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Postoperative Infusion of Amino Acids Induces a Positive Protein Balance Independently of the Type of Analgesia Used

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Background: **Net loss of body protein is a prominent feature of the catabolic response to surgical tissue trauma. Epidural analgesia with hypocaloric dextrose has been demonstrated to attenuate leucine oxidation but was unable to make protein balance positive. The current study was set to determine whether an infusion of amino acids on the second day after colon surgery would revert the catabolic state and promote protein synthesis while maintaining glucose homeostasis in patients receiving epidural analgesia as compared with patient-controlled analgesia with morphine (PCA).**

Methods: **Sixteen patients undergoing colorectal surgery were randomly assigned to receive epidural blockade or PCA as analgesic techniques and underwent a 6-h stable isotope infusion study (3 h fasted, 3 h fed) on the second postoperative day. Whole body glucose kinetics and protein turnover were measured using [6,6-$^{2}H_{2}$]glucose and l-[1-^{13}C]leucine as tracer.**

Results: **The infusion of amino acids caused a decrease in endogenous glucose rate of appearance in both groups ($P < 0.05$), with greater changes in the PCA group ($P < 0.05$). Administration of amino acids suppressed the appearance of leucine from protein breakdown in both groups ($P < 0.05$), although the decrease was greater in the PCA group ($P < 0.05$). Leucine oxidation increased in both groups ($P < 0.05$), with greater change in the epidural group ($P < 0.05$). Protein synthesis increased to the same extent in both groups ($P < 0.05$). Protein balance became positive after the infusion of amino acids, and the effect was greater in the PCA group ($P < 0.05$).**

Conclusions: **Infusion of amino acids decreased the endogenous glucose production and induced a positive protein balance independent of the type of anesthesia provided, although such effects were greater in the PCA group.**

STRATEGIES to preserve lean body mass after major surgery have targeted protein breakdown and amino acid oxidation as principal mechanisms inducing a catabolic state.[1,2] Manipulation of the endocrine response *per se*, either by inhibiting catabolic hormones such as catecholamines, cortisol, and glucagon or stimulating insulin and insulin-growth factors, has resulted in significant suppression of the catabolic response.[3,4] Neuraxial block of afferent and efferent stimuli (epidural analgesia) with local anesthetics, by decreasing the excretion of catabolic hormones and decreasing insulin resistance, has been shown to attenuate postoperative nitrogen excretion, to minimize the increase in whole body protein breakdown, and to arrest the decrease in muscle protein synthesis in patients receiving parenteral nutrition.[5–8]

Subsequent studies aimed at controlling the feeding regimen and assessing the effect of postoperative epidural analgesia on aspects of protein and glucose metabolism identified the necessity of providing sufficient nutritional substrate to manipulate effectively the catabolic state.[9–11] The studies were conducted on the second postoperative day after an overnight fasting and using a fasted and fed 6-h period to mimic the metabolic response associated with feeding. Stable isotopic methodology was chosen to determine the dynamic effect of feeding and to quantify the changes in glucose and protein metabolism.

In patients receiving epidural analgesia, but not patient-controlled analgesia (PCA), administration of hypocaloric dextrose suppressed the postoperative increase in amino acid oxidation but had no impact on whole body protein breakdown and synthesis.[11] In a subsequent study using the same methodology in which intravenous amino acids were supplied with dextrose, protein balance became positive and endogenous protein breakdown and glucose production decreased independent of the postoperative analgesia used (epidural *vs.* parenteral opioids).[10] Protein synthesis increased in both groups but was higher in the epidural group.

This series of studies, conducted under controlled feeding conditions, confirmed the modulatory role of epidural blockade on protein economy and glucose production and utilization.

Despite these positive results, administration of hypocaloric dextrose was associated with an increase in circulating blood glucose (average 10 mM). Acute hyperglycemia has been shown to be responsible for increased morbidity and mortality in both surgical and medical patients,[12–15] and therefore, it can be argued whether glucose should be used in the postoperative period.

Amino acids infusion in volunteers causes a decrease in whole body protein breakdown, and an increase in protein synthesis resulting in a positive protein balance

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despite an increase in oxidation.[16,17] In addition, endogenous glucose production (EGP) has been reported either to increase or to remain unchanged, indicating that amino acids can also be acting as substrate for gluconeogenic pathways.[18,19] Studies conducted in patients after major surgery and trauma showed that amino acid infusion stimulated protein synthesis, with a small decrease in endogenous glucose production.[20,21] This could imply that amino acids supplied might have been made available for synthetic rather than oxidative or gluconeogenic pathways.

The current study was designed to determine whether an infusion of amino acids on the second day after colon surgery in patients receiving either epidural or parenteral opioid analgesia would reverse the catabolic state and maintain glucose homeostasis.

Materials and Methods

Patients

Sixteen patients scheduled to undergo elective colon resection for benign and malignant lesions were studied between October 2004 and March 2005. Exclusion criteria were as follows: more than 20% loss of body weight in the past 6 months, evidence of metastatic disease, severe cardiac and respiratory diseases, diabetes and albumin below 35 g/l, and anemia (hemoglobin less that 100 g/l). The Ethics Committee of the McGill University Health Center, Montreal, Quebec, Canada, approved the study (REC#03-039), and informed consent was obtained from all patients. The patients were assigned to two groups, A (PCA) and B (epidural analgesia), using a computer-generated randomization schedule.

Anesthesia and Surgical Care

No premedication was administered. General anesthesia in both groups consisted of propofol, nitrous oxide in 40% oxygen, desflurane, fentanyl, and rocuronium. In group B, an epidural catheter was inserted between T9 and T11 before induction of general anesthesia. Neuraxial blockade was established with 15 ml bupivacaine, 0.5%, to achieve a bilateral sensory block (to ice and pinprick) from T4 to S5 and maintained with intermittent boluses of 5 ml bupivacaine, 0.25%, every hour.

At the end of surgery, analgesia in group A was maintained with PCA with intravenous morphine, adjusted to obtain a visual analog scale score less than 4 at rest (scale: 0 = no pain to 10 = worst pain imaginable). Group B received a continuous epidural infusion with a mixture of 0.1% bupivacaine and 2 μg/ml fentanyl administered at a rate between 8 and 15 ml/h with supplemental top-ups of 0.125% bupivacaine to maintain a sensory block from T7 to L3 and a visual analog scale score less than 4 at rest. In both groups, pain was assessed twice a day, at 8:00 AM and 8:00 PM.

During surgery, patients were kept normothermic, using a warming blanket spread over the body, and well hydrated with 0.9% isotonic sodium chloride solution infused at a rate of 6 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}. After surgery, patients received only clear fluids till the end of isotope infusion. Lactated Ringer's solution was infused at a rate of 1.7 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} as patients arrived in the ward. All fluid administration was stopped at the beginning of the isotope infusion.

Experimental Protocol

All patients were studied on the second postoperative day beginning at 8:00 AM. The protocol included two periods: a fasted state of 3 h followed by a 3-h fed state during which patients received a solution of 10% amino acids without electrolytes (Travasol; Baxter, Montreal, Canada) infused for 3 h at a rate of 0.02 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, equivalent to 2.9 g $\cdot$ kg^{-1} $\cdot$ day^{-1}.

The kinetics of whole body leucine and glucose were measured using an isotope dilution technique and the stable isotope tracers l-[1-^{13}C]leucine and [6,6-$^{2}H_2$]glucose (Cambridge Isotope Laboratories, Cambridge, MA). A superficial vein in the dorsum of the hand was cannulated, and the catheter was kept patent with heparinized saline to withdraw blood samples. A second catheter was placed in a vein of the contralateral arm to provide access for the infusion of the tracers. After collecting blood and expired-air samples to determine baseline enrichments, priming doses of $NaH^{13}CO_3$ (1 μmol/kg), l-[1-^{13}C]leucine (4 μmol/kg) and [6,6-$^{2}H_2$]glucose (22 μmol/kg) were administered and followed by a continuous infusion of L-[1-^{13}C]leucine (0.06 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) and [6,6-$^{2}H_2$]glucose (0.22 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}) for a total period of 6 h (3 h of fasted state and 3 h of fed state). During the latter period, the dose of L-[1-^{13}C]leucine was increased to 0.12 μmol $\cdot$ kg^{-1} $\cdot$ min^{-1}. Toward the end of the fasted and fed states, four blood and expired-air samples were collected at 10-min intervals to determine isotope enrichments. Blood samples for the analysis of plasma concentrations of glucose and hormones (cortisol, glucagon, and insulin) were collected once during each state, at 150 and 330 min into the isotopic infusion. Each blood sample was immediately transferred to a heparinized tube and centrifuged at 4°C (3,000 rpm for 15 min) and then stored at −70°C until analysis. Expired-air samples were collected in a 2-l latex bag and then transferred immediately to 10-ml tubes (Vacutainer; Becton Dickinson, Franklin Lakes, NJ) for carbon dioxide isotope enrichment analysis.

Whole body oxygen consumption and carbon dioxide production were measured using indirect calorimetry (Vmax 29N; SensorMedics, Yorba Linda, CA) in the last hour of the fasted and fed states. Measurements were performed for 20 min on each occasion, and average values of whole body oxygen consumption, carbon dioxide production, and calculated respiratory quotient

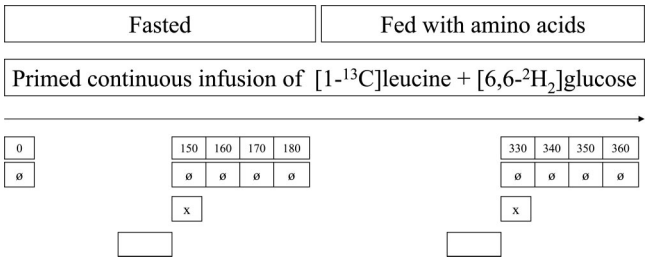

Fig. 1. Time course of the infusion of isotopes and collection of plasma and expired air samples (Ø) indirect calorimetry (*open rectangles*), and collection of plasma for the determination of metabolic substrates and hormones (x) in the fasted state and during the infusion of amino acids.

were calculated, with a coefficient of variation less than 10%. A graphic illustration of the study protocol is presented in figure 1.

Isotopic Enrichments

Plasma ketoisocaproate was analyzed to represent intracellular leucine enrichment, and it was determined by positive chemical ionization gas chromatography–mass spectrometry, as previously described.[11] Expired $^{13}CO_2$ enrichment was analyzed by means of isotope ratio mass spectrometry (Analytical Precision AP2003; Manchester, United Kingdom). Plasma glucose was derivatized to its penta-acetate compound, and the [6,6-$^2H_2$] glucose enrichment was determined by gas chromatography–mass spectrometry using electron impact ionization. In each analysis run, duplicate injections were performed, and their means of enrichment at four time points were taken to represent enrichment at isotopic steady state.

Plasma Metabolites and Hormones

Plasma concentration of glucose was measured by a glucose oxidase method using a glucose analyzer 2 (Beckman Instruments, Fullerton, CA). Circulating concentrations of insulin and glucagon were measured by sensitive and specific double-antibody radioimmunoassays (Amersham International, Bucks, United Kingdom). Cortisol plasma concentration was measured using the Ciba Corning ACS 180 automated immunoassay (Ciba Corning Diagnostic, East Walpole, MA).

Calculations

Whole body leucine kinetic was calculated by conventional isotope dilution practice using a two-pool stochastic model during steady state conditions, obtained at each study phase (fasted or fed). When an isotopic steady state exists, the rate of appearance (R_a) of a substrate in plasma can be derived from the plasma enrichment (atom percent excess [APE]) calculated by $R_a = (APE_{inf}/APE_{pl} - 1) \cdot F$, where F is the infusion rate of the labeled tracer ($\mu mol \cdot kg^{-1} \cdot min^{-1}$), APE_{inf} is the isotopic enrichment in the infusate, and APE_{pl} is the tracer enrichment in plasma at steady state. The APE value used in this calculation represents the mean of the APE values determined during each isotopic plateau. The accuracy of the isotopic enrichments at isotopic plateau was tested by evaluating the scatter of the APE values above their mean, expressed as a coefficient of variation. A coefficient of variation less than 5% was used as a confirmation of a valid plateau. Under steady state conditions, leucine flux (Q) is defined by the equation Q = S + O = B + I, where S is the rate at which leucine is incorporated into body protein, O is the rate of leucine oxidation, B is the rate at which unlabeled leucine enters the free amino acid pool from endogenous protein breakdown, and I is the rate of dietary intake or the rate of infusion of L-[1-^{13}C]leucine ($\mu mol \cdot kg^{-1} \cdot h^{-1}$) or both. Inspection of that formula indicates that, when studies are conducted in the postabsorptive state, flux is equal to breakdown. Enrichment of plasma ketoisocaproate during infusion of L-[1-^{13}C]leucine has been used to determine whole body leucine kinetics. During amino acid infusion, net leucine flux was calculated by subtracting the leucine infusion rate from the total R_a of leucine. This steady state reciprocal pool model is considered to represent the intracellular precursor pool enrichment more precisely than leucine itself.[22] In the calculation of oxidation, a factor of 0.76 was applied during the fasted state and accounts for the fraction of ^{13}C-carbon dioxide released from leucine but retained within slow turnover rate pools of the body. A factor of 0.92 was used for the fed state.[22]

In the fasted state, the R_a glucose was equal to the endogenous production of glucose. In the physiologic steady state, whole body glucose uptake equals the rate of endogenous glucose production. The glucose clearance, an index of the ability of the tissues to take up glucose, was calculated as R_a glucose divided by the corresponding plasma glucose concentration.

Sample Size and Statistical Analysis

Based on expected difference in protein balance of 5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ between the two groups (SD = 3 $\mu mol \cdot kg^{-1} \cdot min^{-1}$; power 80% and $P = 0.05$), a total of 16 patients was calculated to be sufficient.[10] All data are presented as mean ± SD. Analysis of dependent variables was performed using two-factorial analysis of variance with repeated measures. Significant effects induced by parenteral nutrition were assumed when P values for time dependency were less than 0.05. Influences by analgesic regimen were accepted as significant when the analgesic or the interaction term of the analysis of variance was less than 0.05.

Results

Demographic Characteristics and Clinical Data

Demographic characteristics and clinical data were similar in both groups (table 1). A plateau in the enrich-

Table 1. Patient Characteristics

	PCA	Epidural Analgesia
Number	8	8
Age, yr	59 ± 16	65 ± 14
Height, cm	165 ± 8	166 ± 7
Weight, kg	72 ± 14	68 ± 16
Sex, M/F	4/4	5/3
ASA physical status, I/II/III	3/5/0	2/5/1
Type of surgery		
Hemicolectomy/colectomy	4	5
Sigmoid resection	3	2
Anterior resection	1	1

Values are mean ± SD.

ASA = American Society of Anesthesiologists; PCA = patient-controlled analgesia.

ments of plasma [1-^{13}C]α-ketoisocaproate, expired ^{13}C-carbon dioxide, and [6,6-$^{2}H_2$]glucose was achieved in the fasted and fed states (coefficient of variation $< 5\%$), allowing the application of steady state equation to calculate glucose and protein kinetics.

Visual Analog Scale Score and Consumption of Analgesics

Pain scores at rest were similar between groups during the first and second day (table 2). Patients with epidural analgesia had a lower visual analog scale score on coughing during the first and second day than did patients with PCA (table 2). Consumption of bupivacaine, fentanyl, and morphine are reported in table 2.

Glucose and Leucine Kinetics

In the fasted state, endogenous R_a glucose was higher in the PCA group compared with the epidural group (table 3). The infusion of amino acids caused a decrease in endogenous R_a glucose in both groups, with greater changes in the PCA group (table 3). Glucose clearance decreased in both groups by more than 50%, and there was no difference between the two groups studied (table 3).

Rate of appearance of leucine (equivalent to protein breakdown in the fasted state) leucine oxidation, protein synthesis, and protein balance during the fasted state were similar in both groups (table 3). Administration of amino acids suppressed leucine appearance from protein breakdown in both groups, although the decrease was greater in the PCA group (table 3). Leucine oxidation increased in both groups, with greater change in the epidural group (table 3). Protein synthesis increased to a similar extent in both groups (table 3). Protein balance was negative in the fasted state and became positive during the infusion of amino acids (table 3). This net anabolic effect was greater in the PCA group (table 3).

Table 2. VAS Score and Consumption of Analgesics

	PCA	Epidural Analgesia
VAS score at rest, cm		
Day 1	3.6 ± 2.8	2.5 ± 2.6
Day 2	3.0 ± 2.1	2.4 ± 2.0
VAS score on coughing, cm		
Day 1	6.8 ± 2.4	3.8 ± 2.3*
Day 2	5.5 ± 2.2	3.6 ± 2.0*
Consumption of bupivacaine, mg		
Intraoperative		107 ± 7
Day 1		276 ± 72
Day 2		241 ± 66
Consumption of fentanyl, mg		
Day 1		0.55 ± 0.14
Day 2		0.48 ± 0.13
Consumption of morphine, mg		
Day 1	25.7 ± 19.9	
Day 2	19.4 ± 15.3	

Values are mean ± SD.

* $P < 0.05$.

PCA = patient-controlled analgesia; VAS = visual analog scale.

Glucose and Hormones

Circulating concentration of glucose during the fasted state was similar in both groups, and the small increase observed after the amino acid infusion was not significant (table 4).

During the fed state, plasma concentration of insulin and glucagon increased by the same magnitude, whereas no changes were observed in plasma cortisol and insulin/glucagon ratio (table 4).

Gaseous Exchange

Consumption of oxygen, production of carbon dioxide, and respiratory quotient were not affected by the infusion of amino acids in either group (table 5). Production of carbon dioxide was higher in the epidural group during both the fasted and fed states (table 5).

Discussion

The results of the current study indicate that the infusion of amino acids during the second postoperative day induced a positive protein balance, regardless of the type of analgesia provided, although balance was greater in the PCA group. At the same time, amino acid infusion decreased endogenous glucose production in both groups without affecting plasma glucose concentrations.

The data provided by the isotopic analysis allow us to dissect the different components of whole body protein metabolism and understand the principal metabolic mechanism governing protein economy. From the current findings, a 3-h infusion of amino acids, equivalent to 0.36 $g \cdot kg^{-1} \cdot day^{-1}$, during the second postoperative day, suppressed protein breakdown by more than 25%. Using leucine as a presentative amino acid, approximately 30–40% of the amino acids made available from proteolysis were oxidized, whereas 12–16% were redirected toward protein synthesis.

Table 3. Protein and Glucose Kinetics

	PCA		Epidural Analgesia		*P* Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
Endogenous R_a glucose, $\mu mol \cdot kg^{-1} \cdot min^{-1}$	15.19 ± 2.29	10.71 ± 1.25	12.5 ± 2.1	10.3 ± 1.1	< 0.0001	**0.019**	0.078
Glucose clearance, $ml \cdot kg^{-1} \cdot min^{-1}$	2.88 ± 0.77	1.14 ± 0.24	2.3 ± 0.3	1.1 ± 0.2	< 0.0001	0.083	0.067
R_a leucine, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	124.9 ± 12.4	143.9 ± 11.9	125.9 ± 10.4	161.3 ± 14.7	< 0.0001	0.038	0.058
Endogenous R_a leucine, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	124.9 ± 12.4	90.4 ± 11.9	125.9 ± 10.4	108.5 ± 15.5	< 0.0001	**0.042**	0.066
Leucin oxidation, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	17.9 ± 4.6	30.7 ± 6	17.1 ± 4.3	37.3 ± 3.4	< 0.0001	0.078	**0.028**
Protein synthesis, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	107 ± 11.7	113.2 ± 11.5	108.2 ± 8	124 ± 15.2	0.014	0.165	0.26
Protein balance, $\mu mol \cdot kg^{-1} \cdot h^{-1}$	−17.9 ± 4.6	22.8 ± 5.9	−17.7 ± 3.6	15.5 ± 3.4	< 0.0001	**0.033**	**0.025**

Values are mean ± SD.

* Probability that values are influenced by parenteral alimentation. For each variable, the difference has been tested between the means of the fasted states of the two groups and the means of the fed states of the two groups. † Probability that values are influenced by the type of analgesia whether nutrition was administered or not. For each variable, the differences have been tested between the means of the fasted and fed states of one group and the means of the fasted and fed states of the other group. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

PCA = patient-controlled analgesia; R_a = rate of appearance.

In a previous investigation using a similar protocol and infusing the same amount of amino acids supplemented by dextrose, at a rate of 4 $mg \cdot kg^{-1} \cdot min^{-1}$, it was found that protein balance was positive in both groups, but patients who received epidural analgesia had a slightly greater increase (27 $\mu mol \cdot kg^{-1} \cdot h^{-1}$) compared with patients treated with PCA (25 $\mu mol \cdot kg^{-1} \cdot h^{-1}$).[10] It was proposed that the greater insulin sensitivity in patients with epidural analgesia, as reflected by a greater increase in glucose clearance in these patients, could be responsible for such difference. Such difference was not evident in the current study, as shown by the same variation in glucose clearance in both groups. In addition, the modifications of the hormonal levels were the same whether patients had epidural or PCA. Therefore, it is not possible to explain the observed anabolic differences between the two analgesic techniques on the basis of the underlying hormonal mechanisms.

It has been shown consistently that epidural analgesia compared with intravenous opioid analgesia attenuates the postoperative nitrogen loss in patients undergoing upper abdominal surgery.[5,7,8] However, nitrogen balance cannot differentiate the contribution from changes in protein synthesis and in protein degradation. Therefore, it cannot provide any information about how changes in protein balance are achieved. In other studies conducted using the stable isotope technique, epidural analgesia was found to attenuate protein breakdown or decrease leucine oxidation.[6,11] These beneficial effects should be considered in relation to the type of nutritional support. In fact, in a previous study, conducted after an overnight fast and using the same measurement methodology, epidural analgesia attenuated postoperative protein breakdown without affecting protein synthesis, resulting in patients being in negative protein balance.[23] When dextrose was infused, epidural analgesia compared with PCA induced a decrease in leucine oxidation during the second postoperative day, but protein balance remained negative in both groups, with no differences between the analgesic techniques, indicating that hypocaloric amounts of dextrose could not reverse negative postoperative protein balance.[11]

To quantify the difference in magnitude in anabolism between nutritional support and type of analgesia, the infusion of amino acids in the current study caused an average increase in protein balance of 36.7 $\mu mol \cdot kg^{-1} \cdot h^{-1}$, whereas the increase in protein balance was 7.3 $\mu mol \cdot kg^{-1} \cdot h^{-1}$ as a result of the analgesia technique.

Table 4. Plasma Concentrations of Glucose and Hormones

	PCA		Epidural Analgesia		*P* Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
Glucose, mM/l	5.85 ± 1.49	6.44 ± 1.20	5.79 ± 1.03	6.21 ± 0.44	0.26	0.843	0.732
Insulin, pM/l	67.00 ± 50.09	155.00 ± 93.94	64.38 ± 30.40	123.63 ± 56.47	**0.002**	0.345	0.40
Glucagon, pM/l	39.7 ± 20	90.3 ± 41	34.8 ± 20	72.8 ± 28	**0.0001**	0.280	0.548
Cortisol, nM/l	342.53 ± 250.93	355.52 ± 157.63	299.37 ± 113.85	322.98 ± 151.67	0.843	0.559	1
I/G ratio	1.7 ± 1.05	1.7 ± 1.05	1.7 ± 2.1	1.7 ± 1.4	0.743	0.403	0.559

Values are mean ± SD.

* Probability that values are influenced by parenteral alimentation. For each variable, the difference has been tested between the means of the fasted states of the two groups and the means of the fed states of the two groups. † Probability that values are influenced by the type of analgesia whether nutrition was administered or not. For each variable, the differences have been tested between the means of the fasted and fed states of one group and the means of the fasted and fed states of the other group. ‡ Probability that the effect of nutrition is greater in one distinct analgesic group.

I/G = insulin/glucagon; PCA = patient-controlled analgesia

Table 5. Gaseous Exchange in the Fasted and Fed States

	PCA		Epidural Analgesia		*P* Values		
	Fasted	Fed	Fasted	Fed	Nutrition*	Analgesia†	Interaction‡
REE/day, kcal/day	1,532 ± 461	1,797 ± 575	1,883 ± 527	2,067 ± 885	0.2	0.08	0.8
$\dot{V}O_2$, l/min	0.222 ± 0.074	0.258 ± 0.087	0.272 ± 0.085	0.292 ± 0.060	0.3	0.1	0.7
$\dot{V}CO_2$, l/min	0.170 ± 0.042	0.193 ± 0.058	0.223 ± 0.048	0.245 ± 0.045	0.2	**0.005**	1
RQ	0.78 ± 0.08	0.75 ± 0.05	0.83 ± 0.08	0.84 ± 0.1	0.8	**0.03**	0.6

Values are mean ± SD.

* Probability that values are influenced by parenteral alimentation. For each variable, the difference has been tested between the means of the fasted states of the two groups and the means of the fed states of the two groups. † Probability that values are influenced by the type of analgesia whether nutrition was administered or not. For each variable, the differences have been tested between the means of the fasted and fed states of one group and the means of the fasted and fed states of the other group. ‡ Probability that the effect of analgesia is greater in one of the two nutritional states.

PCA = patient-controlled analgesia; REE = rest energy expenditure; RQ = respiratory quotient; $\dot{V}CO_2$ = carbon dioxide production; $\dot{V}O_2$ = oxygen consumption.

Similarly, in the study where glucose and amino acids were infused together, the protein balance increased by 26 μmol · kg^{-1} · h^{-1}, whereas epidural accounted for only an increase of 2.1 μmol · kg^{-1} · h^{-1}.[10] Therefore, in both studies, the effects of amino acids on protein balance were 5–10 times more powerful than the type of analgesia used.

In the current study, the rate of infusion of amino acids was 2.9 g · kg^{-1} · day^{-1}, such that the plasma amino acid concentration was maintained twofold to threefold above basal value.[24] Three hours of amino acid infusion was found to be sufficient for maximal incorporation of amino acids into whole body and tissue compartments.[25] The quantity of amino acids administered was 0.36 g · kg^{-1} · day^{-1}, less than the daily recommended intake of 1.5 g · kg^{-1} · day^{-1};[26] nevertheless, a consistent anabolic effect was shown. This is in agreement with previous findings demonstrating that amino acids are more efficiently utilized for maintaining lean body mass when given in divided doses rather than with continuous infusion.[25]

Suppression of gluconeogenesis reduces the need for muscle protein breakdown to supply gluconeogenic amino acids. If the rate of gluconeogenesis from amino acids is decreased, that amount of nitrogen is available for reincorporation into protein rather than for excretion as urea. In the current study, EGP was slightly decreased (15–30%), whereas in the previously described study,[10] where the nutritional support was amino acids plus glucose, EGP was almost totally suppressed (80–90%). Paradoxically, amino acid oxidation was similar in both studies, but protein balance was greater in the current study. Therefore, even if the inhibition of EGP should spare amino acids, these do not become automatically available for the synthetic pathways.

Glucose is produced endogenously by both glycogenolysis and gluconeogenesis. Under normal overnight postabsorptive conditions, glycogenolysis constitutes approximately 50% of whole body glucose production, with the remainder being derived from gluconeogenesis.[27] Gluconeogenesis progressively increases with the duration of fasting, contributing to more than 90% of glucose production after 42 h of fasting.[28] Considering the long perioperative fasting, the endogenous glucose production was primarily of gluconeogenic origin in our study.

The observed reduction in EGP during an amino acid infusion is in agreement with previous studies in the postoperative period and on the third day after trauma where an infusion of an amino acids mixture at a similar rate decreased endogenous glucose production by 8–12%.[20,29] However, in contrast with these observations in patients, infusion of amino acids in volunteers increased endogenous glucose production. Tappy *et al.*[18] showed increases in EGP and gluconeogenesis by 84% and 235%, respectively, after an infusion of amino acids at a rate of 4.8 g · kg^{-1} · day^{-1}. In contrast, Krebs *et al.*[19] measured EGP by stable isotopes and glycogenolysis by ^{13}C nuclear magnetic resonance spectrometer in volunteers after overnight fasting and found that gluconeogenesis increased by 100% after the amino acid infusion at a rate of 4.8 g · kg^{-1} · day^{-1}. Such increase had been explained as a result of a direct effect of amino acids acting as substrate for the gluconeogenic pathway and indirectly by increased plasma glucagon concentration, which stimulates gluconeogenesis.

Despite the decrease in EGP in both groups, a decrease in glucose clearance was observed, implying that glucose uptake was decreased. The amino acids effect of decreasing glucose consumption has been found also in studies of volunteers, where it has been demonstrated that they inhibit glucose transport/phosphorylation resulting in a decrease in intracellular utilization of glucose.[30]

In conclusion, a short-term infusion of amino acids after colorectal surgery inhibits protein breakdown and stimulates protein synthesis, thus rendering protein balance positive in both groups, although balance was greater in the PCA group. The effect of amino acids on postoperative glucose metabolism was characterized by a decrease glucose clearance indicating a state of insulin

resistance and by a decrease in endogenous glucose production.

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