leucine R\(_a\), glucose R\(_a\), and leucine oxidation rate in the fasted state were not elevated compared with values obtained in healthy volunteers after an overnight fast (28). This lack of difference can also be explained by the different nutritional status of postabsorptive subjects and fasting surgical patients. Patients who participated in the present study fasted for ~38 h before surgery (due to bowel preparation) and received only minimal amounts of glucose on the first postoperative day. It is well recognized that starvation causes a progressive fall in urinary nitrogen excretion accompanied by a decrease in the release of amino acids from the muscle and a decrease in whole body glucose production (19). Patients undergoing colorectal surgery, who were continuously fed starting 6 days before the operation until 4 days after surgery, showed higher rates of leucine breakdown and oxidation than patients in the present protocol (5). In contrast, protein kinetics in patients after abdominal surgery receiving perioperative hypocaloric nutrition were similar to those observed in this study (6).

A weak but significant correlation between leucine R\(_a\) and glucose R\(_a\) was observed in the fasted state, suggesting a direct relationship between whole body protein breakdown and glucose production. This assumption is supported by investigations in healthy volunteers (16) and surgical patients (30) reporting parallel changes in urea production, an indirect marker of protein catabolism, and whole body glucose production. Based on the results of these studies, it has been concluded that muscle protein is broken down to
provide gluconeogenic amino acids for de novo gluconeogenesis in the liver (35). Whole body glucose production is, depending on the metabolic state, composed (to a varying extent) of glycogenolysis and gluconeogenesis. The use of [6,6-2H2]glucose does not allow differentiation between the two metabolic pathways. Considering the long preoperative fasting period of the patients entering this study protocol and the fact that only little glucose was administered after surgery, it seems likely that the patient's glycogen stores were depleted. The results of a recent study show that gluconeogenesis accounts for almost all of the glucose produced after 42 h of fasting (9). Thus the rate of glucose production measured on the second day after colorectal surgery presumably was equivalent to gluconeogenesis.

The nitrogen-sparing effect of glucose is well documented in surgical patients and has been primarily ascribed to a decrease in urea production (32). Urea is synthesized in the liver when amino acids are deaminated, leaving the carbon skeleton for glucose production. It has been proposed that hepatic ureagenesis is inhibited either via suppression of gluconeogenesis or via reduction in the release of amino acids from peripheral tissues, resulting in a decrease in ureagenic amino-nitrogen supply to the liver (16, 23). Administration of glucose in the present study at 4 mg·kg⁻¹·min⁻¹ almost completely suppressed glucose production in all patients but did not affect protein breakdown, as reflected by the unchanged leucine Ra. This finding is consistent with previous observations in normal subjects and surgical patients that low-dose glucose administration causing a doubling of insulin concentration (similar to the insulin response in the present study) does not influence the degradation of peripheral protein (13, 20, 28). This does not, however, rule out the possibility that decreased mobilization of amino acids may be a major component of the nitrogen-sparing effect elicited by massive infusions of glucose and insulin. Infusion of exogenous insulin, which increases plasma insulin concentrations >150 μU/ml, blocks the release of muscle amino nitrogen (25), whereas insulin clamped at a plasma level of 80 μU/ml induces a marked decrease in whole body leucine breakdown (10).

Provision of energy and thereby minimizing the need of amino acid oxidation for energy coverage has been regarded as a second mechanism responsible for the protein-preserving effect of glucose during catabolic illness. It has been suggested that, once maximal inhibition of gluconeogenesis has been achieved, infused glucose will be oxidized to a greater extent (35). The validity of this hypothesis is further confirmed by the present results demonstrating a significant inverse correlation between changes in whole body glucose clearance and endogenous leucine oxidation. The significant increase in glucose clearance in patients with epidural blockade is accompanied by a decrease in leucine oxidation, although both parameters do not significantly change in the control group. This observation is in line with the previous notion that neural blockade with local anesthetics is able to normalize impaired glucose tolerance and insulin sensitivity during surgical stress (15, 17). Because no direct relationship exists between the ability of tissues to clear glucose from the blood and subsequent glucose oxidation (35) and absolute values of glucose oxidation were not obtained in the present study, the exact amount of glucose oxidation is not known. However, the calorigraphic data in patients with epidural blockade revealing a significant increase in the RQ during glucose infusion give indirect evidence that glucose oxidation increased.

It can therefore be concluded that the improvement of uptake and oxidative utilization of glucose by epidural blockade results in the inhibition of endogenous amino acid oxidation, leading to a better preservation of whole body nitrogen.

From the present study, it is difficult to ascertain the mechanisms involved in the modifying effects of epidural blockade upon glucose and protein metabolism in the fed state. The fact that glucose clearance was higher in the EDA group during glucose administration while the insulin response was unaffected indicates a greater insulin sensitivity. It remains questionable, however, if improved insulin sensitivity also was responsible for the suppression of leucine oxidation. Regarding the impact of insulin on endogenous protein oxidation, conflicting results have been provided in the literature reporting stimulatory (8), inhibitory (24), or no effects (11). Furthermore, a direct influence of increased glucose availability cannot be separated from the insulin response that is induced by hyperglycemia because the observed changes in protein and glucose metabolism during glucose administration can occur independently of the action of insulin. Urea production is suppressed to the same degree when insulin secretion is blocked by somatostatin as when insulin plasma concentration increases after 2 h of glucose infusion at 4 mg·kg⁻¹·min⁻¹ (37). Whole body glucose clearance and oxidation also rise regardless of whether insulin is held at the basal level or is allowed to change spontaneously (37).

Because our study protocol was not designed to dissect the biochemical factors responsible for the changes in postoperative substrate utilization in the EDA group, we can only speculate on the underlying endocrine mechanisms. Epidural blockade with local anesthetics has been frequently shown to suppress the cortisol and sympathoadrenergic response to abdominal surgery, thereby facilitating the antianabolic action of insulin (18). Thus the improvement of insulin sensitivity observed in the EDA group might have resulted from the inhibitory effect of epidural local anesthetics on the perioperative increase in the circulating levels of cortisol, epinephrine, and norepinephrine. Plasma catecholamine concentrations were not measured in the present study, and there was no significant difference in the plasma cortisol concentrations between the two groups, neither in the fasted nor in the fed state. It cannot be ruled out, however, that...
more frequent intra- and postoperative cortisol measurements could have revealed such a difference.

To optimize postoperative analgesia in the EDA group, a combined infusion of bupivacaine and fentanyl was administered in the present investigation. The effects of epidural opioids on the metabolic endocrine changes induced by surgical trauma have been demonstrated to be less pronounced compared with local anesthetics in spite of equivalent satisfactory pain relief (18). According to the results of several studies, epidural opioids in contrast to epidural local anesthetics failed to attenuate the hyperglycemic, sympathoadrenergic, and catabolic response to surgery (14, 18). Although a potential metabolic impact of epidural fentanyl cannot be entirely excluded in the current study, this effect was probably small.

In conclusion, epidural blockade established before and continued after abdominal surgery does not influence protein catabolism and glucose metabolism in the fasted state. Intravenous administration of glucose improves glucose uptake and spares body protein, as reflected by a decrease in endogenous protein oxidation only in the presence of epidural blockade.

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