ELSEVIER

Journal of Nutritional Biochemistry 12 (2001) 631–639

THE JOURNAL OF Nutritional Biochemistry

β-hydroxy-β-methylbutyrate (HMB) kinetics and the influence of glucose ingestion in humans

Matthew D. Vukovich[a,*], Gary Slater[d], Martina B. Macchi[b], Michael J. Turner[c], Keiren Fallon[d], Tanya Boston[d], John Rathmacher[e]

[a]*Applied Physiology Laboratory, South Dakota State University, Brookings, South Dakota, USA*
[b]*Human Performance Laboratory, Wichita State University, Wichita, Kansas, USA*
[c]*Department of Health Promotion and Kinesiology, University of North Carolina, Charlotte, Charlotte, North Carolina, USA*
[d]*Sports Science Sports Medicine Division, Australian Institute of Sport, Belconnen ACT Australia, Office of Rural Health Department of Health and Aged Care Canberra ACT, Australia*
[e]*Metabolic Technologies, Inc. Ames, Iowa, USA*

Received 14 December 2000; received in revised form 5 May 2001; accepted 16 July 2001

Abstract

The dietary supplement, β-hydroxy-β-methylbutyrate (HMB), has been shown to decrease muscle proteolysis during the stress of exercise and disease. The aim of this investigation was to determine the time course kinetics of HMB and to determine whether oral glucose ingestion alters the kinetics. In Study 1, eight males (32 ± 10 yrs) participated in two randomize trials: 1) oral ingestion of 1g of HMB with water in capsule form (HMB), and 2) placebo. Blood samples were obtained prior to ingestion of treatment and at 30, 60, 90, 120, 150, and 180 min for the measurement of plasma HMB. Additional blood samples were obtained at 6, 9, and 12 hr. Urine was collected prior to ingestion and at 3, 6, 9, and 12 h for the measurement of urinary HMB. In Study 2, eight males (25 ± 6 yrs) followed the same study design and testing procedure as for Study 1. Treatments were 1) modified glucose tolerance test (75 g glucose) (GLU), 2) oral ingestion of 3 g of HMB with water (HMB), and 3) ingestion of 3 g of HMB with 75 g of glucose (HMB+GLU). Blood samples were analyzed for insulin, glucose, and HMB. Additional blood samples were obtained at 24h and 36h for the measurement of HMB. Additional urine samples were collected at 24h and 36h. In Study 1, plasma HMB peaked at 120 nmol/ml at 2.0 ± 0.4 hr in HMB trial. Half-life was 2.37 ± 0.1 hr. Following the consumption of 1g of HMB, ~14% of the HMB consumed accumulated in the urine. In Study 2, plasma glucose and insulin levels were significantly greater in GLU and HMB+GLU treated subjects compared to HMB treated subject at minutes 30, 60 and 90. Plasma HMB peaked at 487.9 ± 19.0 nmol/ml at 1.0 ± 0.1 hr in the HMB treated subjects and at 352.1 ± 15.3 nmol/ml at 1.94 ± 0.2 hr when subjects consumed HMB+GLU. The time to reach peak was different ($P < 0.001$) between HMB and HMB+GLU. The plasma HMB half-life was less ($P = 0.08$) 2.38 ± 0.1 hr in HMB trial compared to 2.69 ± 0.2 hr in HMB+GLU trial. Area under the plasma HMB curve during the first 3 hr was less ($P = 0.002$) in the HMB+GLU trial compared to the HMB trial. From 3 h through 36 h the area under the HMB curve tended to be less ($P = 0.106$) for the HMB+GLU compared to the HMB alone. HMB accumulation in the urine as well as the area under the curve were similar with both HMB (94875.8 ± 15159.5 nmol/36 hrs) and HMB+GLU (80678.2 ± 3863.1 nmol/36 hrs). The percentage of the HMB dose that accumulates in the urine was 27% for HMB+GLU and 29% for HMB alone. In conclusion, HMB plasma levels peak within 60 to 120 min depending on the amount of HMB consumed and whether glucose is consumed with HMB. The plasma half-life is ~2.5 hr. Plasma HMB reaches baseline levels at ~9 hr following ingestion. However, 70 to 85% of the ingested oral HMB is retained in the body for further metabolism.

Keywords: Pharmokinetics; Plasma; Urine; Insulin; Glucose; OGTT; HMB

1. Introduction

Leucine has been reported to play a significant role in regulating protein synthesis [1]. In addition, it has recently been reported by Kimball et al. [2,3] that the removal of leucine from the medium bathing L6 myoblasts, reduced protein synthesis by ~53%, while the re-addition of leucine rapidly returned protein synthesis to the control value; indicating the importance of leucine in maintaining protein synthesis. Furthermore, Anthony et al. [4] have reported that orally administered leucine stimulates protein synthesis in rat skeletal muscle.

* Corresponding author. Tel.: +1–605-688–6580; fax: +1–605-688–5999.

0955-2863/01/$ – see front matter
PII: S0955-2863(01)00182-6

A metabolite of leucine, β-hydroxy-β-methylbutyrate (HMB), has been hypothesized to be responsible for leucine's ability to stimulate protein synthesis or prevent proteolysis [5,6,7]. It has be reported that the addition of HMB to the bathing medium containing muscle strips of rats and chicks resulted in a ~20% increase in protein synthesis, while proteolysis was inhibited by ~80% [7]. In humans, the supplementation of HMB (3 g/day for 3 weeks) resulted in a significant reduction in 3-methylhistidine (3-MH) excretion during intense resistance exercise; 3-MH is a marker of skeletal muscle breakdown [5]. Because of these studies, HMB was introduced as a dietary supplement which has been marketed as a protein breakdown suppressor.

A reliable method of determining compliance in dietary supplement studies is to test for the product or a metabolite of the product in the blood and/or urine. To assess the amount of product in the blood or urine, it is necessary to measure the pharmacokinetics. Studies in animals have reported that HMB is derived exclusively from leucine with ~5% of the leucine being metabolized to HMB [8]. Feeding leucine (50 g) or HMB (2 g) can increase plasma HMB levels by 6 fold [7,9]. Furthermore, kinetic studies in pigs and sheep indicate that a standard 2 g dose results in about a 2 hr half-life of HMB in the plasma and following intravenous infusion of HMB about one-third of the HMB is excreted in the urine [8].

It has been demonstrated that the kinetics of supplements may be altered by the macronutritient profile of the diet. Green et al. [10,11] has reported that carbohydrate intake alters creatine retention, probably through the action of insulin. Therefore, the kinetics of HMB may also be affected by the macronutrient intake.

While the kinetics of HMB has been established in some animals; currently, it is not know what the half-life and retention of HMB is in humans following the oral administration of HMB. Therefore, the primary purpose of this study was to measure plasma HMB and the accumulation of HMB in the urine following a single one gram and three gram dose. A secondary purpose of this study was to determine whether glucose and the concomitant rise in insulin had any affect on HMB kinetics following a three gram dose.

2. Methods

2.1. Subjects

Sixteen males (mean age ± SE, Study 1: 32.9 ± 10.5 and Study 2: 25 ± 6 yrs) volunteered for two different studies and signed an informed consent in accordance with the Human Subjects Committee of Wichita State University and the Australian Institute of Sport. Subjects participating in the studies were not consuming any prescription medications or dietary supplements, including HMB, prior to the study. Mean height, weight, and body composition for Study 1 and Study 2, respectively were 179 ± 2 cm and, 72.3 ± 2.7 kg and 43.3 ± 1.6 mm (sum of 7 skinfolds) or 7.12 ± 0.9%, and 182 ± 6 cm, 85.9 ± 7.1 kg and 20.3 ± 4.3% body fat, respectively.

2.2. Study one

2.2.1. Study design

Subject screening sessions were held one week prior to the experimental procedure. Screening sessions included resting blood pressure and heart rate, height, weight, and body composition by skinfold [12].

The experimental protocol was conducted over a three week period with 7 days separating each trial. Dietary and physical activity records were kept for three consecutive days prior to the first trial and during the trial. For subsequent trials, subjects were asked to duplicate the diet and activity pattern that were recorded for the first trial.

2.2.2. Testing procedures

Subjects reported to the laboratory at 0700 following an overnight fast. Subjects were required to void. The volume of urine was measured and a 2 ml sample was stored at −40°C. A 20 gauge polyethylene catheter was placed into an upper arm vein for blood sampling. The catheter was kept patent with a 0.9% NaCl solution. After obtaining a fasting blood sample, subjects ingested one of two treatments: 1) 1 g of Ca^{2+}-HMB; and 2) 1 g of placebo, rice flour. The order of the trials was randomly assigned in a double-blinded fashion and counterbalanced.

Three 5 ml blood samples were taken prior to ingestion of the supplement and at minutes 30, 60, 90, 120, 150, and 180 min following the ingestion of the treatment for the measurement of HMB. Additional blood samples (5 ml) were obtained at hours 6, 9, and 12. Blood was collected in syringes and transferred into test tubes containing ethylenediaminetetraacytate (EDTA). Samples were centrifuged at 4200 rpm for 10 min at 4°C. Plasma was taken off, placed in separate test tubes and frozen at −40°C for later analysis.

Urine samples were collected at 0, 3, 6, 9 and 12 hr after the ingestion of the treatment. Total urine volume was recorded for each time point and a 2 ml sample was placed in a test tube and frozen at −40°C for later analysis of HMB.

2.3. Study two

The purpose of this study was to determine if glucose consumption altered HMB kinetics. For Study 2, subjects followed the same study design and testing procedure as for Study 1. However, treatments were different for Study 2. Subjects ingested one of the three treatments following the fasting blood sample: 1) 75 g of glucose (TruGlu, Fisher Scientific); 2) 3 g of Ca^{2+}-HMB; and 3) 75 g of glucose and 3 g of Ca^{2+}-HMB.

Furthermore, blood samples were analyzed for insulin and glucose, in addition to HMB. Additional blood samples (5 ml) were obtained at hours 24 and 36 for the measurement of HMB. Additional urine samples were collected at 24 and 36 hr after the ingestion of the treatment. During the 12 to 24 and 24 to 36 hr periods after the ingestion of the treatment, subjects collected their urine in urine sampling containers. Total urine volume was recorded for each time point and a 2 ml sample was placed in a test tube and frozen at −40°C for later analysis of HMB.

2.3.1. Plasma analysis

Plasma and urine HMB were analyzed by a modified method of Nissen et al. [13]. Briefly, a 0.1 M phosphate buffer was used to extract the HMB from the ethyl ether and tetrahyrofuran was used as the derivatizing solvent was used prior to being heated at 50°C for 20 min. Absolute recoveries (quantitative amount of HMB) are ~50% and relative recoveries (HMB relative to internal standard) are ~100%. Intra-assay variation is ~4%. Samples were later analyzed for plasma glucose (Sigma Diagnostics, St. Louis, MO; procedure No. 16) and insulin by double-antibody radioimmunoassay [14].

2.3.2. Calculations and statistics

Incremental plasma glucose, insulin, and HMB areas during the test were calculated using the trapezoidal model that summates the area above baseline. Half-life for plasma HMB was calculated from the following equation.

$$k = (ln(C_{peak}) - ln(C_{trough}))/T_{interval}$$

$$t_{1/2} = 0.693/k$$

The peak for each individual was used and the 12 hr concentration was used as the trough concentration. The 12 hr was used because of the fact that it was not significantly different than the baseline sample. HMB production for each time point was calculated from equation below. HMB accumulation in the urine was calculated by summing the production of HMB for each time point; while the percent accumulation was calculated by dividing the accumulation by the dose.

Production = [urine volume × HMB concentration (μmol/mL)] − [natural urine HMB concentration (μmol/mL) × urine volume]

A two-way repeated measures ANOVA were used to determine the effect of time and treatment on plasma levels of glucose, insulin, and HMB. A one-way repeated measures ANOVA was used to determine the effect of treatment on areas under the curve of the independent variables as well as half-life and time for HMB to peak in the plasma. When a significant F ratio ($P < 0.05$) was obtained, a Tukey post-hoc test was used to locate significant differences. Pearson's Correlation analysis was performed to determine the effect of fasting plasma HMB levels on urinary excretion of HMB. A one-way RMANOVA was performed on the placebo data to determine the effect of time only. This analysis was not part of the original design, it was thought that the extremely high levels of HMB in the other two trials may have masked an effect of glucose or possibly insulin on plasma HMB, therefore justifying this analysis. All data are reported as mean ±SE.

3. Results

3.1. Study one

3.1.1. Plasma HMB

Plasma HMB peaked within 2.0 ± 0.4 hrs following consumption at 115 nmol/L (Figure 1). Values remained stable for the next 90 min after which there was a gradual decline until 9 hr at which time values were not significantly different from baseline. Half-life of peak plasma HMB occurred at 2.37 ± 0.1 hr. Plasma HMB was unaffected by placebo consumption.

3.1.2. Urinary HMB

The percent accumulation of HMB in the urine reached a level of about 14% of the given dose following the consumption of 1 g of HMB (Figure 2). Urinary HMB was unaffected by the placebo.

3.2. Study two

3.2.1. Plasma HMB

A two-way RMANOVA resulted in a significant time, treatment and interaction effect (Figure 3). During the HMB only trial, plasma levels of HMB increased significantly following consumption with the peak level occurring at 1.0 ± 0.1 hr (~480 nmol/L). The peak for the HMB+GLU occurred at 1.9 ± 0.2 hrs and was significantly different ($P < 0.001$) from HMB only trial. The half-life for HMB in the plasma during the HMB trial was 2.38 ± 0.1 hrs and 2.69 ± 0.2 hrs for the HMB+GLU trials. The difference between these two trials approached significance ($P = 0.08$). Plasma levels of HMB in the HMB trial were significantly higher than baseline from 30 min until 6 hr. From hour 9 through hour 36, plasma HMB values were not different from baseline. A similar finding was seen in the HMB+GLU trial. However, the plasma concentration of HMB remained significantly higher than baseline until hour 9; and from hour 12 through hour 36 plasma levels of HMB had returned to levels similar to baseline. During the glucose only trial, the two-way RMANOVA reported no significant effect of glucose on plasma HMB levels. However, a one-way RMANOVA post-hoc analysis of plasma HMB during the glucose only trial revealed a significant reduction in plasma HMB, so that the 3 hr sample was significantly lower than the half-hour sample. While this analysis was not part of the original design it was thought that the extremely high levels of HMB in the other two trials might have masked an effect

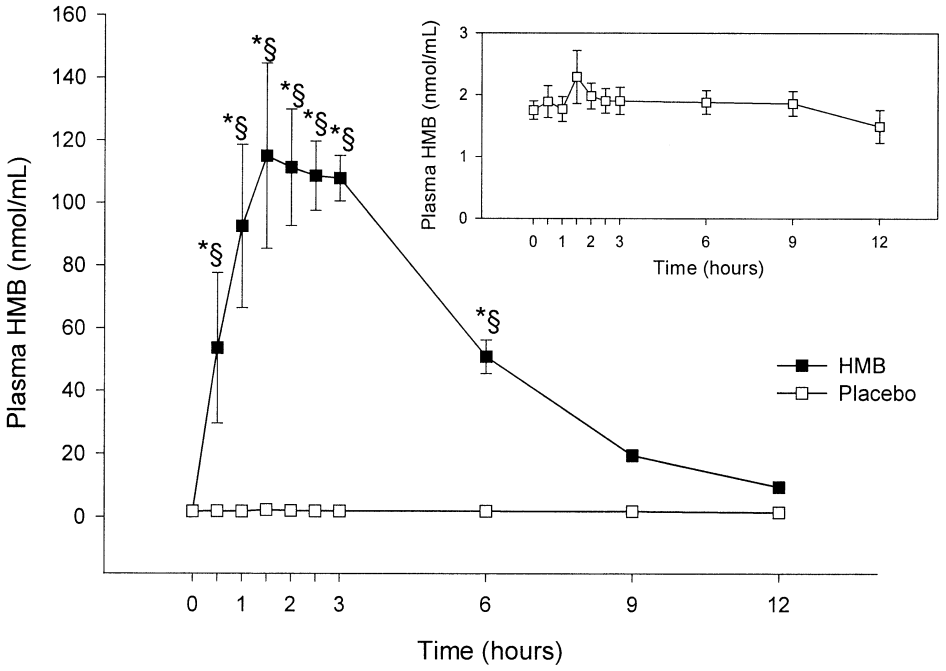

Fig. 1. Plasma HMB concentration following the consumption of 1 g of HMB or 1 g of placebo. *, P <0.05 value different from baseline for that trial. §, P <0.05 HMB trial different than Placebo trial.

of glucose or possibly insulin on plasma HMB, therefore justifying the post-hoc analysis.

The consumption of HMB with or without glucose resulted in significantly higher concentrations of HMB in the plasma than when only glucose was consumed until hour 12 when the levels of HMB in the plasma had returned to values similar to baseline. The consumption of glucose with HMB resulted in significantly lower concentrations of HMB in the plasma compared to the consumption of HMB alone. The time points of significance were hours 2, 3, 6 and 9.

The area under the curve for plasma HMB was compared only for the HMB and HMB+glucose trials. The total area for the 36 hr was calculated as well as the area for hour 0 through 3 and for hours 3 through 36 (Table 1). The area for the first 3 hr for HMB+glucose trial was less (P = 0.002) than the HMB only trial. The area under the curve for hours

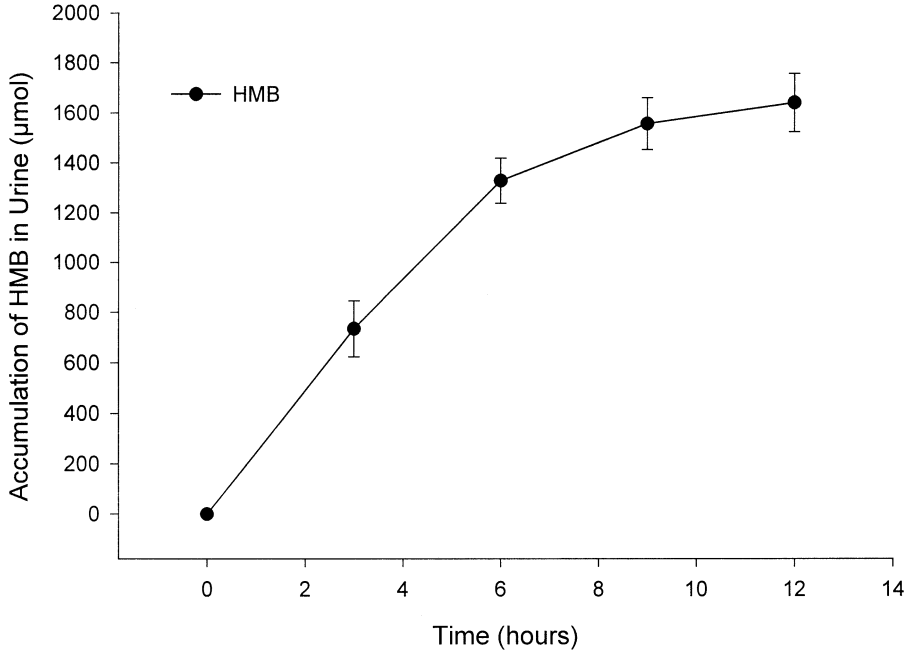

Fig. 2. Accumulation of HMB in the urine following the consumption of 1 g of HMB. All times points different (P <0.05) than each other.

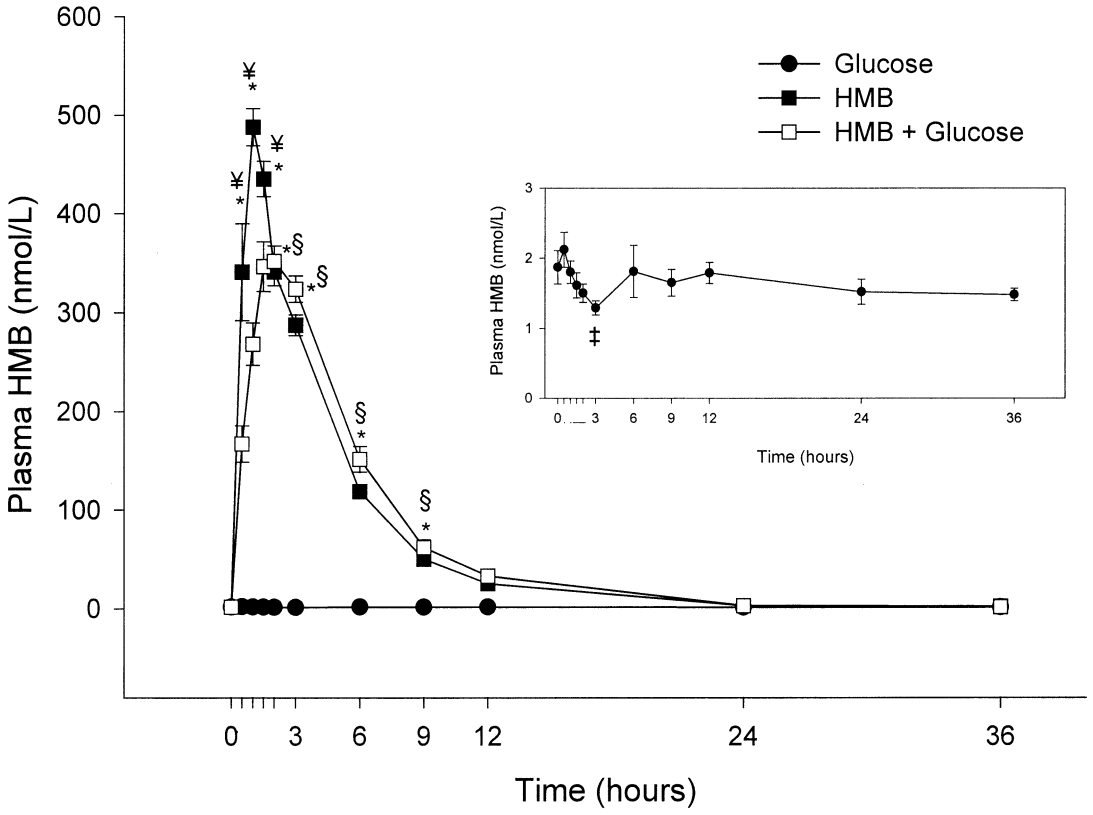

Fig. 3. Plasma HMB concentration following the consumption of 3 g of HMB with and without glucose (75 g) and following the consumption of glucose (75 g) only. [yen], $P < 0.05$; all trials significantly different from each other at that time point. §, $P < 0.05$ HMB trial and HMB+GLU trial greater than Glucose only trial. *, $P < 0.05$ value different from baseline for that trial. ‡, $P < 0.05$ compared to 0.5 hr. Values are represented as mean ±SE.

3 through 36 was also less than the HMB only trial but not as significant ($P = 0.106$). The overall area under the curve was similar for the two trials.

3.2.2. Urinary HMB

The accumulation of HMB in the urine as analyzed with a two-way RMANOVA revealed a time, treatment, and interaction effect (Figure 4). In both the HMB only and HMB+glucose trials the accumulation of HMB in the urine reached a level of significance at hour 6 and remained elevated through hour 36 compared to hour 3. There was no difference between HMB and HMB+glucose trials, but both were significantly higher than the glucose only trial.

A one-way RMANOVA post-hoc analysis of the urinary HMB in the glucose only trial was also performed for the same reasons as stated above. The accumulation of HMB in the urine increased over time and reached a level of significance at hour 12 compared to hour 3 (Figure 2). This elevation remained significant at hour 24 and hour 36, compared to hour 3.

The area under the curve for urinary HMB was not significantly different between the HMB and HMB+glucose trials (Table 2). The percent accumulation of HMB in the urine increased over time and reached a level of about 29% in the HMB trial and about 27% in the HMB+glucose trial (Table 3).

The plasma concentration of HMB prior to the ingestion of HMB with or without glucose had no affect on the amount of HMB excreted in the urine (HMB: $r = 0.125$, $P = 0.768$; HMB+GLU: $r = 0.016$; $P = 0.97$).

Table 1
Area under the curve for plasma HMB following the consumption of 3 g of HMB with or without 75 g of glucose

	0 to 3 hours nmol/180 min	3 to 36 hours nmol/1980 min	Total nmol/2160 min
HMB	61,629.36 ± 2,099.29	67,486.24 ± 3,394.49	129,115.60 ± 4,617.72
HMB + Glu	48,679.68 ± 2,692.49†	81,450.49 ± 7,388.02‡	130,130.17 ± 8,596.81

Values are reported as mean ±SE.
†, $P = 0.002$; ‡, $P = 0.106$.

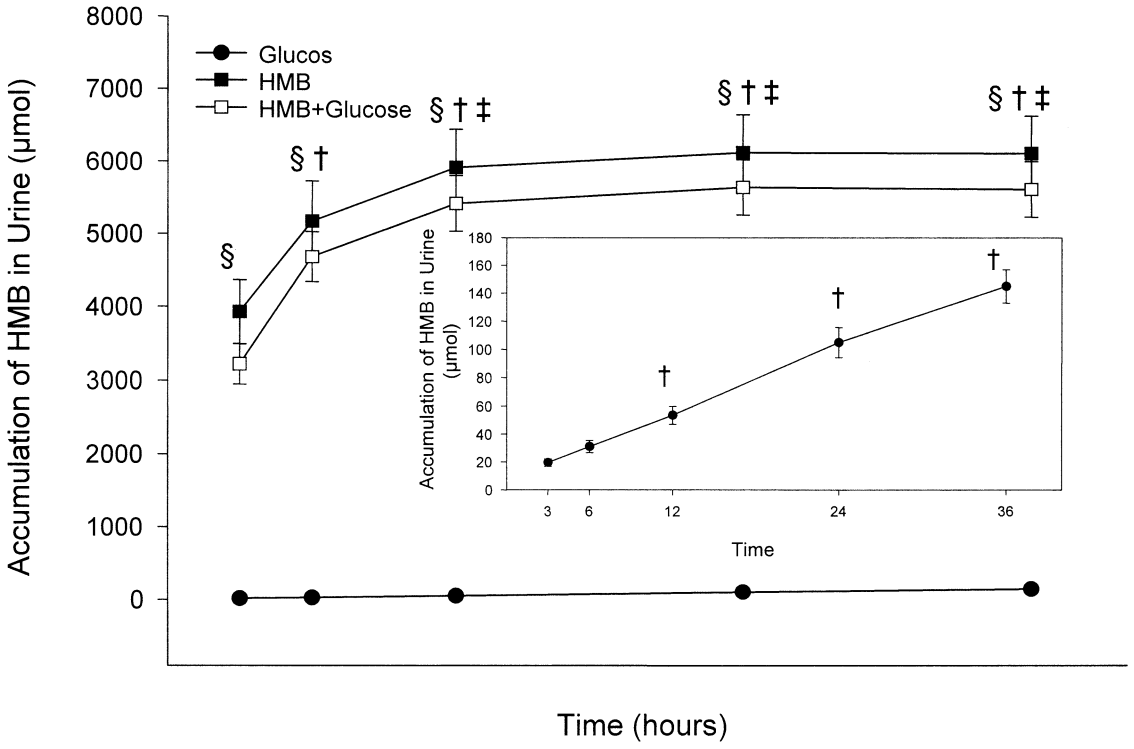

Fig. 4. Urinary HMB accumulation following the consumption of 3 g of HMB with and without glucose (75 g) and following the consumption of glucose (75 g) only. §, P <0.05 HMB trial and HMB+GLU trial greater than Glucose only trial. †, P <0.05 compared to hour 3. ‡, P <0.05 compared to hour 6.

3.2.3. Plasma glucose and insulin

The consumption of 3 g of HMB had no effect on plasma glucose or insulin concentrations (Figure 5). The concentrations of glucose and insulin in the plasma were identical in the glucose and HMB+glucose trials, and were significantly higher than those values measured in the HMB trial.

4. Discussion

The primary purpose of this study was two-fold; 1) to determine the kinetics of HMB in the plasma and urine following the consumption of 1 g and 3 g of HMB; and 2) to determine whether the consumption of glucose with HMB altered the kinetics. The results of this study demonstrated that plasma levels of HMB peaked at ~120 nmol/L within 2.0 ± 0.4 hr following the consumption of 1 g of HMB, while it only took 1.0 ± 0.1 hr to peak at ~480 nmol/L following the consumption of 3g of HMB. The plasma half-life of HMB was 2.37 ± 0.1 and 2.38 ± 0.1 hr following the consumption of 1 g and 3 g of HMB, respectively. The percent accumulation of HMB in the urine reached ~14% following a 1g dose of HMB and about 29% following a 3g dose. A secondary purpose of this study was to determine whether glucose and the associated rise in insulin had an affect on HMB kinetics. The time to reach peak was significantly longer when HMB was consumed with glucose; and the plasma half-life was prolonged. While there were some significant differences in plasma HMB and the area under the curve between the HMB trial and HMB+glucose trial, there were no apparent differences in urinary HMB accumulation. This would indicate that HMB may be slower to empty from the stomach when consumed with glucose.

Studies in animals have reported that the half-life of HMB in the plasma is about 2 hr and about 34% of HMB is excreted into the urine [6,8]. The results of the present study

Table 2
Area under the curve for urinary accumulation of HMB following the consumption of 3 g of HMB with or without 75 g of glucose

	nmol/36 hours
HMB	94875.8 ± 15159.5
HMB + Glu	80678.2 ± 3863.1

Values are reported as mean ±SE.

Table 3
Percent accumulation of HMB in the urine following the ingestion of 3 g of HMB with or without glucose

Time (hours)	HMB (%)	HMB + Glucose (%)
3	19.23 ± 2.11	15.68 ± 1.32
6	25.19 ± 2.7	22.79 ± 1.68
12	28.81 ± 2.56	26.38 ± 1.88
24	29.87 ± 2.54	27.47 ± 1.86
36	29.79 ± 2.52	27.35 ± 1.87

Values are reported as mean ±SE.

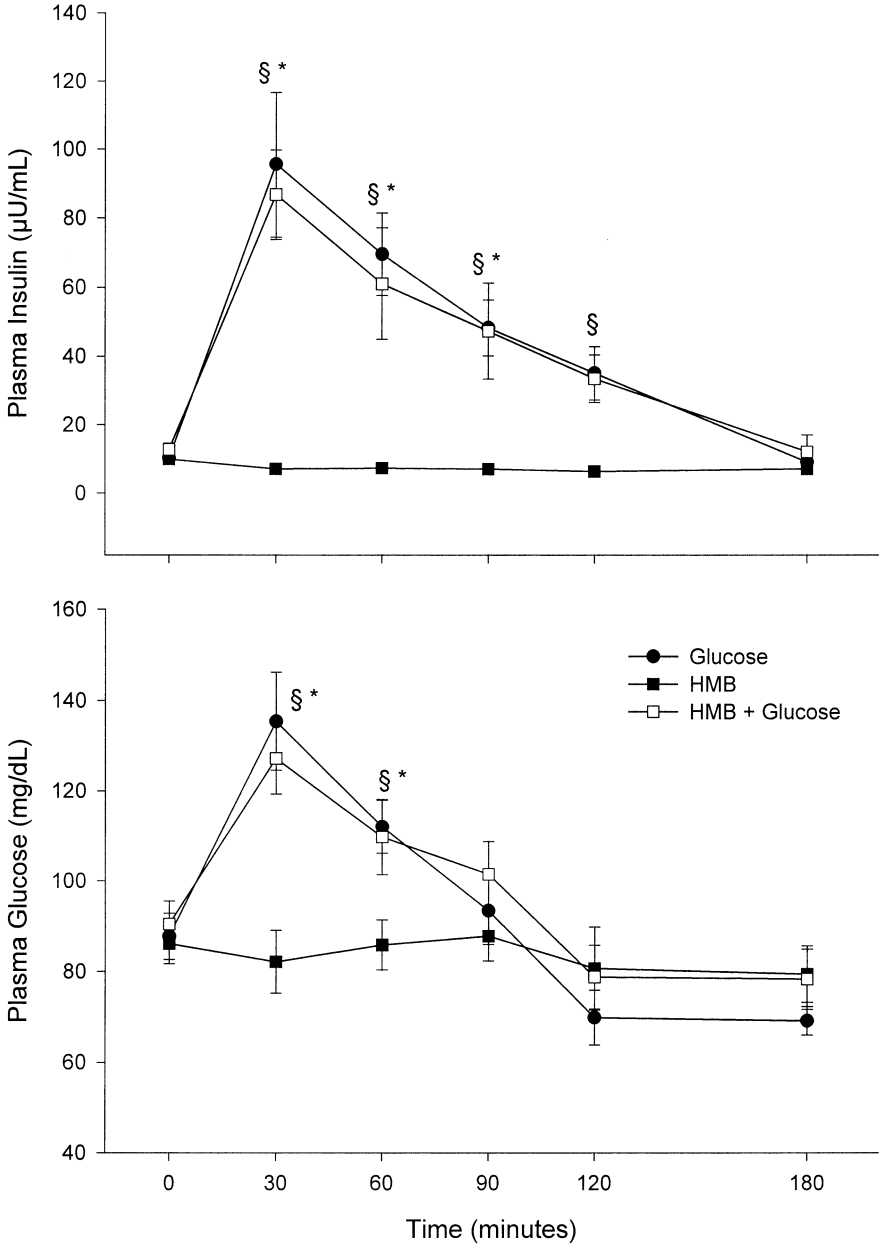

Fig. 5. Plasma glucose and insulin following the consumption of 3 g of HMB with and without glucose (75 g) and following the consumption of glucose (75 g) only. §, $P < 0.05$ Glucose trial and HMB+glucose trial greater than HMB trial. *, $P < 0.05$ compared to baseline.

show that the half life for HMB in humans is also about 2 hr (range, 2.37 to 2.69) while only about 14 to 27% of the HMB is excreted in the urine, depending on the dose. There may be a number of factors that influence HMB levels in the plasma and HMB excretion in the urine. The first of these is food consumed with the HMB. To reduce the chance that the macronutrient composition of the diet may have influenced HMB kinetics, the subjects maintained a dietary record for the first trial and were supplied copies of the record for subsequent trials. Dietary macronutrients as well as dietary fiber may influence HMB absorption and excretion. For example, in the present study the consumption of glucose (75 g) resulted in a significant reduction in plasma HMB levels and a longer time to reach peak plasma levels, and a longer plasma half-life. Furthermore, there was a reduction in urinary HMB accumulation. The high concentration glucose probably resulted in a delay of stomach emptying. Increasing the glucose concentration of a drink has been reported to reduce gastric emptying rate [15]. The high carbohydrate content of the drink used in the present study (75 g in 296 ml) could possibly delay the emptying rate thus causing the lower plasma HMB levels and the increase in time to reach peak, and possibly the increase in half-life. It is not known whether this reduction in urinary

accumulation of HMB is associated with a greater retention of HMB by the body tissues or to a reduction in HMB absorption from the GI tract. It is possible that there was a greater retention of HMB by the tissues due to the action of insulin. In the glucose only trial, plasma HMB concentrations did significantly decrease. In support of this argument, Green et al. [10,11] demonstrated that the consumption of creatine in conjunction with carbohydrate resulted in a greater retention of creatine by the muscle, presumably due to the greater insulin concentrations. It is possible that carbohydrate and insulin could affect plasma HMB levels since there was a drop in plasma HMB during the glucose only trial. However, this assumption is speculation at this point since it is not known at this time which tissues (liver, muscle or adipose) HMB acts upon or is metabolized by. However, Nissen and Abumrad [6] have provided evidence that the primary fate of HMB is probably conversion to β-hydroxy-β-methylglutaryl CoA (HMG-CoA) in the liver. HMG-CoA is a precursor to cholesterol biosynthesis. How this pathway affects protein synthesis and breakdown is unknown at this point. To further understand insulin's role in HMB regulation, hyperinsulinemic clamps would need to be performed.

A second factor that may influence HMB kinetics is that of initial HMB levels. The pharmacokinetic response to acute HMB supplementation may be different among individuals with varying levels of HMB. Individuals with higher initial values may excrete the surplus rapidly resulting in higher urinary HMB levels. To determine whether the pre-supplementation level of HMB in the plasma influenced the amount of HMB accumulation in the urine a correlational analysis was performed. Based on the correlation coefficient for fasting plasma HMB and 12 hr urinary HMB accumulation there was no affect.

A third factor that could influence the pharmacokinetics could be the amount of HMB consumed. In the present study, the subjects consumed 1 and 3 g of HMB. It did take longer for the HMB to reach peak levels in the blood following the consumption of 1 g versus 3 g. However, the plasma half-life for HMB following the consumption of 1 g and 3 g was identical. The percent of HMB which accumulated in the urine was 14% following the 1g dose of HMB and ~29% following the 3 g dose. The lower accumulation of HMB in the urine could be due to a smaller rise in plasma HMB levels and possibly less spillover into the urine. Again, this is speculation but deserves further research.

Finally, the activity level of the individual could affect plasma and urinary HMB levels. While the metabolism of HMB is not fully known [6], the oxidation of leucine has been reported to be affected by exercise. Leucine oxidation during exercise has been reported to increase up to 7 fold [16,17,18]. Whether exercise or training status affects HMB metabolism is yet to be determined, but is possible. Acute exercise does not appear to affect plasma HMB levels. Vukovich et al. [19] has reported that plasma HMB is unaffected during a maximal oxygen consumption test on a cycle ergometer. To control for this possibility, subjects were required to avoid physical activity during the trials. The only activity allowed was to perform normal daily activities and to walk to class. Since trials were conducted one week apart, the daily activities, including walking to class, should have been similar.

In conclusion, the ingestion of HMB results in a rise of plasma HMB which peaks between one and two hours, with a half-life of approximately 2.3 hr. A small proportion of the HMB is excreted in urine with the remaining being retained in the body for further metabolism. The ingestion of glucose with HMB alters the kinetics of HMB by lowering the peak plasma concentration, the time to reach peak concentration and increasing the half-life.

Acknowledgments

Funding for this study was provided by Metabolic Technologies, Inc. Ames, IA. 50010 and Experimental and Applied Sciences, Golden, CO 80401.

References

[1] M.E. May, M. G. Buse, Effects of branched-chain amino acids on protein turnover, Diabetes/Metab. Reviews 5 (1989) 227–245.

[2] S.R. Kimball, R.L. Horetsky, L.S. Jeffereson, Implication of eIF2B rather than eIF4E in the regulation of global protein synthesis by amino acids in L6 myoblasts, J. Biol. Chem. 273 (1998) 30945–30953.

[3] S.R. Kimball, L.M. Shantz, R.L. Horetsky, L.S. Jefferson, Leucine regulates translation of specific mRNAs in L6 myoblasts through mTOR-mediated changes in availability of eIF4E and phosphorylation of ribosomal protein S6, J. Biol. Chem. 274 (1999) 11647–11652.

[4] J.C. Anthony, T.G. Anthony, S.R. Kimball, T.C. Vary, L.S. Leonard, Orally administered leucine stimulates protein synthesis in skeletal muscle of postabsorptive rats in association with increased eIF4F formation, J. Nutr. 130 (2000) 139–145.

[5] S. Nissen, R. Sharp, M. Ray, J.A. Rathmacher, D. Rice, J.C. Fuller, A.S. Connelly, N. Abumrad, Effect of leucine metabolite β-hydroxy-β-methylbutyrate on muscle metabolism during resistance-exercise training, J. Appl. Physiol. 81 (1996) 2095–2104.

[6] S.L. Nissen, N.N. Abumrad, Nutritional role of the leucine metabolite β-hydroxy-β-methylbutyrate (HMB), J. Nutr. Biochem. 8 (1997) 300–311.

[7] P. Ostaszewski, S. Kostiuk, B. Balaskinska, I. Papet, F. Glomot, S. Nissen, The effect of the leucine metabolite 3-hydroxy-3methylbutyrate (HMB) on muscle protein synthesis and protein breakdown in chick and rat muscle, J. Anim. Sci. 74 (1996) 138. (Abstract)

[8] M. Van Koevering, S. Nissen, Oxidation of leucine and α-ketoisocaproate to β-hydroxy-β-methylbutyrate in vivo, Am. J. Physiol. 262 (1992) E27–E31.

[9] Z. Zhang, V. Talleyrand, J. Rathmacher, S. Nissen, Change in plasma β-hydroxy-β-methylbutyrate (HMB) by feeding leucine, α-ketoisocaprate (KIC) and isovaleric acid (IVA) to pigs, FASEB J. 7 (1993) A392. (Abstract).

[10] A.L. Green, E.J. Simpson, J.J. Littlewood, I.A. Macdonald, P.L. Greenhaff, Carbohydrate ingestion augments creatine retention during creatine feeding in humans, Acta Physiol. Scand. 158 (1996) 195–202.

[11] A.L. Green, E. Hultman, I.A. Macdonald, D.A. Sewell, P.L. Greenhaff, Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans, Am. J. Physiol. 271 (1996) E821–E826.
[12] M.L. Pollock, D.H. Schmidt, A.S. Jackson, Measurement of cardiorespiratory fitness and body composition in the clinical setting, Comprehensive Therapy 6 (1980) 12–27.
[13] S. Nissen, M. Van Koevering, D. Webb, Analysis of beta-hydroxy-beta-methyl butyrate in plasma by gas chromatography and mass spectrometry, Anal. Biochem. 188 (1990) 17–19.
[14] D.R. Morgan, A. Lazarow, Immunoassay of insulin: two antibody system, Diabetes 12 (1963) 115–126.
[15] D.L. Costill, B. Saltin, Factors limiting gastric emptying during rest and exercise, J. Appl. Physiol. 37 (1974) 679–683.
[16] S.A. Hagg, E.L. Morse, S.A. Adibi, Effect of exercise on rates of oxidation turnover, and plasma clearance of leucine in human subjects, Am. J. Physiol. 242 (1982) E407–E410.
[17] M.J. Rennie, D. Halliday, C.M.T. Davies, R.H.T. Edwards, S. Krywawych, D.J. Millward, D.E. Matthews, Exercise induced increase in leucine oxidation in man and the effect of glucose, Develop. Biochem. 18 (1981) 361–366.
[18] R.R. Wolfe, R.D. Goodenough, M.H. Wolfe, G.T. Royle, E.R. Nadel, Isotopic analysis of leucine and urea metabolism in exercising humans, J. Appl. Physiol. 52 (1982) 458–466.
[19] M.D. Vukovich, G.D. Dreifort, The effect of β-hydroxy β-methylbutyrate (HMB) on the onset of blood lactate accumulation and VO_2peak in endurance trained cyclists. J. Strength Cond. Research. In press.