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Intensive Insulin Treatment in Critically Ill Trauma Patients Normalizes Glucose by Reducing Endogenous Glucose Production

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Critical illness is associated with insulin resistance and hyperglycemia. Intensive insulin treatment to normalize blood glucose during feeding has been shown to improve morbidity and mortality in patients in intensive care. The mechanisms behind the glucose-controlling effects of insulin in stress are not well understood.

Six previously healthy, severely traumatized patients (injury severity score > 15) were studied early (24–48 h) after trauma. Endogenous glucose production (EGP) and whole-body glucose disposal (WGD) were measured (6,6-$^2H_2$-glucose) at basal, during total parenteral nutrition (TPN), and during TPN plus insulin to normalize blood glucose (TPN+I). Six matched volunteers served as controls.

At basal and TPN, concentrations of glucose and insulin were higher in patients ($P < 0.05$). During TPN+I, insulin concentrations were 30-fold higher in patients. At basal, WGD and EGP were 30% higher in patients ($P < 0.05$). During TPN, EGP decreased in both groups but less in patients, resulting in 110% higher EGP than controls ($P < 0.05$). Normoglycemia coincided with reduced EGP, resulting in similar rates in both groups. WGD did not change during TPN or TPN+I and was not different between the groups.

In conclusion, in healthy subjects, euglycemia is maintained during TPN at physiological insulin concentrations by a reduction of EGP, whereas WGD is maintained at basal levels. In traumatized patients, hyperglycemia is due to increased EGP. In contrast to controls, normalization of glucose concentration during TPN needs high insulin infusion rates and is accounted for by a reduction in EGP, whereas WGD is not increased. (*J Clin Endocrinol Metab* 89: 5382–5386, 2004)

INSULIN RESISTANCE IS a central feature of stress metabolism in postoperative patients, trauma patients, sepsis, and critical illness in general. In insulin resistance, glucose uptake is reduced in peripheral, insulin-sensitive tissues, whereas endogenous glucose production is increased, resulting in hyperglycemia. This phenomenon has earlier been suggested to be a pathophysiological adaptation to ensure substrate supply to non-insulin-dependent vital tissues, such as the brain. However, an increasing body of evidence strongly suggests that hyperglycemia is harmful by itself and that attenuation and/or treatment of insulin resistance have major impact on clinical outcome. For example; insulin resistance after elective surgery has been shown to be an independent variable determining the variability of length of stay (1). By attenuating postoperative insulin resistance with a preoperative carbohydrate load, not only subjective well-being but also length of stay improved compared with patients operated on in the fasted state (2). Furthermore, complications after cardiac surgery were reduced when preoperative glucose was given, suggesting that organ-specific function is affected by insulin resistance (3, 4). Also, treatment of postoperative insulin resistance with sufficient amounts of insulin during total parenteral nutrition (TPN) to normalize blood glucose improved other important measures of metabolism, such as substrate utilization and nitrogen balance, indicating that the effect of this treatment is not limited to carbohydrate metabolism only (5).

More recently, in a randomized, controlled study including some 1548 patients in the intensive care unit, most of them postsurgical, clinical effects of intensive insulin treatment of stress-induced insulin resistance were investigated (6). Remarkable effects on outcome in terms of sepsis, renal failure, need for blood transfusion, and ventilatory support as well as mortality were found in favor for insulin treatment. Using multivariate logistic regression in all subjects, it was concluded that the normalization of hyperglycemia rather than the insulin dose was responsible for most of the beneficial clinical effects (7). Furthermore, in a subset of patients requiring intensive care for more than 7 d, insulin effects on blood lipid profile seemed to be more important for outcome (8). In the same cohort of patients, muscle and liver specimens were obtained from nonsurvivors for analysis of mRNA levels of skeletal muscle glucose transporting protein-4, hexokinase (8), and phosphoenolpyruvate carboxykinase (9). From these indirect *ex vivo* data, it was suggested that the main defect in glucoregulation in critical illness is located in the liver rather than in peripheral tissues. To further elucidate this, as well as to define the location (the liver *vs.* peripheral tissues) responsible for the glucose-lowering effects by insulin in critical illness, *in vivo* kinetic studies need

Abbreviations: EGP, Endogenous glucose production; TPN, total parenteral nutrition; TPN+I, TPN plus insulin to normalize blood glucose; WGD, whole-body glucose disposal.

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to be performed. Therefore, in the present study, we determined glucose kinetics by the use of stable isotope techniques before and during intensive insulin treatment in injury-induced insulin resistance.

Our results show that in severely traumatized patients, hyperglycemia in the early phase is mainly due to an increase in endogenous glucose production (EGP), and normalization of blood glucose by insulin infusion occurs by suppression of EGP as opposed to by further stimulation of peripheral glucose disposal.

Subjects and Methods

Subjects

Six previously healthy, severely traumatized patients (two females, four males, aged 44.8 ± 17.5, range 24–67 yr, body mass index 25.7 ± 2.6, range 21–29) with an Injury Severity Score greater than 15 were included in the study. Six healthy age- and gender-matched volunteers served as controls. Subjects' characteristics and description of injuries are given in Table 1.

Consent was obtained from control subjects and patients' relatives after written as well as oral information had been given, explaining the nature and purpose of the study. The study was approved by the Institutional Ethics Committee at the hospital and was carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association.

Study protocol

Patients were studied 24–48 h after trauma. Studies were performed during three consecutive phases: a basal period, a period of infusion of TPN and a period of TPN+insulin (TPN+I, feedback hyperinsulinemic euglycemic clamp) (Fig. 1). The study was initiated at 0800 h preceded by an 8-h fast, with a 120-min period for determination of basal glucose turnover (see below). At 1000 h, subjects were given TPN (Kabimix Basal; Pharmacia Upjohn, Stockholm, Sweden) with added glucose (Glucos B Braun, 200 mg/ml), at a constant infusion rate corresponding to 120% of energy expenditure, as measured by indirect calorimetry (Deltatrac, Dansjöö, Sweden) during the last 30 min of the basal period. Based on the results from indirect calorimetry measurements, the glucose infusion rates were 2.2 ± 0.1 and 2.3 ± 0.7 mg glucose/kg·min for controls and trauma patients, respectively. In total, calories were given as 50% carbohydrates, 40% fat, and 10% amino acids. The duration of the TPN period varied slightly due to variable length of time needed to achieve and maintain steady-state blood glucose concentrations (9.1 ± 0.9 and 5.9 ± 0.2 mM in patients and controls, respectively).

Stable blood glucose concentrations were maintained for 60 min during which glucose turnover measurements were performed, followed by a variable infusion of insulin (Actrapid; Novo, Copenhagen, Denmark) in amounts sufficient to achieve normoglycemia (TPN+I). After steady-state blood glucose [5.2 ± 0.4 and 4.6 ± 0.1 mM (mean ± SEM), patients and controls, respectively] the TPN+I period proceeded for an additionally 60 min to measure glucose turnover, after which the infusion of insulin was discontinued. Energy expenditure was measured using indirect calorimetry during the last 30 min of each study period.

Glucose turnover measurements

A stable isotopomer of glucose, 6,6-$^2H_2$-D-glucose (Isotec Inc., Miamisburg, OH), was given as a primed (3 mg/kg^{-1})-continuous (2.4 mg/kg^{-1}·h^{-1}) infusion starting at 0800 h and continued during the entire study. The TPN infusate was enriched with the same isotopomer (molar excess 0.85%) to minimize fluctuations in plasma tracer enrichment during clamps (10). Whole-body glucose disposal (WGD) rates and EGP rates were calculated. WGD values were corrected for differences in glucose concentrations between the commencement and the end of the respective steady-state periods (glucose pool assumed to be 250 ml/kg^{-1} body weight with a pool correction factor of 65%) (10).

Controls underwent the same protocol starting at 0800 h after an overnight fast.

Sampling and analysis

Blood samples were arterial or arterialized venous blood (with a heater sleeve set at 50 C; KAN Med, Stockholm, Sweden) (11) from cannulas inserted in the upper limbs (radial artery or antecubital vein). Samples, for data given, were collected at 30-min intervals during the last hour of each steady-state period, and values for each subject are calculated as the mean value of these samplings. Also, samples for blood glucose and lactate concentrations were collected every 5–15 min throughout the entire experiment and analyzed immediately on collection using the glucose and lactate oxidase methods (Yellow Springs Instruments Inc., Yellow Springs, OH) (12).

Plasma insulin concentrations were analyzed by insulin RIA (Phar-

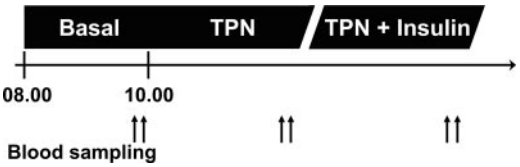

FIG. 1. Study protocol. Six severely traumatized subjects and six healthy controls were studied in the early posttraumatic period. Studies were performed in the postprandial state (basal), during infusion of TPN, and during TPN+insulin.

TABLE 1. Characteristics of patients and healthy control subjects included in the study

Patient	Gender	Age (yr)	Injuries	ISS	Control	Gender	Age (yr)
1	F	24	Open tibial fracture, vertebral, pelvic, clavicular, costal, facial fractures, Pnthx	34	1	F	26
2	M	24	Vertebral fractures with dislocation (Th 12–L4), costal, pelvic, and radial fractures, Pnthx., cerebral concussion	34	2	M	33
3	M	32	Extensive thoracic injuries, multiple vertebral fractures with sustained paraplegia	32	3	M	37
4	M	61	Subarachnoid hemorrhage, wrist, costal, and facial fractures, Pnthx	22	4	M	52
5	F	62	Thoracic trauma with flail chest, facial fractures (Le Fort II)	25	5	F	64
6	M	67	Head injury with subdural/intracerebral hemorrhage, wrist fracture	25	6	M	66

F, Female; M, male; ISS, Injury Severity Score; Pnthx, pneumothorax.

macia, Stockholm, Sweden). Plasma was sampled for determination of 6,6-$^2H_2$-D-glucose enrichment every 10 min during the last 30 min of each steady-state period. The trimethyl-silyl-*O*-methyloxime derivative of plasma and infusate glucose was measured with a gas chromatography mass spectrometer (13). All serum samples were permitted to clot, whereas plasma samples were immediately centrifuged at 4 C at 2000 × *g* during 10 min. All samples were stored at −20 C for later batch analysis.

Statistics

Values are means (SEM). Between-within ANOVA was used for repeated measures to assess effects of treatment (basal *vs.* TPN and TPN + I) with *post hoc* least significant difference tests where appropriate. Statistical significance was accepted at $P < 0.05$.

Results

Glucose/lactate/insulin

Compared with controls, blood glucose concentrations were 50% higher in patients at basal and during TPN ($P < 0.05$, Table 2). During TPN+I, insulin infusion successfully normalized blood glucose in patients to concentrations not statistically significant different from controls (Table 2). Similarly, insulin concentrations were 3-fold higher, compared with controls, at basal as well as during TPN. During TPN+I, an infusion rate of 1.0 ± 0.2 U/h insulin was given in controls, whereas the corresponding figure in patients was 21.0 ± 4.8 (range 1.9–63.8) U/h to achieve normoglycemia, rendering pharmacological plasma concentrations of insulin (Table 2). Blood lactate concentrations were 3-fold increased in patients, compared with controls, during all periods. Infusion of TPN as well as combined TPN+I had little effect on blood lactate concentrations in both groups (Table 2).

Glucose turnover

In controls, euglycemia during TPN and TPN+I was maintained by suppression of EGP, whereas no significant increase in WGD was seen (Fig. 2). At basal, while no exogenous infusions were given, there was a 30% higher rate of WGD in trauma patients, compared with controls, corresponding to similar rates of EGP (Fig. 2). As in controls, no increase in WGD was seen in trauma patients during infusion of TPN despite 3-fold higher insulin concentrations (Table 2). However, the high endogenous insulin response (106 mU/liter) in trauma patients during TPN suppressed EGP only to levels still 110% above EGP in controls (Fig. 2). Despite intensive insulin stimulation during TPN+I, WGD was not stimulated further in patients (Fig. 2). At these pharmacological insulin concentrations (corresponding to approximately 15 times the expected response to a regular meal), EGP decreased in patients ($P < 0.05$) to reach values not different from controls. Thus, the reduction in blood glucose concentrations in response to insulin infusion in trauma patients was exclusively accounted for by a reduction in EGP.

Discussion

The data from the present study show that in injury-induced insulin resistance, increased blood glucose concentrations in the early phase are due to an increased rate of EGP. Furthermore, when normoglycemia is induced by insulin infusion, this occurs solely by a reduction in EGP, rather than by an increase in glucose utilization in peripheral tissues.

Infusion of glucose at a rate of 2 mg/kg·min, similar to the total rate of glucose infusion during TPN in the present study, has been shown to mainly affect EGP in healthy volunteers, whereas higher infusion rates (>4 mg/kg·min) were needed to increase insulin to levels at which glucose disposal rates were stimulated (14). Accordingly, in the current study, a prompt reduction of EGP was seen in controls during TPN, whereas this response was blunted in trauma patients. This indicates the presence of hepatic insulin resistance because the insulin response was, if anything, supranormal (plasma concentration > 100 mU/liter). EGP in man occurs mainly in the liver, although the kidneys may also contribute to EGP. The magnitude of renal glucose release in the postabsorptive state is unclear due to methodological difficulties (15). It has been suggested that the renal contribution to EGP in the postabsorptive state in health is between 4 and 18% (15). For simplicity, in this context alterations in EGP kinetics are referred to as hepatic, although it is recognized that they may also involve renal glucose release.

When blood glucose was normalized by insulin infusion, a normalization of EGP was achieved. Notably, the response in peripheral tissues (WGD) to TPN as well as to TPN in combination with insulin was similar in patients and con-

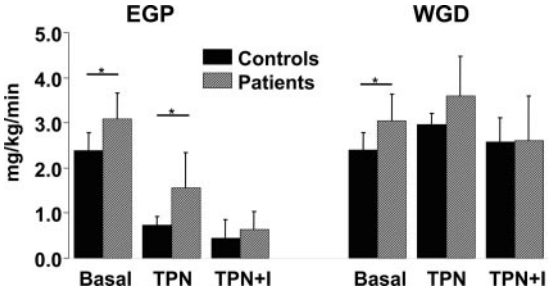

FIG. 2. Glucose kinetics. Glucose turnover was studied using stable isotopes (6,6-$^2H_2$-D-glucose) in six severely traumatized subjects and six healthy controls in the postprandial state (basal), during TPN, and during TPN+I. Values are given as mean ± SE. *, $P < 0.05$ *vs.* control.

TABLE 2. Circulating concentrations of glucose, insulin, and lactate in patients and healthy control in the basal state (B), during infusion of TPN (TPN), and during combined infusion of TPN and insulin in sufficient amounts to normalize blood glucose concentrations (TPN + I)

	Blood glucose (mM)		Plasma insulin (mU/liter)		Blood lactate (mM)	
	Controls	Patients	Controls	Patients	Controls	Patients
B	4.3 ± 0.3	6.7 ± 1.5[a]	10 ± 1	30 ± 6[a]	0.5 ± 0.1	1.4 ± 0.4[a]
TPN	5.9 ± 0.2	9.1 ± 0.9[a]	35 ± 3	106 ± 24[a]	0.6 ± 0.1	1.5 ± 0.2[a]
TPN + Ins	4.6 ± 0.1	5.2 ± 0.4	29 ± 2	996 ± 861[a]	0.4 ± 0.1	1.5 ± 0.4[a]

[a] $P < 0.05$ *vs.* controls, ANOVA (1 mU/liter insulin = 6.0 pmol/liter).

trols. However, taking into account the increased insulin response in trauma patients during TPN and the pharmacological insulin concentrations induced by exogenous infusion during TPN + I, peripheral tissues seemed to be almost refractory to insulin stimulation in the trauma patients. Of clinical importance was the finding that, although not evident from the mean lactate values given, one patient developed high lactate concentrations resulting in acidemia. Hence, this observation calls for caution and acid-base monitoring when giving high doses of insulin to severely insulin-resistant trauma patients.

It has been shown in healthy volunteers that variations in insulin concentrations within a low range mainly affect EGP, whereas insulin concentrations exceeding approximately 40 mU/liter are needed to increase WGD (14, 16). Thus, in the control situation, suppression of EGP is more sensitive to insulin, compared with peripheral tissues. In contrast, the current data demonstrate that hyperglycemia in severely traumatized subjects in the fasted state and during iv nutrition is due to an increase in EGP, suggesting the presence of hepatic insulin resistance. However, when insulin infusion is given to normalize blood glucose concentrations, this is achieved by reduction of EGP, whereas WGD does not increase, demonstrating a simultaneous unresponsiveness (17) for insulin in peripheral tissues, as reported earlier after surgical trauma (18). This therefore suggests that at plasma insulin concentrations in the physiological range, hepatic insulin resistance seems to be responsible for hyperglycemia in the early phase of critical illness. However, during intensive insulin treatment to achieve blood glucose normalization, this occurs by suppression of EGP, whereas peripheral glucose disposal does not respond further.

These results are somewhat in contrast to earlier reports from Van den Berghe's group (8, 9), in which it was suggested that hepatic insulin resistance could not be overcome by insulin treatment in critical illness. There could be several plausible explanations for the diverging conclusions. First is the time-course. The conclusions from Van den Berghe's studies are based on data from critically ill patients after prolonged intensive care. It might well be that the relation between insulin sensitivity in the liver and periphery, respectively, changes with time. This has been reported earlier in insulin-resistant patients after surgery. In the early postoperative phase (0–1 d) it is mainly peripheral tissues that are affected (16), whereas 3 d postoperatively, the liver is more resistant to insulin (19). Second, the patients selected for analysis in Van den Berghe's studies were the nonsurvivors, a cohort that might not be representative for normal pathophysiology. Third and perhaps most important, results in the previous studies (8, 9) are based on analyses of expression of mRNA in specimens obtained postmortem after periods of end-stage critical illness of varying length, which might not be directly comparable with our *in vivo* kinetic data.

The increase in EGP noted in patients in the current study is in concordance with earlier reports on glucose turnover in stress, such as after major trauma (20) and elective surgery (16) using stable isotope methodology as well as in infected and noninfected burn victims using direct catheterization of the hepatic vein (21). EGP might originate from breakdown of glycogen stores and/or gluconeogenesis from amino acids, lactate, or glycerol. A marked ongoing glycogenolysis is less likely to have been present in the trauma patients studied currently because all measurements were performed in the fasted state (22). It is therefore more reasonable to suggest that gluconeogenesis accounted for the major part of EGP. Although the present data do not enable estimation of the relative contributions to gluconeogenesis from adipose tissue, lactate, and protein, respectively, it is likely that the increased EGP observed is indicative of an ongoing breakdown of tissue protein. This is also supported by the data from a study by Long *et al.* (23), who demonstrated by direct measurement of conversion of labeled alanine to glucose, that septic patients have an increased gluconeogenesis from alanine, despite glucose infusion.

The effects of blood glucose normalization by insulin infusion on EGP could be assumed to potentially render functional benefits. Earlier studies in patients undergoing elective surgery demonstrated that attenuation of postoperative insulin resistance by means of preoperative carbohydrate loading is associated with reduced nitrogen losses (24) as well as better preservation of lean tissues (25) and muscle strength (26) postoperatively. Furthermore, infusion of insulin has been shown to decrease muscle catabolism, as suggested by a decreased efflux of amino acids from skeletal muscle and reduced excretion of 3-methyl histidine and nitrogen after surgical trauma (27). A reduction of protein catabolism by insulin infusion has been reported after accidental trauma as well (28). The finding of reduced need for ventilatory support in insulin-treated patients in the study by Van den Berghe *et al.* (6) is also indicative of improved muscle function in response to normalization of hyperglycemia by insulin. These observations, taken together, suggest a link between carbohydrate and protein metabolism in postinjury metabolism. An increase in EGP could thus constitute a drive for liberation of gluconeogenic amino acids from skeletal muscle. Indeed, alternatively, these results could, at lest in part, be explained by a direct effect of insulin on protein metabolism.

In summary, the data from the current study suggest that in critical illness, hyperglycemia in the basal state is mainly accounted for by an increase in EGP, suggesting the presence of hepatic insulin resistance. In response to insulin during feeding, normoglycemia is achieved and maintained by suppression of EGP, whereas peripheral glucose uptake is not stimulated despite pharmacological concentrations of insulin in plasma. It is therefore suggested that defects in insulin action in the liver as well as in peripheral tissues contribute to hyperglycemia in critical illness. However, the observation that suppression of EGP by insulin is responsible for blood glucose normalization raises the possibility that reduced gluconeogenesis might be an important mechanism by which insulin treatment renders positive clinical effects in catabolic states.

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