Effect of Hyperinsulinemia on Myocardial Amino Acid Uptake in Patients With Coronary Artery Disease

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Branched-chain amino acids (BCAAs) are oxidative energy substrates for the heart and may exert anabolic effects on myocardial protein. The factors regulating their myocardial uptake in patients with ischemic heart disease are therefore of interest. To examine whether myocardial BCAA utilization is influenced by the circulating insulin concentration, in 10 patients with chronic ischemic heart disease, we measured transmyocardial amino acid balance during fasting and again during a 90-minute euglycemic insulin infusion (plasma insulin, 218 ± 25 $\mu U \cdot mL^{-1}$) with plasma BCAA concentrations held constant by coinfusion. In the fasting state, the myocardial fractional extraction of leucine (8%), isoleucine (9%), and valine (5%) from arterial plasma was slightly greater than that of glucose (3%), while net myocardial BCAA uptake (leucine, 409 ± 207 $nmol \cdot min^{-1}$; isoleucine, 220 ± 144 $nmol \cdot min^{-1}$; valine, 407 ± 326 $nmol \cdot min^{-1}$; and total BCAA uptake, 1.0 ± 0.3 $\mu mol \cdot min^{-1}$) was about 13% that of glucose (8 ± 2 $\mu mol \cdot min^{-1}$). During euglycemic hyperinsulinemia, myocardial glucose uptake increased 3-fold, but there was no change in the arterial-coronary sinus balance or net myocardial uptake of any BCAA under conditions where their plasma concentrations were held constant. Instead, the myocardial uptake of each BCAA correlated positively with its concentration in arterial plasma. These results demonstrate that in patients with cardiovascular disease, myocardial utilization of BCAAs is insensitive to the circulating insulin level and is regulated instead by their availability in arterial plasma. Hyperinsulinemia reduced the magnitude of both net glutamate uptake and alanine release, suggesting a possible salutary effect on myocardial oxidative efficiency.

UNDER MOST CONDITIONS, the heart exhibits significant net uptake of only a few circulating substrates including glucose, lactate, fatty acids, ketone bodies, and the three branched-chain amino acids (BCAAs) leucine, isoleucine, and valine.[1] The BCAAs are present in appreciable quantities in plasma ($\sim$0.5 $mmol \cdot L^{-1}$) and can be oxidized by the myocardium.[2] During prolonged fasting or under conditions of ischemia[3-4] or high energy demand,[5-6] BCAAs derived from the mobilization of muscle protein may be an important alternative energy substrate for the heart. BCAAs may also exert anabolic effects on cardiac protein[7-10] and protect against myocardial ischemia.[11] These considerations suggest that BCAA supplementation might be a useful adjunctive therapy for some patients with ischemic heart disease. Nevertheless, the factors regulating BCAA utilization by the human heart in vivo remain incompletely defined.

Patients with ischemic heart disease appear to differ from healthy subjects in the myocardial uptake and release of amino acids.[12-17] In a previous study of such patients, we observed that the myocardial uptake of each BCAA could be increased by increasing its plasma concentration via supplemental infusion.[10] In that study, the potential influence of insulin action on heart BCAA uptake was not examined. This question has recently assumed importance with the publication of evidence that insulin administration improves the outcome from acute myocardial ischemia,[18] by an unknown mechanism. Accordingly, in the current study, we tested the hypothesis that myocardial uptake of BCAAs in patients is influenced by the circulating insulin concentration. To allow an evaluation of insulin's effect isolated from other potential influences on myocardial substrate metabolism, the plasma insulin level was manipulated by physiologic substrate clamp techniques with plasma glucose and BCAA levels held constant.

SUBJECTS AND METHODS

Subjects

Ten men aged 56 ± 4 years (range, 46 to 69) were enrolled from patients referred for elective coronary angiography to evaluate stable angina pectoris. Patients were excluded if they had diabetes mellitus, previous myocardial infarction, or chest pain within the 24 hours preceding study. The subjects were mildly obese (body mass index, 27.8 ± 1.2 $kg \cdot m^{-2}$), 6 had essential hypertension, and all were sedentary. Medications included calcium-channel antagonists in 6 subjects, β-adrenergic blockers in 6, and nitrates in 5. The study protocol was approved by the Human Studies Committee of the Connecticut Department of Veterans Affairs Medical Center, and all subjects provided written informed consent. Other results from these subjects have been reported previously.[19]

Experimental Protocol

Subjects fasted for 12 to 16 hours and were mildly sedated with diazepam. Plastic cannulae were placed in an antecubital vein for infusions and in the proximal coronary sinus and femoral artery for blood sampling. A #7 French thermodilution catheter (Baim catheter; Electrocatheter, Rahway, NJ) was used to cannulate the coronary sinus to allow both coronary venous blood sampling and measurement of coronary sinus blood flow.

Following catheter placement, paired samples of arterial and coronary sinus blood were drawn in quadruplicate at 5-minute intervals and placed in heparinized tubes on ice for subsequent measurement of plasma insulin, glucose, and amino acid concentrations. Coronary sinus blood flow was then measured in triplicate by the continuous thermodilution method[20] and the results were averaged.

Next, a primed (100 $mU \cdot m^{-2} \cdot min^{-1}$ for 10 minutes) continuous (50 $mU \cdot m^{-2} \cdot min^{-1}$) intravenous infusion of regular insulin (Humu-

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lin; Lilly, Indianapolis, IN) was administered for 90 minutes. The arterial blood glucose level was measured every 5 to 10 minutes and maintained at the basal level using a variable-rate infusion of 20% glucose. An amino acid solution (10% Travasol; Baxter Healthcare, Deerfield, IL) was infused simultaneously at 0.08 mL · kg^{-1} · min^{-1} (1.3 mg amino N_2 · kg^{-1} · min^{-1}) to maintain the plasma concentrations of most amino acids constant during insulin infusion. Quadruplicate paired samples of arterial and coronary sinus blood were obtained again during the final 10 minutes of insulin infusion. Following completion of these measurements, coronary angiography and left ventriculography were performed using standard techniques.

Chemical Analyses

Whole blood and plasma glucose concentrations were measured by an automated glucose oxidase analyzer (YSI analyzer; Yellow Springs Instrument, Yellow Springs, OH). The plasma insulin concentration was measured by a double-antibody radioimmunoassay kit (New England Nuclear, Boston, MA). Amino acid concentrations were measured in sulfosalicylic acid extracts of plasma using an automated ion-exchange chromatographic technique (D-500 Amino Acid Analyzer; Dionex, Sunnyvale, CA).

Calculations

The net myocardial balance (in micromoles per liter) for individual amino acids and for glucose was calculated by subtracting their coronary venous from their arterial concentration. The percent extraction from arterial plasma was calculated by dividing this arterial-coronary venous difference by the simultaneous arterial concentration and multiplying by 100. Net myocardial uptake (in nanomoles per minute) was then calculated by multiplying the net balance by the corresponding coronary sinus plasma flow (coronary sinus blood flow × [1 − hematocrit]) in milliliters per minute at each sampling time.

Statistical Analysis

Measurements from quadruplicate plasma samples were averaged to yield value for each of the measured quantities at each of the two (basal and insulin-infused) sampling times in each subject. Comparisons between the two sampling times were made by 2-tailed Student's paired *t* tests. Differences were considered significant at a *P* value less than .05.

RESULTS

Hemodynamics and Coronary Sinus Flow

Basal systolic and diastolic blood pressure was 130 ± 11 and 82 ± 7 mm Hg and the heart rate was 68 ± 7 bpm, and these parameters were not affected by insulin infusion. Coronary sinus blood flow was 61 ± 6 mL · min^{-1} in the basal state, and during insulin infusion, it increased modestly in every subject to 68 ± 7 mL · min^{-1}. With angiography, all patients were found to have significant (<50%) atherosclerotic narrowing of at least one major coronary artery, but left ventricular systolic function was normal (left ventricular ejection fraction, 53% ± 3%). No patients demonstrated clinical, hemodynamic, or electrocardiographic evidence of myocardial ischemia during the study.

Blood Glucose and Insulin Levels and Whole Body Glucose Utilization

The arterial plasma insulin concentration was 22 ± 4 μU · mL^{-1} in the fasting state (normal for our assay, <10 μU · mL^{-1}) and increased to 218 ± 25 μU · mL^{-1} during insulin infusion. Arterial blood glucose was 4.8 ± 0.2 mmol · L^{-1} during fasting and was maintained between 5.0 and 5.9 mmol · L^{-1} during insulin infusion. The glucose infusion rate required for this was 11 ± 1 μmol · kg^{-1} · min^{-1}.

Plasma Amino Acid Concentrations

Arterial plasma concentrations of representative amino acids are shown in Table 1. In the fasting state, the most abundant amino acids in arterial plasma were glutamine (467 ± 8 μmol · L^{-1}) and the BCAAs (total concentration, 417 ± 5 μmol · L^{-1}). During experimental infusion, there was a significant increase in the arterial plasma concentration of the amino acids present at high concentration in 10% Travasol (glycine, alanine, and phenylalanine) and a slight reduction in the concentration of tyrosine and glutamate. In the case of the BCAAs, the 10% Travasol infusion succeeded in maintaining the plasma concentrations close to the basal level during insulin infusion.

Table 1. Amino Acid Plasma Concentration and Myocardial Uptake

	Arterial Concentration (μmol · L^{-1})		A-CV Balance (μmol · L^{-1})		Myocardial Uptake (nmol · min^{-1})	
Amino Acid	Fasting	Insulin	Fasting	Insulin	Fasting	Insulin
Threonine	133 ± 12	159 ± 13	−5 ± 10	−4 ± 3	−183 ± 366	−163 ± 122
Glutamate	95 ± 5	87 ± 5	70 ± 2	47 ± 4*	2,562 ± 83	1,918 ± 150*
Glutamine	467 ± 18	431 ± 12	−18 ± 4	−21 ± 4	−659 ± 146	−857 ± 163
Glycine	192 ± 14	326 ± 20*	−1 ± 1	−4 ± 8	−39 ± 369	−165 ± 318
Alanine	238 ± 14	314 ± 15*	−26 ± 14	−12 ± 10	−954 ± 510	−491 ± 670
Phenylalanine	46 ± 5	76 ± 6*	0 ± 3	3 ± 2	0 ± 105	126 ± 43
Tyrosine	52 ± 6	46 ± 7*	0 ± 4	1 ± 2	0 ± 160	41 ± 87
Leucine	131 ± 12	151 ± 13	11 ± 5	11 ± 4	409 ± 207	444 ± 226
Isoleucine	64 ± 8	75 ± 7	6 ± 4	5 ± 4	220 ± 144	204 ± 159
Valine	222 ± 14	250 ± 12	11 ± 9	9 ± 5	407 ± 326	371 ± 204
BCAAs	417 ± 25	452 ± 22	28 ± 16	24 ± 11	1,041 ± 319	1,017 ± 238

NOTE. Results are the arterial concentration, arterial (A) minus coronary venous (CV) balance, and myocardial uptake of amino acids in the fasting state and during the final 15 minutes of a 90-minute insulin infusion.

*$P < .05$ *v* fasting.

Myocardial Glucose and Amino Acid Balance

Amino acid balance data are shown in Table 1. In the fasting state, there was significant myocardial uptake of each BCAA, as well as glutamate, and net release of glutamine and alanine. Fractional extraction of BCAAs from arterial plasma by the heart averaged 5% for valine, 8% for leucine, and 9% for isoleucine; the corresponding net myocardial uptake values were 407 ± 326, 409 ± 207, and 220 ± 144 nmol · min^{-1}, respectively (total BCAA uptake, 1.0 ± 0.3 μmol · min^{-1}). By comparison, fractional extraction of glucose in the fasting state was 3% ± 1% and net myocardial glucose uptake 8.1 ± 2.0 μmol · min^{-1}.

During insulin infusion, fractional glucose extraction increased to 8% ± 1% and myocardial uptake to 25.5 ± 4.1 μmol · min^{-1}. Glutamate uptake declined, but there were no significant changes in the arterial-coronary venous balance or myocardial uptake of any other amino acid. Specifically, under conditions of constant arterial plasma BCAA concentration, insulin had no effect on the myocardial uptake of any BCAA. Myocardial uptake of each of the BCAAs instead correlated positively with their concentration in arterial plasma (Fig 1).

DISCUSSION

In this study, patients with ischemic heart disease exhibited net myocardial uptake of each of the three BCAAs in the overnight-fasted state, with total net BCAA uptake averaging about 13% that of glucose. Systemic insulin infusion increased glucose uptake by both the heart and tissues of the whole body, demonstrating a generalized stimulatory effect of insulin on muscle glucose consumption. In contrast, insulin infusion did not change the net arterial-coronary sinus balance or myocardial uptake of any of the BCAAs under conditions in which their circulating concentration remained constant. Instead, the myocardial uptake of each BCAA correlated positively with its concentration in arterial plasma.

Early studies of insulin action in vitro generally reported positive effects on amino acid uptake by the isolated crystalloid perfused rat heart.[8,21-22] The effect of insulin on amino acid uptake by muscles in vivo has been more difficult to assess, in part because systemic insulin administration reduces the plasma concentration of many amino acids and thus their availability to tissues.[5,23-24] Most previous examinations of insulin's effects on heart substrate metabolism in vivo have not attempted to control the circulating amino acid concentration, or indeed the glucose concentration, and often involved nonphysiologic insulin doses as well.[5,12,15,25] The main experimental refinement of the current study is the administration of insulin by the hyperinsulinemic-euglycemic clamp technique with plasma BCAA levels held constant; this permitted an examination of the effect of the circulating insulin level on heart uptake of BCAAs absent changes in their plasma availability. The finding that insulin did not stimulate BCAA uptake by the heart under these conditions, while novel in humans, agrees with previous suggestions from studies of insulin and amino acid infusions in canines.[24] It also agrees with previous observations that insulin is without a direct effect on leucine uptake by tissues of the human forearm[26] or whole body[27] under conditions of constant plasma leucine concentration. Taken together, the current findings extend our previous observations on supraphysiologic BCAA administration,[10] and demonstrate that BCAA availability in circulating plasma is the principal physiologic determinant of BCAA uptake by the human heart throughout their physiologic concentration range.

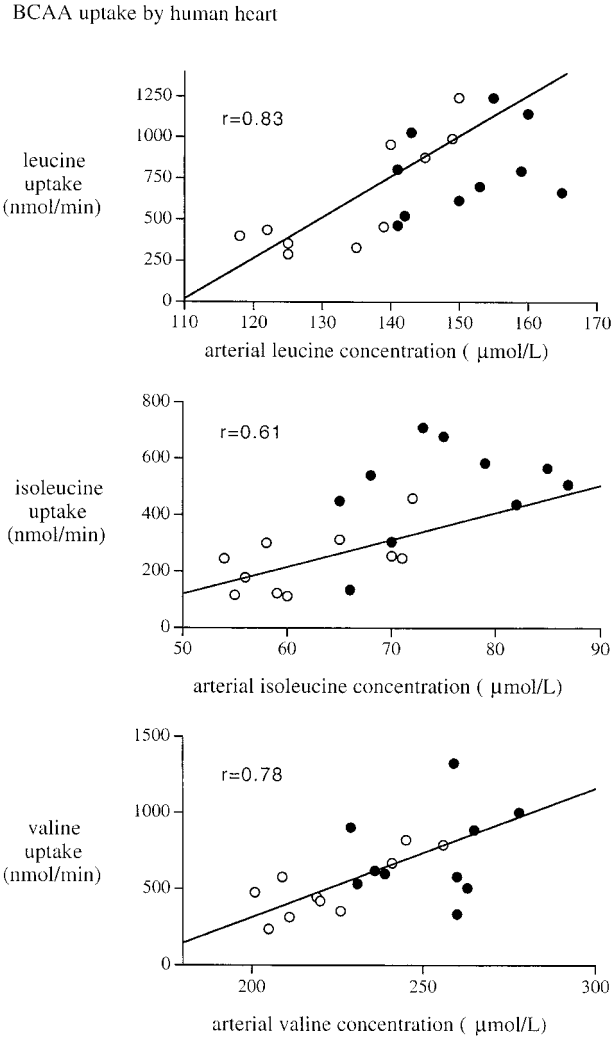

Fig 1. Plasma concentration versus myocardial uptake for leucine, isoleucine, and valine. Each point represents a measurement made at 1 time point (basal or insulin-infused) in 1 subject. Linear correlation plots are shown along with corresponding *r* values. (○) Fasting; (●) insulin-infused.

While the study does not address the mechanism by which BCAAs are imported into the myocardium in vivo, the findings are consistent with the observation that myocyte BCAA uptake in vitro is effected primarily by the sarcolemma L transporter system. In vitro, this system transports most large neutral amino acids and is generally considered insensitive to insulin, while the A system, which transports small neutral amino acids, appears to be stimulated by insulin.[28-30] The hypothesis that BCAA uptake by the human heart is mediated by an insulin-insensitive cardiomyocyte transporter would be consistent with the quantitative relationship we observed between the uptake of BCAAs and glucose, whose uptake is mediated almost entirely by the insulin-sensitive GLUT4 transporter. By this hypothesis,

in the hypoinsulinemic fasting state, the relative myocardial uptake of glucose versus BCAAs should be determined simply by their relative availability in arterial plasma, and thus approximate the 10:1 difference in their plasma concentrations. This in fact approximates the 8:1 proportion we actually observed for glucose versus BCAA uptake during fasting. During hyperinsulinemia, sarcolemma GLUT4 density and myocardial glucose uptake would be predicted to increase about 3- to 4-fold,[31] which matches the increase in the myocardial uptake of glucose versus BCAAs during insulin infusion.

We also observed significant net myocardial uptake of glutamate and net release of glutamine and alanine in the fasting state. This observation is consistent with several previous reports[12-13,16-17] that the hearts of patients with coronary artery disease extract more glutamate from the arterial circulation and release more alanine into coronary venous blood than those of healthy subjects. Mudge et al[12] proposed an explanation for this observation more than 20 years ago, namely that subclinical ischemia of some cardiomyocytes causes glycolytic pyruvate to be shunted through the alanine transaminase reaction by mass action, thereby consuming glutamate and producing alanine. By this hypothesis, increased glutamate uptake is an adaptive response to myocardial ischemia, acting to buffer cellular lactate accumulation and prevent the depletion of citric acid cycle intermediates.[17,32] While our study does not directly address this hypothesis, our results would be consistent with it in that we continued to observe net myocardial alanine efflux during insulin infusion, despite the fact that hyperinsulinemia of the magnitude we produced almost completely inhibits the release of amino acids from heart protein into coronary sinus blood[19] and in fact produces net alanine uptake by the healthy heart.[24] Insulin infusion reduced the magnitude of myocardial glutamate consumption in our patients, and marginally reduced the magnitude of net alanine efflux; by the same reasoning, this would be consistent with an effect of hyperinsulinemia to facilitate myocardial pyruvate oxidation, for example, by reducing the circulating fatty acid concentration and thus myocardial fatty acid oxidation. Our observations regarding the effect of insulin infusion on myocardial glutamate and alanine balance would thus suggest a salutory effect of insulin on subclinically ischemic cardiomyocytes, since increasing the fraction of citric acid cycle flux supported by pyruvate (relative to fatty acids) should reduce the oxygen cost of adenosine triphosphate production.

Study Limitations

During insulin infusion, the 10% Travasol coinfusion increased plasma alanine and glycine moderately. Because these amino acids may potentially compete with BCAAs for sarcolemma L-system transport, this increase in plasma levels could theoretically have partly masked a stimulatory effect of insulin on BCAA uptake. However, observations from both in vitro[29] and in vivo[24] studies suggest that the magnitude of this interference in vivo should be small. We studied patients referred for cardiac catheterization to evaluate ischemic heart disease, who may differ from healthy subjects in their response to insulin. For example, our patients had elevated fasting insulin levels and required lower glucose infusion rates to maintain plasma glucose stable during insulin infusion versus either young healthy subjects[33] or age-matched subjects without heart disease,[34] indicating significant whole-body insulin resistance. While less is known regarding the insulin sensitivity of the heart itself, the magnitude of insulin-stimulated cardiac glucose uptake in our patients was also less than that observed in healthy middle-aged subjects.[34] Thus, we cannot be certain that hyperinsulinemia would have been similarly without effect on myocardial BCAA uptake in a more insulin-sensitive group of subjects.

In summary, the hearts of patients with chronic ischemic heart disease import small but consistent quantities of BCAAs from arterial plasma under most physiologic conditions. Heart BCAA uptake is insensitive to the circulating insulin level, but is directly proportional to plasma BCAA concentrations throughout their physiologic range. This suggests that the most effective way to increase heart BCAA uptake in the clinical setting would be via supplemental infusion of the BCAAs themselves, since infusion of insulin alone, which decreases plasma BCAA levels,[23,26] would be predicted to reduce their myocardial uptake. However, administration of insulin alters myocardial glutamate and alanine balance in a manner that would be consistent with a salutory effect on cardiomyocyte oxidative efficiency.

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