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Acute Effects of Insulin-like Growth Factor I on Interorgan Glucose and Lactate Flux in Protein-Catabolic Dogs

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Insulin-like growth factor-I (IGF-I) is a potent protein-anabolic hormone with a glucose-lowering effect and is therefore a possible agent for treating catabolic patients. In this study we investigated the effect of recombinant human (rh) IGF-I on the interorgan flux of glucose under hypo- and normoglycemic conditions in catabolic, anaesthetized, and catheterized dogs. We administered a primed (40 μg/kg) continuous (1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion of rhIGF-I (Kabi Biopharma, Stockholm, Sweden) for 180 min together with either a saline (0.9% NaCl) or an amino acid solution (2.2 mg $AA \cdot kg^{-1} \cdot min^{-1}$ solution of Vamin, Kabi Nutrition, Stockholm, Sweden). RhIGF-I administration lowered plasma glucose levels for approximately 50% of the baseline ($P < 0.001$) and stimulated glucose uptake from skeletal muscle about twofold ($P < 0.01$), but did not modify glucose balances across the gut and liver. The same effects were found when infusing rhIGF-I together with AA. A co-infusion of rhIGF-I and glucose to maintain normoglycemic conditions stimulated glucose uptake from skeletal muscle by about fivefold ($P < 0.001$) and glucose uptake across the gut by about 50%, but reduced the hepatic glucose liberation (−65%; $P < 0.01$). The rhIGF-I infusion did not alter arterial lactate levels, but stimulated lactate release from skeletal muscle ($P < 0.05$) and lactate uptake across the liver ($P < 0.05$). We conclude that rhIGF-I reduces plasma glucose levels mainly by stimulating glucose uptake across skeletal muscle. Because muscular glucose uptake was higher than lactate release, rhIGF-I possibly stimulated glycogen synthesis or ATP formation in skeletal muscle and therefore may have positive effects on the peripheral energy deficit in catabolic state.

INTRODUCTION

Elective surgery, accidental injuries, sepsis, and burns generate similar effects on overall metabolism characterized by increased metabolic rate and stimulated protein loss. Associated with this are alterations of carbohydrate metabolism such as hyperglycemia and hyperinsulinemia, an increased gluconeogenesis, and a shift from glucose to fat oxidation [1].

Several studies have shown that the provision of excess calories or nitrogen by parenteral nutrition can reduce but not prevent nitrogen wasting. Protein catabolism can sometimes be countered in other ways, for example by the administration of anabolic hormones such as growth hormone or insulin-like growth factor-I (IGF-I) [2, 3]. Because IGF-I has a protein-sparing and glucose-lowering effect, it may be advantageously used in catabolic patients with hyperglycemia [4–7]. However, only a few studies have investigated the impact of an IGF-I infusion on organ-specific glucose metabolism. Recombinant human IGF-I (rhIGF-I) infusion increased the rate of peripheral glucose clearance in lambs made catabolic by the infusion of rTNF by about 50% and in awake fasted rats by 100% [8, 9]. In the later study it was shown that the stimulated muscular glucose uptake was used for glycogen synthesis, whereas hepatic glucose production was unaffected by IGF-I under euglycemic conditions. In depancreatized dogs, IGF-I was more potent in stimulating glucose utilization and less effective in reducing hepatic glucose production than insulin [4].

In this study we investigated the impact of IGF-I administration on glucose and lactate balances across skeletal muscle, liver, and gut under co-infusion of glucose and amino acids in anesthetized, catabolic dogs. The aim was to quantify the glucose-lowering potency of IGF-I in the immediate postoperative state.

METHODS

Animal Preparation

Male beagle dogs with an age of about 2 years (10–15 kg) were used. The dogs were fasted overnight (12 hr). On the morning of the study all dogs were subjected to general anaesthesia using nitrous oxide and oxygen (1:1)

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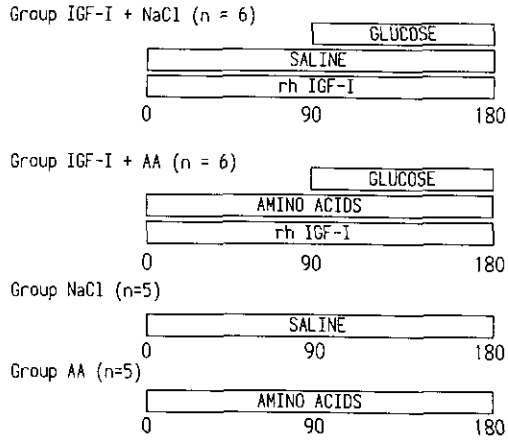

FIG. 1. Experimental protocol. In groups 1 and 2 (rhIGF-I + saline and rhIGF-I + AA) a primed (40 μg/kg), continuous (1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion of rhIGF-I, together with either NaCl or an amino acid solution (2.2 $mg \cdot kg^{-1} \cdot min^{-1}$) was given. In both groups glucose infusions were started 90 min after the start of rhIGF-I administration. Euglycemic conditions were reached 60 min after the start of glucose infusions. The control groups were matched concerning AA and fluid supply.

plus 0.5% halothane. A laparotomy was performed through a midline abdominal incision, for the placement of silicone rubber catheters (1 mm inner diameter; 2.2 mm outer diameter; Dow Corning, Midland, MI,). The catheters were implanted into the femoral artery, portal vein, hepatic vein, and femoral vein as described previously [10, 12]. Another catheter was placed in the internal jugular vein and was used for the infusion of either saline (0.9% NaCl) or amino acids, and glucose with or without IGF-I. Flow probes of appropriate inner and outer diameters (Heilige GmbH, Freiburg, Germany) were placed around the vena cava and the portal vein. The operation and the implantation of the catheters took about 1 hr. The experiment was started 30 min after completion of these procedures. Previous studies have proved that anaesthesia, operation (midline incision), and catheter insertion as used in this experimental protocol caused an enhanced amino acid (and nitrogen) flow from skeletal muscle to the gut and liver, which is significantly higher than in conscious dogs [10, 11, 13].

Experimental Design

We compared two groups of experimental animals (six dogs per group) with two groups of control animals (five dogs per group). Each animal of the experimental groups received a primed (40 μg/kg) continuous (1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion of rhIGF-I (Kabi Biopharma, Stockholm, Sweden) for 180 min and either a saline (0.9% NaCl) or an amino acid (AA) infusion (2.2 mg $AA \cdot kg^{-1} \cdot min^{-1}$ solution of 10% Vamin, Kabi Nutrition, Stockholm, Sweden) (Fig. 1). All dogs in the two experimental groups received glucose solutions for 90 min after the start of rhIGF-I administration.

Euglycemic conditions with glucose levels comparable to those before rhIGF-I infusion were held between 60 and 90 min after the start of the glucose load. The control animals received either NaCl or amino acids (same dosage as the experimental group) for 180 min without the infusion of glucose.

For the determination of arterial plasma concentrations of IGF-I, glucose, insulin and glucagon, blood was drawn 10 min before and at the start of rhIGF-I administration, at 10-min intervals thereafter to 90 minutes, and at 150, 165, and 180 min. After the start of the glucose infusions, arterial glucose levels were determined every 5 min. Organ balances were analyzed 60, 75, 90, 150, 165, and 180 min after the start of the infusion program (Fig. 1). At these time points, blood flow measurements were performed and blood was drawn simultaneously from the femoral artery and the hepatic, portal, and femoral veins.

Analytical Methods

Plasma glucose, lactate, and urea were determined enzymatically (Boehringer–Mannheim Biochemicals, Indianapolis, IN). Total plasma IGF-I was determined after acid ethanol extraction and measured with a double antiimmunoassay method (IRMA-mat IGF-I test kit; Byk. Sangtec, Dietzenbach, Germany). Glucagon, insulin (Serono, Milano, Italy), and cortisol (Incstar, MN) were estimated by commercial radioimmunoassay methods.

Epinephrine and norepinephrine were analyzed with hplc and electrochemical detection [14] and plasma amino acids with hplc.

Blood flow in the respective vessels (artery and portal vein) was measured electromagnetically and was corrected for the corresponding packed cell volume to obtain plasma flow values. The hindlimb was assumed to contain 25% of the total skeletal muscle; therefore, plasma (blood) flow in the hindlimb was multiplied by four to calculate plasma flow of the total skeletal muscle [13]. The hepatic and muscle plasma flows determined in the present experiment were similar to those that we and others had reported previously.

Calculation and Statistics

Net release or removal of glucose or lactate was calculated by multiplying the arteriovenous plasma concentration differences by the rate of plasma flow. In the case of the liver there is a dual supply of substrates, by the portal vein and the hepatic artery, respectively. It was assumed that 72% of the hepatic blood flow was through the portal vein and 28% via the hepatic artery [15, 16]. These plasma flow figures were multiplied by the respective concentrations in the portal vein and artery to calculate the total amount of substrate inflow into the liver. Balances across the hindlimbs were assumed to be representative of balances across skeletal muscle. We chose

TABLE 1

Blood Chemistry Before and After Operation

	Preop	Post (after catheter insertion)
Glucose (m*M*)	5.8 ± 0.16	7.0 ± 0.27*
Urea (m*M*)	4.3 ± 0.2	8.3 ± 0.4*
Total AA (μmole/liter)	2850 ± 170	2703 ± 97
Insulin (IU/ml)	10.6 ± 0.9	11.4 ± 0.76
Glucagon (pg/ml)	120 ± 12	231 ± 21**

* $P < 0.001$ vs preop.
** $P < 0.01$.

to refer to the substrate balance across the extrahepatic splanchnic tissue as that of the gut." A positive balance indicates net substrate uptake (disappearance), and a negative balance indicates net substrate release (formation). Neutral balance is defined as not being different from zero. Organ balances were determined at 60, 75, and 90 (hypoglycemic state") and 150, 165, and 180 (normoglycemic state") min after the start of rhIGF-I administration. Since there was no significant difference among the balances done at either 60, 75, and 90 minutes or those at 150, 165, and 180 minutes, they were averaged.

Analysis of variance with repeated measures was used to determine whether there was a difference between the values obtained for the experimental and control groups, respectively. Analysis of statistical differences was performed by using Wilcoxon's matched-pairs signed rank test, and (exact permutational) *P*-values were derived in view of the small sample size. All data are expressed as means ± SEM.

RESULTS

As shown in Table 1, the plasma levels of glucose, urea, and glucagon were significantly higher in the postoperative state. No concentration differences were found for total amino acid and insulin concentrations.

The average plasma flow rates in the hindlimbs, liver, and gut of all dogs were 6.6 ± 0.2, 18.6 ± 1.2, and 13.8 ± 1.0 $ml \cdot min^{-1} \cdot kg^{-1}$ in the basal period and did not change during the infusion of rhIGF-I.

Effect of rhIGF-I on Plasma IGF-I and Insulin Levels

As shown in Fig. 2, the infusion of rhIGF-I produced an 8- to 10-fold increase in plasma IGF-I concentrations above baseline.

rhIGF-I had no influence on the plasma insulin levels in the NaCl group (12.3 ± 0.8 vs 11.2 ± 1.0 μU/ml) but evoked a significant decrease of plasma insulin in the AA group (13.8 ± 1.4 vs 8.9 ± 0.6 μIU/ml; $P < 0.05$). The combined infusions of glucose and rhIGF-I caused an increase of plasma insulin levels to 14.3 ± 2.1 μU/ml in the NaCl group ($P < 0.05$) and to 14.4 ± 2.8 μU/ml in the AA group (n.s.). Insulin levels in the two control groups remained unchanged (Table 2).

Effect of rhIGF-I on Counterregulatory Hormone Levels

Hypoglycemia, evoked by the rhIGF-I administration, increased plasma glucagon and plasma epinephrine levels significantly ($P < 0.05$). However, during the euglycemic study period, plasma glucagon and epinephrine values decreased to concentrations not different from the control groups (Fig. 3).

Effect of rhIGF-I on Organ-Specific Glucose Metabolism

Under rhIGF-I, the plasma glucose concentrations fell rapidly, reached a minimum of about 50% of baseline after 60 min, and remained constant during the next 30 min (Fig. 4). Afterward, we started with the infusion of glucose and reached blood levels comparable to those of the control groups (7.2 ± 0.4 mmole/liter in the saline + rhIGF-I group, 7.8 ± 0.46 in the AA ± rhIGF-I group) after 60 min. Substrate balances were repeated at this point and done three times under euglycemic conditions.

RhIGF-I increased glucose uptake from skeletal muscle about twofold (from 4.5 ± 1.2 $\mu mole \cdot min^{-1} \cdot kg^{-1}$ to 10.5 ± 2.4 in the saline group and from 5.5 ± 0.3 $\mu mole \cdot min^{-1} \cdot kg^{-1}$ to 10 ± 2.5 in the amino acid group; $P < 0.001$), but did not modify glucose balances across the gut and liver. RhIGF-I administered together with glucose stimulated muscular glucose uptake nearly fivefold (24 ± 3.5 $\mu mole \cdot min^{-1} \cdot kg^{-1}$ in the saline group, 24.5 ± 4 in the amino acid group; $P < 0.001$ compared to basal state) and glucose uptake across the gut by about 50%, but reduced hepatic glucose liberation by about 65% (from −13.3 ± 1.1 $\mu mole.min^{-1} \cdot kg^{-1}$ to −5 ± 0.65 in the saline group and from −15 ± 2.7 $\mu mole \cdot min^{-1} \cdot kg^{-1}$ to

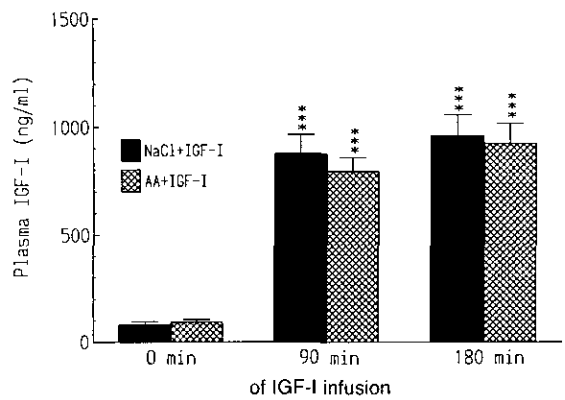

FIG. 2. Plasma levels of IGF-I. Plasma levels of IGF-I before IGF-I infusions (0 min) and after 90 min of IGF-I infusions under intravenous saline (■, NaCl) or amino acid (▨, AA) administration. The values at 180 min of IGF-I infusions represent the concentration under co-infusion of glucose (glucose load). Results are expressed as the mean ± SEM. ***$P < 0.001$ vs respective control groups.

TABLE 2

Plasma Concentrations of Insulin in the Control and Experimental Groups ($\bar{x} \pm 1$)

Insulin [μIU/ml] (mean ± SEM)	Controls			IGF-I	
	NaCl	AA		NaCl	AA
Pre	8.7 ± 0.2	9.2 ± 0.8	Pre	12.3 ± 0.8	13.8 ± 1.4
60—90 min	8.9 ± 1.5	11.2 ± 5.9	Hypoglycemia	11.2 ± 1.0	8.9 ± 0.6*
150—180 min	9.5 ± 1.0	11.5 ∓ 4.9	Euglycemia	14.3 ± 2.1	14.4 ± 2.8

*$P < 0.05$ vs pre IGF-I group.

-4.3 ± 0.6 in the amino acid group; $P < 0.01$ vs control group). These alterations were independent of whether NaCl or AA were co-infused (Fig. 5).

Effect of rhIGF-I on Organ-Specific Lactate Metabolism

The rhIGF-I infusion did not alter arterial lactate levels (2.4 ± 0.4 mmole/liter in saline controls; 2.74 ± 0.5 in saline + IGF-I; 2.4 ± 0.7 in amino acid group; and 2.9 ± 0.4 in amino acid + IGF-I group). IGF-I infusion stimulated lactate release across skeletal muscle from a net release of -8.1 ± 2 $\mu mole \cdot kg^{-1} \cdot min^{-1}$ to -11.3 ± 1.2 $\mu mole \cdot kg^{-1} \cdot min^{-1}$ in the saline group ($P < 0.05$), and from a net release of -10.3 ± 2.4 $\mu mole \cdot kg^{-1} \cdot min^{-1}$ to -14.8 ± 2.5 $\mu mole \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.05$) in the group infused with amino acids. The co-infusion of glucose did not affect lactate release from skeletal muscle. The infusion of rhIGF-I stimulated net hepatic lactate uptake in both experimental groups from 4.8 ± 0.2 $mmole \cdot kg^{-1} \cdot min^{-1}$ to $+9.2 \pm 1$ $\mu mole \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.01$) in the saline group and from $+10.4 \pm 1.2$ $\mu mole \cdot kg^{-1} \cdot min^{-1}$ to 20.2 ± 2.3 $\mu mole \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$) in the amino-acid-infused groups. Lactate balances across the gut remained neutral in all groups studied (Fig. 6).

DISCUSSION

The immediate postoperative phase is characterized by hyperglycemia. This response initially results from enhanced glycogenolysis and is subsequently due to increased glucose production coupled with reduced peripheral glucose utilization. Also in the current study, postoperative plasma glucose levels were higher than in the preoperative state. Glucose flux between liver and skele-

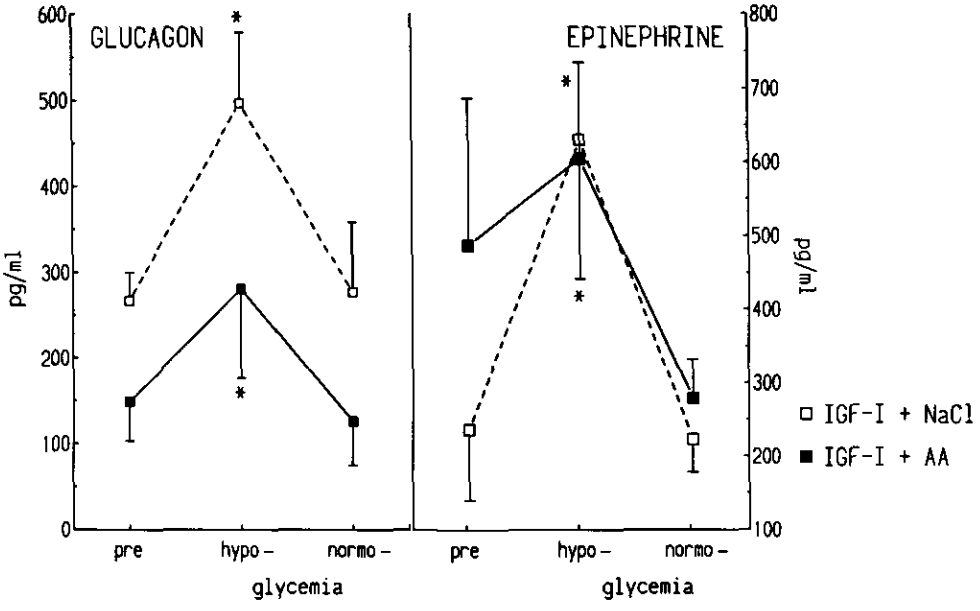

FIG. 3. Course of plasma levels of glucagon and epinephrine before administration of rhIGF-I (pre) and during hypo-and normoglycemic state. Rh-IGF-I was infused together with NaCl (□) or amino acids (■). Results are expressed as mean ± SEM. *$P < 0.05$ vs beginning of the study (pre).

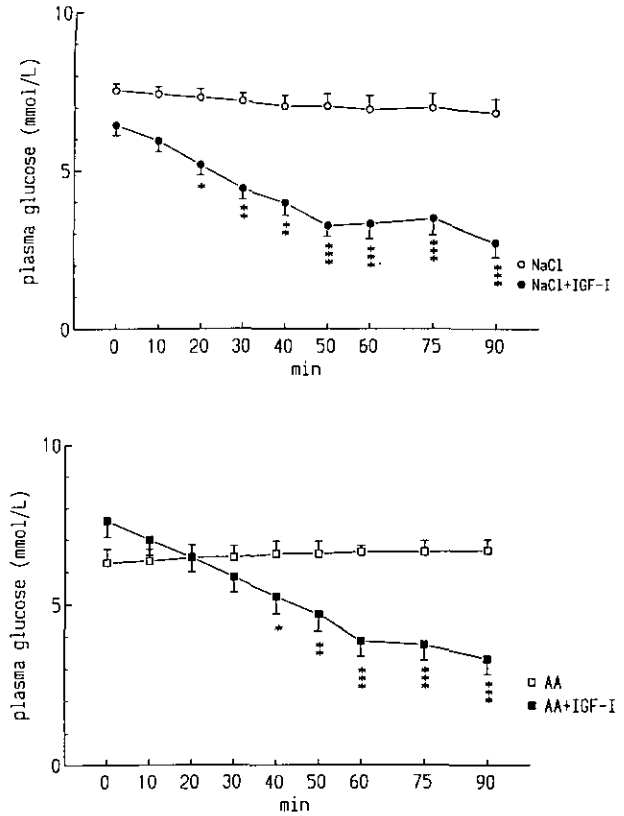

FIG. 4. Arterial glucose levels. Arterial glucose levels under saline (○, NaCl) and amino acids (□, AA; 2.2 mg AA·min^{-1}·kg^{-1}) or during infusions of IGF-I (40 μg·kg + 1.5 μg·min^{-1}·kg^{-1}) together with either saline (●, NaCl + IGF-I) or amino acids (■, AA + IGF-I). Results are expressed as the mean ± SEM. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs the respective control groups.

tal muscle in the control group was comparable to results obtained in dogs on the second and fourth postoperative day [17]. Altered organ-specific glucose metabolism in the postoperative state is due to increased sympathetic activity and impairment of the direct action of insulin in stimulating glucose uptake across skeletal muscle [18]. In our experiment, the postoperative glucagon levels were also higher than preoperative levels.

IGF-I has a variety of biological functions such as promoting glucose uptake and stimulating glycogen synthesis in rat heart and diaphragm muscle [19, 20], accelerating amino acid transport in fibroblasts, and increasing protein synthesis in cartilage [21]. The metabolic effects of IGF-I are dependent on the mode of administration [22]. Given chronically in low doses, IGF-I is the major growth-promoting factor *in vivo* [23]. At supraphysiological doses, IGF-I has been found to lower blood glucose in nondiabetic animals and humans [8, 24, 25]. In the current study we administered large amounts of rhIGF-I over a period of 180 min. The basal total IGF-I levels after operation and catheter insertion in our dogs were similar to those observed in beagle dogs before fasting [4]. The administration of rhIGF-I increased total IGF-I levels 8-to 10-fold and reduced plasma glucose levels by about 40%. Reduced concentrations of IGF-I have been found in critically ill patients [26, 27]. Preliminary studies in humans and mice have shown that the administration of IGF-I increases plasma levels of IGF-I and reduces weight loss in catabolic situations [28, 29]. However, IGF-I could not reduce amino acid efflux from skeletal muscle in the catabolic dog model [12].

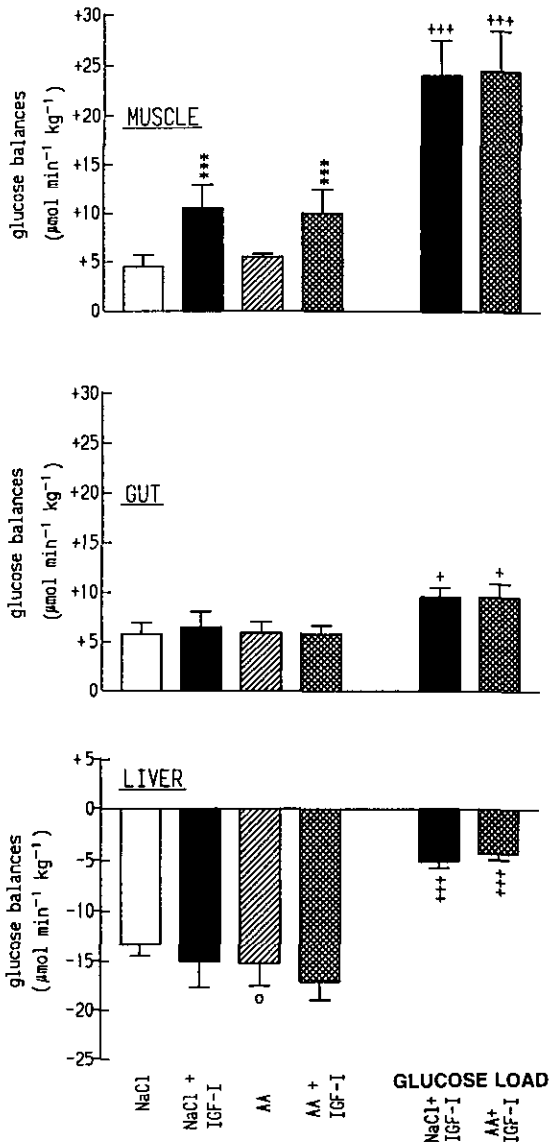

FIG. 5. Effects of IGF-I, amino acid, and glucose infusions on organ-specific glucose flux. Glucose balances (μmole·min^{-1}·kg^{-1}) across skeletal muscle, gut, and liver during infusions of either saline (□, NaCl), saline plus IGF-I (■, NaCl + IGF-I), amino acids (▨, AA) or amino acids plus IGF-I (▩, AA + IGF-I). The two columns on the right side of the figure represent the glucose balances during a glucose load under euglycemic conditions under the infusion of either saline plus IGF-I (■, NaCl + IGF-I) or amino acids and IGF-I (▩, AA + IGF-I). A plus sign (+) denotes uptake and a minus sign (−) denotes release. Values are expressed as mean ± SEM. $^{***}P < 0.001$ vs the respective control groups. $^{*}P > 0.05$ vs NaCl group; $^{+}P < 0.05$, $^{+++}P < 0.01$ vs the respective IGF-I groups without glucose loading.

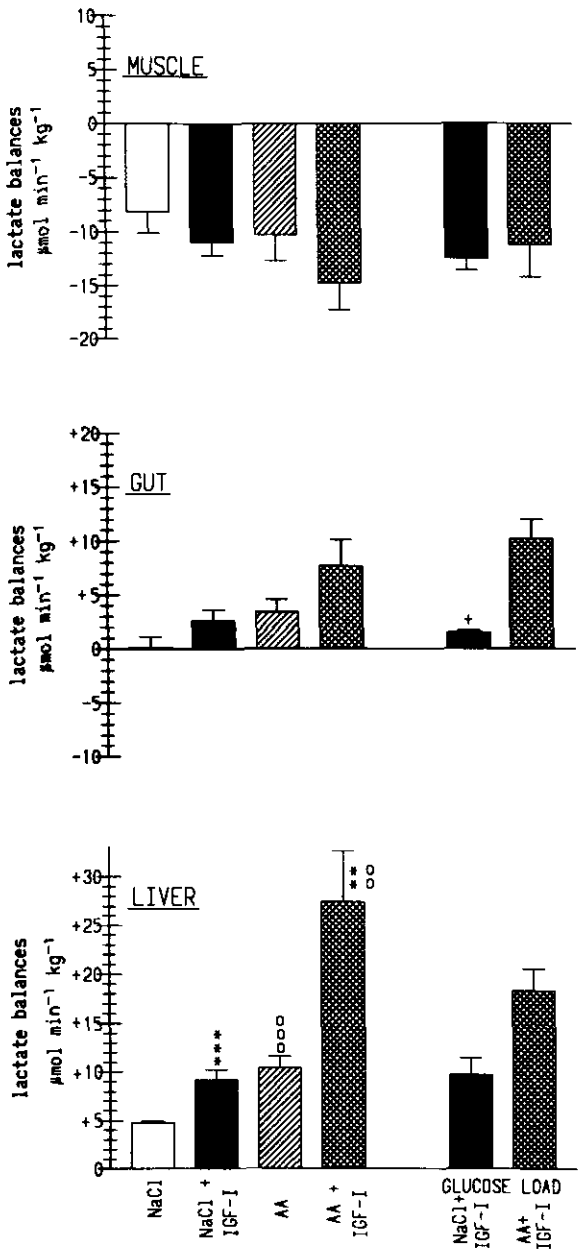

FIG. 6. Effects of IGF-I, amino acid, and glucose infusions on organ-specific lactate flux. Lactate balances (μmole·min^{-1}·kg^{-1}) across skeletal muscle, gut, and liver during infusions of saline (□, NaCl), saline plus IGF-I (■, NaCl + IGF-I), amino acids (▨, AA) or amino acids plus IGF-I (▩, AA + IGF-I). The two columns on the right side of the figure represent the lactate balances during a glucose load under euglycemic conditions under the infusion of either saline plus IGF-I (■, NaCl + IGF-I) or amino acids and IGF-I (▩, AA + IGF-I). A plus sign (+) denotes uptake and a minus sign (−) denotes release. Values are expressed as mean ± SEM. $^{***}P < 0.001$ vs the respective control groups. $^{*}P > 0.05$ vs NaCl group; $^{+}P < 0.05$, $^{+++}P < 0.001$ vs the respective IGF-I groups without glucose load.

We performed our glucose balances under conditions of steady-state hypoglycemia and again when normoglycemia was reached under co-infusion of rhIGF-I and glucose. During IGF-I-induced hypoglycemia the glucose uptake across skeletal muscle was approximately doubled, whereas the glucose balance across liver and gut remained unaffected. These results reveal that the stimulation of peripheral glucose uptake by rhIGF-I in the immediate postoperative state is comparable with the effects in conscious fasted rats [8], but twofold higher than in lambs made catabolic by the infusion of TNF-α [9]. This difference may be due to the distinction between the two models. In agreement with results obtained in conscious fasted rats, rhIGF-I infusion did not affect glucose balances across the liver and the gut.

The organism's defense against the deleterious effects of prolonged hypoglycemia is the same whether hypoglycemia is induced by insulin or IGF-I [25]. Hypoglycemia triggers the release of various counterregulatory hormones such as glucagon, epinephrine, norepinephrine, and cortisol [30]. The impact of counterregulatory hormones on glucose metabolism is time-dependent [31]. Stimulation of systemic glucose metabolism under glucagon exposure reaches a maximum at about 100 min after administration, whereas epinephrine and cortisol reach their peak levels at about 2.5 and 9 hr after hormone exposure [31]. In the current study, the plasma levels of glucagon and epinephrine were enhanced, whereas cortisol and norepinephrine concentrations remained unchanged during hypoglycemia. Because of the prolonged response time of glucose metabolism to epinephrine, the raised epinephrine levels should not have influenced the glucose balance data. Several studies have shown that stimulated glucagon secretion causes a rise in hepatic glucose production [30, 32]. However, in the current study, the hepatic glucose balances were not altered under rhIGF-I-evoked hypoglycemia. A possible explanation for the unchanged hepatic glucose balance is that glucagon and IGF-I have an antagonistic mode of action on hepatic glucose production, namely, that glucagon stimulates and IGF-I suppresses the glucose formation in the liver. Rh-IGF-I did not suppress gluconeogenesis in conscious rats, but reduced glucose production by 25% in depancreatized dogs [4, 8]. In the second study period, when glucose co-infusions caused normoglycemic conditions (glucose clamp technique), the glucagon and epinephrine returned to normal levels and the balances measured at this time point were scarcely affected by hormones other than IGF-I.

Infusion of rhIGF-I did not influence plasma insulin levels in the saline group. Co-infusion of rhIGF-I and amino acids reduced, while the administration of rhIGF-I together with glucose increased, plasma insulin levels. However, these changes (controls, about 12 μU/ml; AA group, 9 μU/ml; and glucose group, 4.5 μU/ml) were minimal by comparison with insulin level fluctuations found in Intensive Care Unit patients and can scarcely account for the enormous changes of glucose balances found in this study.

Infusion of amino acids together with rhIGF-I had no additional effect on the peripheral glucose balances

when compared to the saline group, but evoked a significant higher hepatic glucose formation, possibly via gluconeogenesis stimulated by the infused amino acids.

Infusion of glucose together with rhIGF-I (glucose clamp) stimulated glucose uptake across the hindlimb by a factor of five compared to saline and of 2.5 compared to saline plus rhIGF-I infusion. Thus, rhIGF-I infusion with maintenance of euglycemia produced a sustained rise in muscular glucose uptake. In addition to skeletal muscle, the gut participates in the enhancement of glucose disposal by IGF-I. Previous studies have already demonstrated that the principal site of enhanced glucose uptake during hyperinsulinemia is muscle tissue [33] and that the same is true for IGF-I. In awake, fasted rats, rhIGF-I increased glycogen synthesis in the liver [8]. Although we did not measure glycogen synthesis in our experiment, our data show that rhIGF-I when given together with glucose suppresses hepatic glucose release. The suppression of IGF-I on hepatic glucose balance was also found in pancreatectomized dogs, but not in normal conscious rats [4, 8].

The methods used in the current study do not allow us to conclude whether the glucose taken up from the muscle is metabolized via glycolysis or used for glycogen synthesis. However, we have measured lactate balances across skeletal muscle and have found that rhIGF-I stimulates peripheral lactate release, but to a degree insufficient to account for additional glucose uptake under rhIGF-I. Accordingly, rhIGF-I seems to promote glycogen synthesis.

Several *in vitro* and *in vivo* experiments have shown that IGF-I stimulates glucose incorporation into glycogen [8, 24]. In spite of a stimulated peripheral lactate release under rhIGF-I, the plasma lactate levels remained unchanged, because this increased release was compensated by a stimulated lactate uptake from liver and gut.

In conclusion our data show that in the catabolic state, rhIGF-I is a powerful agent for lowering blood glucose levels, mainly by stimulating glucose uptake across skeletal muscle. A stimulated glucose extraction across skeletal muscle may reduce the peripheral energy deficit which is characteristic of catabolic illness [34]. An additional advantage of postoperative IGF-I administration is that it can suppress hepatic glucose formation when infused together with glucose. This may be advantageous in septic patients with a sustained stimulation of gluconeogenesis [35].

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