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Effect of Epidural Blockade on Protein, Glucose, and Lipid Metabolism in the Fasted State and during Dextrose Infusion in Volunteers

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Background: **To interpret correctly the results from studies performed during surgery and anesthesia it is necessary to dissect the separate effect of the anesthetic technique itself. The purpose of this study was to investigate the metabolic effects of epidural blockade (T7-S1) with bupivacaine 0.25% after 12 h fasting and during administration of 4 mg · kg^{-1} · min^{-1} dextrose in six healthy volunteers.**

Methods: **Each volunteer was assigned to randomly undergo a 6-h multiple stable isotope infusion study (3 h fasted, 3 h dextrose infusion) with or without epidural blockade. L-[1-^{13}C]leucine, [6,6-$^{2}H_2$]glucose, and [1,1,2,3,3-$^{2}H_5$]glycerol were infused to measure protein synthesis, breakdown, and amino acid oxidation; glucose production and clearance; and lipolysis. Plasma concentrations of glucose, lactate, glycerol, free fatty acids, insulin, and glucagon were determined.**

Results: **Epidural blockade with bupivacaine had no influence on protein oxidation, breakdown and synthesis, glucose production, glucose clearance and lipolysis in the fasted state. Plasma concentrations of metabolic substrates and hormones also were not affected. Dextrose infusion significantly increased glucose clearance and plasma concentrations of glucose and insulin, while endogenous glucose production and lipolysis decreased to a similar degree in both groups. Protein synthesis, breakdown, and oxidation did not change during dextrose infusion.**

Conclusions: **Epidural blockade with bupivacaine in the absence of surgery has no effect on fasting protein, glucose, and lipid metabolism. Epidural blockade does not modify the inhibitory influence of dextrose administration on endogenous glucose production and lipolysis. (Key words: Bupivacaine; glycerol; leucine; stable isotopes.)**

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NOCICEPTIVE blockade by epidural analgesia with local anesthetics profoundly modifies the endocrine and metabolic response to surgical stress.[1] There is ample evidence that epidural blockade initiated before surgery and maintained after operation attenuates the postoperative increase in whole-body protein breakdown[2] and the decrease of muscle protein synthesis.[3] Perioperative epidural blockade also prevents intraoperative hyperglycemia,[4] improves glucose tolerance,[5] and inhibits the increases of plasma concentrations of glycerol and free fatty acids during surgery.[4,6]

To enable correct interpretation of results from investigations performed during and after surgery it is necessary to identify the separate effect of the anesthetic technique used. Epidural blockade established before surgery has been shown to alter minimally plasma concentrations of glucose, free fatty acids, amino acids, and cortisol.[1,4,7] These studies, however, were controlled for neither premedication nor feeding state and thus did not consider the hormonal and metabolic changes associated with fasting and sedation. Furthermore, from the measurement of circulating plasma concentrations of metabolites alone one cannot extrapolate the underlying biochemical mechanisms, *i.e.*, dynamic changes in protein breakdown, oxidation, and synthesis; glucose production and clearance; and lipolysis.

The rationale of providing intravenous dextrose as part of parenteral nutrition in critically ill patients is primarily based on its nitrogen sparing properties. Two mechanisms through which infused dextrose can improve nitrogen balance have been proposed[8]: suppression of gluconeogenesis and, thereby, eliminating the need for protein catabolism to provide gluconeogenic precursors. 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. Provision of energy and thus reduction of the amount of amino acids oxidized for energy production has been regarded as a second mechanism responsible for the

protein-preserving effect of dextrose infusion. In healthy humans significant inhibition of urea synthesis and almost complete suppression of endogenous glucose production has been achieved if glucose was infused at 4 mg · kg^{-1} · min^{-1}.[8] Glucose administration at a higher rate resulted in a more pronounced decrease of urea production and an increase of glucose oxidation but did not further inhibit endogenous glucose production.[8,9]

The aim of this project was to establish, whether epidural blockade (T7–S1) in the absence of surgery influences fasting protein breakdown, amino acid oxidation and protein synthesis, glucose production, and lipolysis assessed by stable isotope kinetics. This segmental area of neural blockade was selected as it represents the area of dermatome innervation of subumbilical abdominal surgical incisions. A second objective of this study was to investigate if dextrose, infused at 4 mg · kg^{-1} · min^{-1} and in the presence of epidural blockade, further improves glucose utilization and attenuates glucose production, thereby enhancing its protein-sparing effect.

Subjects and Methods

This randomized crossover study was approved by the ethics committee of the hospital, and informed consent was obtained from six healthy volunteers (age [mean ± SD], 26 ± 6 yr) with a mean body weight of 62 ± 11 kg and a mean height of 173 ± 10 cm. The subjects were recruited from the general population (neither patients nor coworkers) and received financial compensation. Before the investigation they received medical and physical examinations and routine biochemical analyses. All subjects were admitted twice (1 week apart) to the metabolic unit. Each volunteer was assigned to undergo in random order a 6-h multiple stable isotope infusion study (3 h fasted, 3 h dextrose infusion) either with or without epidural blockade.

Epidural Blockade

An epidural catheter was inserted at thoracic vertebral level T10–T11. Neural blockade was established with bupivacaine 0.5% to achieve a bilateral sensory block to ice and pin prick from thoracic dermatome level 7 (T7) to sacral dermatome level 1 (S1). The block was maintained with a constant infusion of bupivacaine 0.25% set at a rate of 8–12 ml/h.

Dextrose 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^{-1} · min^{-1} for 3 h. The solution was prepared by the local pharmacy under sterile conditions and tested for sterility, stability. and absence of pyrogens before intravenous infusion. The beet dextrose solution was chosen because of its low ^{13}C content and therefore the lack of significant perturbation of $^{13}CO_2$ enrichment in expired air.[10]

Experimental Protocol

Plasma kinetics of leucine, glucose, and glycerol were determined by a primed constant infusion of tracer quantities of L-[1-^{13}C]leucine (99% ^{13}C), [6,6-$^{2}H_2$]-glucose (99% ^{2}H), and [1,1,2,3,3-$^{2}H_5$]-glycerol (99% ^{2}H) obtained from Cambridge Isotope Laboratories (Cambridge, MA). Before each infusion study, sterile solutions of isotopes were prepared in the hospital pharmacy. The solution was passed through a 0.22-μm filter into injection bottles. The bottles were sealed, heat-sterilized at 121°C for 15 min, and kept at 4°C until administration. Each set of solutions was confirmed to be sterile and free of pyrogens (LAL Pyrogen test, Whittaker Bioproducts, Walkersville, MD).

All tests were performed in the fasted state beginning at 8 AM after a 12-h overnight fast. The subjects were studied in a temperature and humidity controlled environment (24°C, 35–42% relative humidity). Electrocardiogram, noninvasive systemic arterial pressure, and oxygen saturation were monitored during the whole study period. A superficial vein in the dorsum of the hand was cannulated and the cannula kept patent with saline 2 ml · kg^{-1} · h^{-1}. This arm was warmed in a heated air box to achieve arterialization of venous blood.[11] 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 NaH$^{13}CO_3$ 1 μmol/kg, L-[1-^{13}C]leucine 4 μmol/kg, [6,6-$^{2}H_2$]glucose 22 μmol/kg, and [1,1,2,3,3-$^{2}H_5$]glycerol 1.2 μmol/kg were administered and followed immediately by continuous infusions of L-[1-^{13}C]leucine 0.06 μmol · kg^{-1} · min^{-1} and [1,1,2,3,3-$^{-}H_5$]glycerol 0.09 μmol · kg^{-1} · min^{-1} lasting 6 h. [6,6-$^{2}H_2$]Glucose was infused a rate of 0.22 μmol · kg^{-1} · min^{-1} during the first 3 h (fasted period) and then changed to 0.44 μmol · kg^{-1} · min^{-1} during the 3 h of dextrose administration. Isotope infusion was uninterrupted throughout the 6-h experimental period. Toward

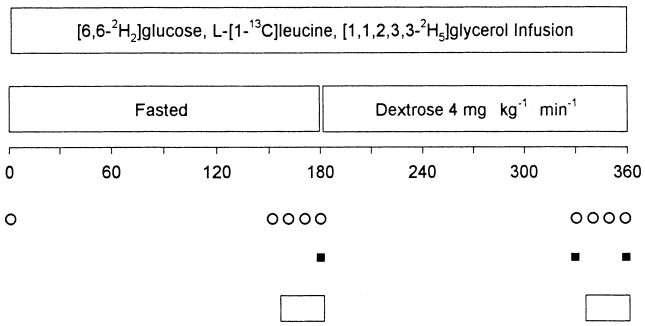

Fig. 1. Time course of the infusion of isotopes and collection of plasma and expired air samples (circles), indirect calorimetry (rectangles), and collection of plasma for the determination of metabolic substrates and hormones (squares) in the fasted state and during the infusion of dextrose.

the end of each 3-h study period four arterialized 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 figure 1.

Gaseous Exchange

Indirect calorimetry (Datex Deltatrac, Helsinki, Finland) was performed in the last hour of the fasted state and of the dextrose infusion. The subjects were lying in a semirecumbent position (20 degrees), breathing room air in the ventilated hood, for 20 min on each occasion. Oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) were measured, and the respiratory quotient was calculated. An average value of $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, and the respiratory quotient was taken, with a coefficient of variation $< 10\%$.

Temperature Measurements

Core body temperature was measured with a thermocouple probe (Mono-a-therm; Mallinckrodt Medical, St. Louis, MO) inserted in the aural canal and positioned adjacent to the tympanic membrane. Skin temperature was recorded at 15 skin sites located in the forehead, cheek, neck, nipple, midarm, midforearm, dorsum of the hand, umbilicus, iliac crest, medial thigh, lateral thigh, knee, medial calf, lateral calf, and dorsum of the foot with an infrared thermometer previously described.[12] The mean unweighted skin temperature was calculated from the 15 sites. Tympanic (core) and skin temperatures were measured at isotopic plateau before and toward the end of dextrose infusion. Ambient temperature also was measured using a mercury in glass thermometer.

Analytic Methods

Isotopic Enrichments. Plasma [1-^{13}C]α-ketoisocaproate enrichment was determined by electron-impact selected-ion monitoring gas chromatography–mass spectrometry using the method previously described by Mamer and Montgomery,[13] except that t-butyldimethylsylyl rather than trimethylsylyl derivatives were prepared. Expired [^{13}C]carbon dioxide enrichment was determined by isotope ratio mass spectrometry (Analytical Precision AP2,003, Manchester, United Kingdom). Plasma glucose was derivatized to its pentaacetate compound and the [6,6-$^2H_2$]glucose enrichment determined by gas chromatography–mass spectrometry using electron-impact ionization.[14] [1,1,2,3,3-$^2H_5$]Glycerol was converted to its triacetylester derivative as recently described[15] and analyzed by positive-ion chemical ionization. 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). The mean intraassay and interassay coefficients of variance were 3.0% and 4.5%, respectively.

Plasma-free fatty acids and glycerol were analyzed by using the Boehringer Mannheim enzymatic colorimetric kit (Boehringer Mannheim, Laval, Quebec, Canada). The mean intraassay and interassay coefficients of variance for free fatty acids were 2.3% and 4.1% and for glycerol 3.1% and 4.0%, respectively.

Circulating concentrations of insulin and glucagon were measured by a sensitive and specific double antibody radioimmunoassay (Amersham International, Amersham, Bucks, United Kingdom). Intraassay and interassay precisions for insulin were 5.6% and 7.3% and for glucagon were 5.4% and 6.0%, respectively.

Calculations

If a physiologic and isotopic steady state exists the rate of appearance (R_a) of unlabeled substrate in plasma can be derived from the plasma isotope enrichment (APE or atom percentage excess) calculated by:

$$R_a = (APE_{inf}/APE_{pl} - 1) \cdot F \quad (1)$$

where F is the infusion rate of the labeled tracer (μmol · kg^{-1} · min^{-1}), APE_{inf} is the tracer enrichment in the infusate and APE_{pl} the tracer enrichment in plasma, respectively. The APE used in this calculation were 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 less than 5% was used as a confirmation of a valid plateau.

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

$$Q = S + O = B = I \quad (2)$$

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 equation 2 indicates that, when studies are conducted after absorption, leucine flux is equal to leucine breakdown.[16] Plasma enrichment of [1-^{13}C]α-ketoisocaproate during infusion of L-[1-^{13}C]leucine has been used as the basis for calculating both flux and oxidation of leucine.[17] This steady-state reciprocal pool model is considered to provide a more precise representation of intracellular precursor pool enrichment than leucine itself.[17] 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 ^{13}C-carbon dioxide released from leucine but retained within slow turnover rate pools of the body.[16]

In the fasted state R_a glucose was equal to the endogenous production of glucose. During the infusion of dextrose, endogenous glucose production was calculated by subtracting the dextrose infusion rate from the total R_a glucose.

The fractional plasma clearance rates of glucose and glycerol were calculated as the R_a of glucose or glycerol divided by the corresponding plasma substrate concentration.

Statistics

All data are presented as mean ± SD. Comparisons for each dependent variable were performed using two-factorial analysis of variance with the two factors epidural blockade and dextrose infusion. Analysis of variance for repeated measurements was applied to analyze any significant change in the plasma concentrations of metabolic substrates (glucose, lactate, glycerol, free fatty acids) and hormones (insulin, glucagon) during dextrose administration. If no significant change was detected the average value of the two measurements obtained after 150 and 180 min of dextrose infusion was compared with the corresponding fasting value. Statistical significance was accepted at $P < 0.05$.

Results

Hemodynamics

Volunteers' hemodynamics (mean arterial pressure: 85 ± 8 mmHg, heart rate: 77 ± 9 beats/min) were not significantly affected by epidural anesthetic before or during dextrose infusion. Mean arterial pressure in the epidural group was 84 ± 11 mmHg before and 79 ± 9 mmHg during dextrose administration; heart rate was 63 ± 10 beats/min before and 64 ± 5 beats/min thereafter. In subjects without epidural blockade postabsorptive mean arterial pressure at 81 ± 6 mmHg remained unchanged at 79 ± 9 mmHg. Heart rate at 62 ± 7 beats/min also did not change during dextrose administration (66 ± 6 beats/min).

Kinetics

In all experiments a plateau in the enrichments of plasma [1-^{13}C]α-ketoisocaproate, [6,6-$^{2}H_2$]glucose, [1,1,2,3,3-$^{2}H_5$]-glycerol, and expired [^{13}C]carbon dioxide was achieved before and after 3 h of dextrose infusion (coefficient of variation < 5%), permitting the use of the steady-state equation.

Epidural blockade had no significant effect upon whole-body protein synthesis, breakdown, or leucine oxidation; glucose production or clearance; or lipolysis (table 1). Administration of dextrose did not affect the kinetics of protein metabolism; total R_a glucose ($P < 0.001$) and glucose clearance ($P < 0.05$) increased in both groups. Dextrose infusion decreased endogenous R_a glucose ($P < 0.001$) and glycerol release ($P < 0.05$) to a similar degree in the two groups.

Metabolites and Hormones

Plasma concentrations of metabolites and hormones obtained after 150 and 180 min of dextrose infusion were not significantly different. As shown in table 2

Table 1. Kinetics of Leucine, Glucose, and Glycerol Metabolism in Volunteers with and without Epidural Blockade in the Fasted State and during Dextrose Infusion

	Nonepidural		Epidural	
	Fasted	Dextrose Infusion	Fasted	Dextrose Infusion
R_a leucine ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	2.11 ± 0.31	1.95 ± 0.39	2.10 ± 0.23	2.04 ± 0.28
Leucine oxidation ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	0.38 ± 0.07	0.34 ± 0.08	0.43 ± 0.08	0.42 ± 0.08
Protein synthesis ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	1.73 ± 0.31	1.61 ± 0.37	1.67 ± 0.22	1.62 ± 0.28
R_a glucose ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	12.87 ± 2.23	24.85 ± 2.96*	12.63 ± 2.11	23.44 ± 1.21*
Endogenous R_a glucose ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)‡	12.87 ± 2.23	2.24 ± 2.28*	12.63 ± 2.11	1.26 ± 1.17*
Glucose clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	2.54 ± 0.29	3.47 ± 0.74†	2.59 ± 0.36	3.50 ± 0.65†
R_a glycerol ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	1.92 ± 0.82	0.98 ± 0.50†	1.95 ± 0.67	0.98 ± 0.15†
Glycerol clearance ($ml \cdot kg^{-1} \cdot min^{-1}$)	20.47 ± 7.24	17.79 ± 9.82	21.88 ± 4.43	21.41 ± 6.31

Data are mean ± SD.

R_a = rate of appearance.

* $P < 0.001$ compared with fasted state.

† $P < 0.05$ compared with fasted state.

‡ Endogenous R_a glucose was calculated by subtracting the rate of exogenous glucose infusion from total R_a glucose.

epidural blockade did not influence circulating concentrations of metabolic substrates and hormones in the fasted state. Dextrose administration increased plasma glucose and insulin concentration ($P < 0.001$) and decreased plasma concentrations of glycerol and free fatty acids ($P < 0.05$). These parameters were not affected by epidural blockade. Plasma concentrations of lactate and glucagon remained unchanged during the study period.

Gaseous Exchange and Temperature

Epidural blockade did not affect whole-body oxygen consumption, carbon dioxide production, or the respiratory quotient indicating unchanged substrate utilization. Dextrose infusion significantly stimulated whole-body carbon dioxide production ($P < 0.05$) in all subjects, resulting in a significant increase in the respiratory quotient ($P < 0.05$, table 3). Core and mean skin temperature showed no significant changes during dextrose administration and were not influenced by epidural blockade (table 3).

Discussion

The results of the present study demonstrate that epidural nerve blockade (T7–S1) with bupivacaine in healthy volunteers does not affect fasting leucine, glucose, or glycerol kinetics or the metabolic responses to dextrose infusion in healthy volunteers.

The metabolic impact of neural blockade with local anesthetics combined with surgery has been extensively

Table 2. Plasma Concentrations of Circulating Metabolites and Hormones in Volunteers with and without Epidural Blockade in the Fasted State and during Dextrose Infusion

	Nonepidural			Epidural		
		Dextrose Infusion			Dextrose Infusion	
	Fasted	150 min	180 min	Fasted	150 min	180 min
Glucose (mM)	5.1 ± 0.4	7.7 ± 1.2*	7.1 ± 1.1*	4.9 ± 0.3	7.4 ± 0.9*	6.8 ± 1.0*
Lactate (mM)	1.0 ± 0.3	1.1 ± 0.2	1.0 ± 0.2	1.3 ± 0.2	1.1 ± 0.1	1.1 ± 0.1
Glycerol (μM)	92 ± 20	60 ± 21†	61 ± 18†	79 ± 20	50 ± 14†	62 ± 13†
FFA (mM)	0.37 ± 0.20	0.12 ± 0.02†	0.13 ± 0.02†	0.30 ± 0.09	0.13 ± 0.01†	0.12 ± 0.01†
Insulin (μU/ml)	7.2 ± 1.3	14.9 ± 3.1*	13.2 ± 2.3*	6.6 ± 1.4	13.8 ± 2.7*	12.8 ± 2.6*
Glucagon (pM)	21 ± 11	17 ± 10	17 ± 10	21 ± 11	17 ± 10	17 ± 10

Data are mean ± SD.

FFA = free fatty acids.

* $P < 0.001$ compared with fasted state.

† $P < 0.05$ compared with fasted state.

Table 3. Gaseous Exchange and Core, Mean Skin, and Ambient Room Temperature in Volunteers with and without Epidural Blockade in the Fasted State and during Dextrose Infusion

	Nonepidural		Epidural	
	Fasted	Dextrose Infusion	Fasted	Dextrose Infusion
$\dot{V}_{O_2}$ (ml/min)	209 ± 40	219 ± 40	212 ± 39	222 ± 30
$\dot{V}_{CO_2}$ (ml/min)	168 ± 31	185 ± 27*	169 ± 30	191 ± 23*
RQ	0.80 ± 0.03	0.86 ± 0.06*	0.80 ± 0.07	0.87 ± 0.04*
Temperature (°C)				
Core	36.5 ± 0.4	36.8 ± 0.5	36.3 ± 0.7	36.7 ± 0.3
Mean skin	33.7 ± 1.2	34.1 ± 1.1	33.7 ± 1.6	33.8 ± 1.6
Room	24.3 ± 0.5	24.7 ± 0.2	24.7 ± 0.7	24.7 ± 0.5

Values are presented as mean ± SD.

$\dot{V}_{O_2}$ = whole-body oxygen consumption; $\dot{V}_{CO_2}$ = whole-body carbon dioxide production; RQ = respiratory quotient.

* $P < 0.05$ compared with fasted state.

studied. Epidural blockade, established before surgery, improved postoperative nitrogen balance,[18] decreased the obligatory postoperative decrease in muscle fractional synthetic rate,[3] and attenuated the rise in whole-body protein breakdown and leucine oxidation with minimal changes in protein synthesis.[2] Epidural blockade with local anesthetics has been shown to ameliorate the hyperglycemic response to surgery,[4] prevent the intraoperative impairment of glucose tolerance,[5] and blunt the increases of the plasma concentrations of glycerol and free fatty acids during surgery.[4,6] Few studies have addressed the independent metabolic effect of epidural blockade, and it has been suggested that epidural blockade in the absence of surgical stress exerts only minimal influence on metabolism. High thoracic or lumbar epidural blockade with bupivacaine for abdominal surgery produced no changes in circulating plasma concentrations of amino acids, glucose, glycerol, or free fatty acids and had no significant effect on splanchnic amino acid uptake and glucose release.[1,4,6,7,19] These studies, however, have been performed exclusively in premedicated patients between the initiation of neural blockade alone or combined with general anesthesia and the start of surgery. To exclude any influence of variables with potential metabolic impact we investigated healthy, unpremedicated volunteers in a controlled environment after 12 h of fasting. In addition we applied stable isotope tracers to study the kinetics of protein, glucose, and lipid metabolism. Efforts were made to maintain the subjects normothermic throughout the study period, therefore limiting the possible effect of hypothermia on protein metabolism, which has been shown to occur in surgical patients.[20]

Whole-body protein breakdown, oxidation, and synthesis were not significantly altered by low thoracic epidural blockade with bupivacaine. Fasting endogenous glucose production, which was identical to values recently reported in healthy volunteers after 12 h of fasting,[21] whole-body glucose clearance and lipolysis also were not affected, lending further support to the contention that neural blockade *per se* does not influence protein, glucose, and lipid metabolism. Epidural nerve blockade, however, by producing a neural blockade of the efferent adrenergic pathways to the pancreas, may contribute to a decrease in glucose tolerance and insulin release, as baseline adrenergic input is important in maintaining normal pancreatic islet function.[22] Because the sympathetic innervation of the pancreas predominantly comes *via* the splanchnic nerves from thoracic cord segments T6–T10, the level of neural blockade plays an important role with regard to glucose metabolism. A recent study demonstrated that sympathetic efferent blockade established with high spinal anesthesia (T2) impaired the acute plasma insulin response to an intravenous glucose load in nonpremedicated patients before elective surgery.[22] On the contrary patients receiving lower dermatome blockade (T9–T12)—similar to the block applied in our subjects—with minimal effect on sympathetic efferents exhibited no alteration of the insulin response to glucose.[22] In the present study a sensory block from T7 to S1 also did not inhibit the plasma insulin and glucose response to dextrose infusion. The magnitude of increase of carbohydrate oxidation during dextrose infusion, reflected by the increase of the respiratory quotient caused by stimulated carbon dioxide production, also was not altered in the epidural group.

The nitrogen-sparing effect of dextrose is well documented in humans. Intravenous glucose administration in fasted volunteers has been reported to decrease nitro-

gen excretion in a dose-dependent manner.[23] This improvement in nitrogen balance has been primarily ascribed to a reduction in urea production. Glucose administration at a rate of 4 mg · kg^{-1} · min^{-1} significantly reduced urea production in healthy volunteers by 15%. Increasing the rate to 8 mg · kg^{-1} · min^{-1} caused a further, modest reduction of urea synthesis.[8] Leucine oxidation and the R_a leucine in our study did not change during dextrose infusion, indicating that dextrose infused at a rate of 4 mg · kg^{-1} · min^{-1} did not alter whole-body protein synthesis, breakdown, and amino acid oxidation. This finding is in agreement with the previous observation that the anticatabolic effect of low-dosage glucose administration did not result from a decreased mobilization of amino acids from peripheral tissues, mediated either through diminished protein degradation or increased protein synthesis in skeletal muscles.[24]

Although ureagenic precursor supply is an important regulator of hepatic urea synthesis, the inhibitory effect of glucose on urea production was not associated with decreased substrate flux to the liver resulting in a reduced flow of aminonitrogen into the urea cycle.[24] If glucose was applied at a rate sufficient to cause a doubling of basal insulin concentration (similar to the endogenous insulin response to dextrose infusion in our study) arterial plasma amino acid concentration and the rate of splanchnic amino acid uptake did not change.[25] Also, the increase of plasma insulin levels from 10 to 20 μU/ml did not suppress the release of amino acids from the muscle bed of normal postabsorptive volunteers.[26] Furthermore, glucose infusion at a rate of 4 mg · kg^{-1} · min^{-1} caused no change in leucine release from forearm muscle in healthy humans.[27] Hence, it has been concluded that low-dosage glucose infusion decreases urea production by direct or insulin-mediated suppression of urea cycle activity or gluconeogenesis from amino acids in the liver.[24] 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. Glucose administration causing a fivefold increase in peripheral insulin levels induced a marked decrease in the splanchnic uptake of the major gluconeogenic amino acids.[25] Infusion of exogenous insulin increasing plasma insulin concentrations above 150 μU/ml blocked the release of muscle aminonitrogen[26]; insulin clamped at a plasma level of 80 μU/ml decreased whole-body leucine flux and oxidative and nonoxidative leucine disposal.[28]

Because muscle protein is broken down to supply the amino acids that serve as precursors for the *de novo* glucose synthesis, gluconeogenesis occupies a central position in catabolic pathways. Urea is produced in the liver when these amino acids are deaminated, leaving the carbon skeleton for glucose production. It has therefore been hypothesized that by reducing gluconeogenesis urea formation and nitrogen, excretion can be diminished, resulting in a better preservation of whole-body protein. Animal studies demonstrating an inverse correlation between gluconeogenesis and hepatic protein synthesizing capacity document the interdependence between glucose and protein metabolism.[29] Dextrose administration at 4 mg · kg^{-1} · min^{-1} significantly suppressed endogenous glucose production in all subjects. This finding is consistent with previous results revealing similar, almost complete reductions of endogenous glucose production in healthy postabsorptive volunteers.[8] Although direct effects of increased glucose availability are difficult to separate from the effects of the increase in insulin that is induced by hyperglycemia, this response has been shown to occur independently of changes in plasma insulin concentration. Total glucose production and gluconeogenesis were all inhibited to the same degree if insulin secretion was inhibited by somatostatin as if insulin plasma concentration increased after 2 h of glucose infusion (4 mg · kg^{-1} · min^{-1}).[30] Whole-body glucose clearance also rose regardless of whether insulin was held at the basal level or was allowed to change spontaneously.[30]

Administration of dextrose caused a significant decrease of the R_a glycerol by 50%, indicating a direct inhibition of lipolysis, regardless of whether subjects received epidural bupivacaine or not. This finding is in line with previous observations reporting similar reductions of lipolysis during glucose administration in healthy postabsorptive volunteers.[31,32] The decrease in free fatty acid plasma concentration was more pronounced than the decrease in plasma glycerol level in our study. This is in accordance with the results of a recent investigation showing that glucose infused at 4 mg · kg^{-1} · min^{-1} stimulated reesterification of fatty acids and triglyceride–fatty acid substrate cycling within adipose tissue.[32] The suppressory effect of glucose on whole-body lipolysis could be explained on the basis of increased plasma insulin concentration and the antilipolytic action of insulin. From previous studies, however, it is apparent that a physiologic rise in plasma glucose *per se* without any concomitant rise in plasma insulin con-

centration can decrease the release of glycerol from adipose tissue.[33]

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