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Amino acid mixture acutely improves the glucose tolerance of healthy overweight adults☆

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Abstract

Certain amino acids have been reported to influence carbohydrate metabolism and blood glucose clearance, as well as improve the glucose tolerance in animal models. We hypothesized that an amino acid mixture consisting of isoleucine and 4 additional amino acids would improve the glucose response of healthy overweight men and women to an oral glucose tolerance test (OGTT). Twenty-two overweight healthy subjects completed 2 OGTTs after consuming 2 different test beverages. The amino acid mixture beverage (CHO/AA) consisted of 0.088 g cystine 2HCl, 0.043 g methionine, 0.086 g valine, 12.094 g isoleucine, 0.084 g leucine, and 100 g dextrose. The control beverage (CHO) consisted of 100 g dextrose only. Venous blood samples were drawn 10 minutes before the start of ingesting the drinks and 15, 30, 60, 120, and 180 minutes after the completion of the drinks. During the OGTT, the plasma glucose response for the CHO/AA treatment was significantly lower than that of the CHO treatment ($P < .01$), as was the plasma glucose area under the curve (CHO/AA 806 ± 31 mmol/L·3 hours vs CHO 942 ± 40 mmol/L·3 hours). Differences in plasma glucose between treatments occurred at 30, 60, 120, and 180 minutes after supplement ingestion. Plasma glucagon during the CHO/AA treatment was significantly higher than during the CHO treatment. However, there were no significant differences in plasma insulin or C-peptide responses between treatments. These results suggest that the amino acid mixture lowers the glucose response to an OGTT in healthy overweight subjects in an insulin-independent manner.

Keywords: Glucose; Insulin; Glucagon; Isoleucine; Leucine; Overweight adults

Abbreviations: AUC, area under the curve; BMI, body mass index; FFA, free fatty acids; IRS-1, insulin receptor substrate 1; mTOR, mammalian target of rapamycin; OGTT, oral glucose tolerance test; PI3K, phosphoinositide 3-kinase; SE, standard error; TG, triglycerides.

1. Introduction

Type 2 diabetes is a metabolic disorder that is primarily characterized by insulin resistance and hyperglycemia. Skeletal muscle is the predominate tissue for the clearance of blood glucose, and 70% to 80% of an oral glucose challenge is cleared by skeletal muscle [1-3]. Recent research has demonstrated that certain amino acids, such as leucine and isoleucine, can improve blood glucose clearance and uptake in skeletal muscles in vivo and in vitro [4-9]. It is currently suggested that the potent hypoglycemic effect of amino acids is mediated by phosphoinositide 3-kinase (PI3K) and atypical isoforms of protein kinase C [4,8,9]. Therefore, it may be possible to develop an amino acid

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supplement as a potent nonpharmaceutical approach to improve glucose tolerance.

Our laboratory recently found that gavaging Sprague-Dawley rats with an amino acid mixture, composed of isoleucine, leucine, cystine, methionine, and valine, improved the blood glucose response during an oral glucose challenge without an increase in the plasma insulin response [10]. The blood glucose–lowering effect of the amino acid mixture was due to an increase in skeletal muscle glucose uptake [10,11]. These results suggest that this amino acid supplement acutely improves muscle insulin sensitivity and blood glucose homeostasis in rats. We, therefore, hypothesized that the amino acid mixture would significantly reduce the blood glucose response to an oral glucose challenge in healthy overweight subjects, and this blood glucose–lowering effect would be insulin independent.

According to the data from the National Center for Health Statistics 2010 [12], it is estimated that two thirds of the adult population and a growing number of children in the United States are overweight or obese. Overweight is considered the single strongest predictor of type 2 diabetes [13]. The primary objective of the present investigation was to study whether the ingestion of an amino acid mixture, composed predominately of isoleucine with added cystine, methionine, valine, and leucine, could improve the blood glucose response of healthy overweight men and women during an oral glucose tolerance test (OGTT). Because hyperinsulinemia is a characteristic of insulin resistance and a precursor to type 2 diabetes, we also aspired to improve glucose tolerance while maintaining or improving the insulin response to the glucose challenge. To test our hypothesis, we used a double-blinded, random-ordered, crossover experimental design.

2. Methods

This study was registered as a clinical trial at http://www.clinicaltrials.gov/ (NCT00974831).

2.1. Subjects

Twenty-two healthy overweight men and women (3 men and 19 women) between 20 and 45 years old volunteered for the study. Subject characteristics are presented in Table 1.

Table 1
Subjects' characteristics

	Male	Female
No.	3	19
Age (y)	25 ± 1.53	31.79 ± 1.75
Weight (kg)	103.31 ± 6.77	91.02 ± 2.65
Height (cm)	180.87 ± 0.62	161.19 ± 2.03
BMI (kg/m^2)	31.53 ± 2.15	35.04 ± 1.16
Waist circumference (cm)	105.67 ± 1.20	105.58 ± 2.27
Screen fasting blood glucose (mmol/L)	4.92 ± 0.46	5.52 ± 0.13

Values are expressed as means ± SE. Fasting blood glucose was measured during screening visit.

Table 2
Average energy consumption and macronutrient composition of meals for the 3 days before the CHO and CHO/AA treatments

Treatments	Day	kJ	Carbohydrate (g)	Protein (g)	Fat (g)
CHO	1	9,886 ± 778	314 ± 20	89 ± 7	81 ± 11
	2	9,736 ± 803	301 ± 22	105 ± 11	90 ± 9
	3	9,836 ± 602	302 ± 22	90 ± 7	90 ± 7
CHO/AA	1	10,339 ± 770	325 ± 27	89 ± 6	88 ± 8
	2	9,987 ± 703	285 ± 18	105 ± 9	92 ± 10
	3	10,454 ± 853	317 ± 28	96 ± 8	90 ± 10

Values are expressed as means ± SE. Food logs were maintained for the 3 days before each OGTT, and the average kilojoules (kJ) and macronutrient composition of the meals were determined.

The subjects habitually engaged in recreational exercise less than 3 hours/wk and were considered sedentary. They were not engaged in any exercise programs over the course of the experiment. A body mass index (BMI) of more than 25 kg/m^2 was required for all subjects. A waist circumference of at least 101 cm was required for all male subjects and 88 cm for female subjects. All subjects' fasting blood glucose levels were between 4.16 and 6.99 mmol/L (75 and 126 mg/dL), and their blood pressures were less than 140/90 mm Hg. The subjects were first screened via telephone to determine if they met the requirements of age, exercise level, and health status and were not on a low-carbohydrate diet before they came for the screening visit. During the screening visit, the experimental procedures and potential risks of the study were fully explained to the subjects, and all subjects signed the informed consent to participate in research and filled out the participation health research screening form. The experimental protocol was approved by The University of Texas at Austin Institutional Review Board.

2.2. Physical activity and nutritional controls

Subjects were asked to keep their habitual exercise pattern and normal dietary intake as constant as possible over the course of the experiment. They were instructed to consume their last meal at least 14 hours before their trial appointment, during which they were allowed to consume only water and an 8-oz can of Ensure (Abbott Nutrition, Columbus, Ohio, USA). The 8-oz can of Ensure was consumed 12 hours before each of the trials. All subjects were required to bring a 3-day food record for analysis of their daily average intake of carbohydrate, and they were advised to eat the same diet 3 days before each trial. The subjects were also refrained from exercise for 24 hours before each of the trials. On reporting to the laboratory, the 3-day food record was analyzed to ensure that subjects had consumed a minimum of 150 g of carbohydrate per day. All subjects were in compliance with these instructions. Analysis of the food records is presented in Table 2.

2.3. Experimental design

Upon reporting to the laboratory, the subjects were weighed and a finger-prick glucose test was performed to