

Oral β -hydroxybutyrate salt fails to improve 4-minute cycling performance following submaximal exercise

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Abstract

The purpose of the present study was to examine the effects of an oral β -hydroxybutyrate (BHB) salt supplement on cycling performance. Using a double-blind, placebo-controlled, crossover design, 12 highly-trained cyclists (mean \pm SD: age; 35 \pm 8 y, mass; 74.5 \pm 7.6 kg, VO_{2peak} ; 68.0 \pm 6.7 ml.min⁻¹kg⁻¹) were supplemented with two 30 ml servings of an oral BHB salt supplement or placebo formula (PLA) prior to and during exercise. Participants cycled at a submaximal intensity (80% of second ventilatory threshold) for 90-min, followed by a 4-min maximal cycling performance test (4PT). The difference in 4PT power output between trials was not statistically significant ($p > 0.05$) and was associated with a *trivial* effect (ES \pm 90%CI = 0.19 \pm 0.37). Ingestion of the BHB salt supplement was associated with a *large* increase in blood BHB concentrations when compared to PLA for the 4PT (ES = 1.75 \pm 0.50, $p < 0.01$). The increased BHB concentration was accompanied by a *moderate* increase in the respiratory exchange ratio (RER) during the submaximal exercise phase (ES = 0.54 \pm 0.45, $p > 0.05$) and a *moderate* increase during the 4PT (ES = 0.78 \pm 0.57, $p = 0.03$). Submaximal VO_2 did not differ between trials, however, VO_2 was higher during the 4PT phase in the BHB trial (ES = 0.28 \pm 0.32; *small*). In conclusion, BHB salt supplementation altered blood BHB concentrations, RER and VO_2 values during steady state sub-maximal exercise, but did not improve 4-minute cycling performance.

Keywords: ketone, ketosis, ketone esters, fat metabolism

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Introduction

The ability to oxidise fat and spare carbohydrate reserves is a key determinant of endurance exercise performance (Holloszy and Coyle 1984), and is an adaptation prevalent in highly-trained compared to recreationally-trained athletes (Hetlelid et al. 2015). This important feature allows for the preservation of muscle and liver glycogen, thereby improving the high-intensity end-spurt ability following prolonged endurance exercise (Rowlands and Hopkins 2002). This is often where many endurance competitions longer than 2 h in duration are won and lost.

Low carbohydrate ketogenic diets increase fat oxidation rates and blood β -hydroxybutyrate (BHB) concentrations (Volek et al. 2015) and have the potential to enhance energy provision to working muscles for prolonged exercise performance (Cox and Clarke 2014). BHB is an efficient substrate, that generates 31% more energy per carbon molecule (C2) than pyruvate (243.6

kcal/mol vs 185.7 kcal/mol, respectively) (Veech 2004). Moreover, elevated BHB concentrations have been suggested to reduce glucose and glycogen metabolism (Cahill Jr 1976; Kashiwaya et al. 1994; Robinson and Williamson 1980), in turn sparing carbohydrate stores during prolonged exercise, potentially aiding subsequent performance in sports like road cycling or triathlon (Lambert et al. 1994; Phinney et al. 1983). However, the personal discipline required to increase blood BHB concentrations and achieve nutritional ketosis, by consuming less than ~50 g of carbohydrate per day, may limit its application for many athletes. Moreover, the inherent low carbohydrate consumption levels required to achieve ketosis have the potential to reduce an athlete's ability to perform high-intensity exercise (Havemann et al. 2006; Hawley and Leckey 2015).

One strategy less considered in the literature to enhance blood BHB levels is the ingestion of a BHB supplement. Indeed, numerous synthetic BHB supplements now available claim the ability to rapidly induce ketosis (defined as > 0.5 mmol/L), but few studies have considered this in the context of exercise performance (Clarke et al. 2012a; Clarke et al. 2012b; Kesi et al. 2016; Pinckaers et al. 2016; Veech 2014). Therefore, the purpose of the current study was to assess the effects of an oral BHB salt supplement in comparison to a placebo supplement on exercise metabolism over 90 minutes' submaximal cycling, and subsequent all-out 4-minute exercise performance in highly-trained cyclists.



Materials and methods

Participants

Twelve highly-trained male cyclists (mean \pm SD: age, 35 \pm 8 y; mass, 74.5 \pm 7.6 kg; VO_{2peak} , 68.0 \pm 6.7 ml.min⁻¹.kg⁻¹) volunteered to participate in the current study. All testing took place during the competitive phase of the New Zealand cycling season where participants raced at either professional, A or B-grade level. Following an explanation of all procedures, risks and benefits, each participant gave their written informed consent to partake in the study, which was approved by the Institution's Human Research Ethics Committee. The current study also adheres to the international ethical standards required by the Journal (Harriss and Atkinson 2011).

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Experimental design

The study implemented a double-blind, placebo-controlled, randomised, crossover design that required participants to visit the laboratory on three separate occasions. Prior to taking part in the study, participants were required to refrain from taking any nutritional supplements in the 4 weeks preceding the study, as well as during the course of the experiment. At the start of the

study, participants all self-reported to be on mixed CHO diets (neither low or high in CHO). Participants were asked to document their food intake via a 48-h food diary and were instructed not to eat within the 2.5-h period before the test. Diet was replicated in the 48-h period prior to the subsequent experimental testing session. In the 24-h preceding each trial, participants were asked to refrain from strenuous activity and abstain from consuming caffeine on the day of the test. On the first visit to the laboratory, participants performed an incremental VO_{2peak} test on their own bicycle attached to a Cyclus II ergometer (RBM elektronik-automation GmbH, Leipzig, Germany), where power output commenced at 150 W, and increased by 40 W every 4 min until volitional exhaustion. VO_{2peak} was determined as the highest 30 sec average of samples attained by participants during the incremental step test. Immediately following the progressive exercise test, a familiarisation trial that simulated the experimental trials (described below) was performed, however, to reduce the demands of the test, the submaximal exercise bout was reduced to 20 minutes.

Exercise testing

The experimental trials, shown in Figure 1, were conducted on a Wattbike cycle ergometer (Wattbike Ltd, Nottingham, UK), set-up to replicate each participant's own bicycle. The 4-minute maximal performance test (4PT) on a Wattbike has been shown to be reliable for testing highly-trained athletes in a laboratory setting, with a test-retest coefficient of variation of \sim 2.7% (Driller et al. 2014). For each experimental trial, participants cycled for 90 min at 80% of their second ventilatory threshold (VT₂, as determined during the VO_{2peak} test); (referred hereafter as submaximal exercise), prior to a paced 4PT, separated by 2 min passive rest allowing athletes to remove the mask if needed to communicate with researchers or drink water. VT₂ was calculated using gas exchange measures and

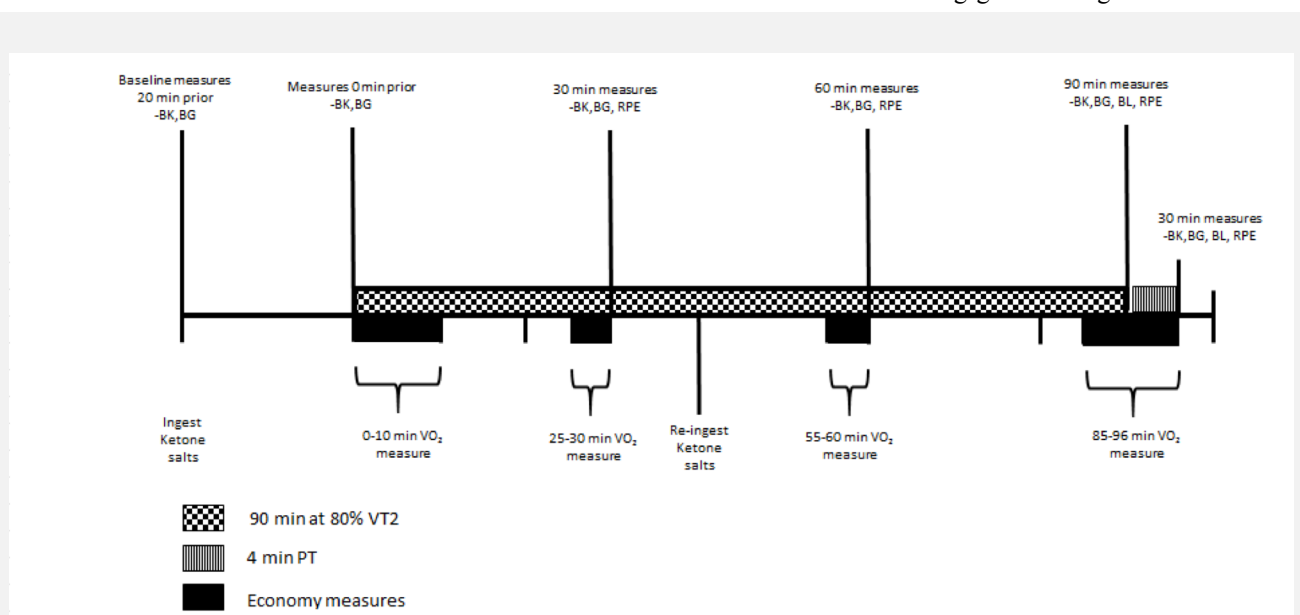


Figure 1. Experimental trial - timeline of events. Abbreviations: BK= blood β -hydroxybutyrate concentration; BG= blood glucose

Table 1. Mean values for the performance and blood measures in the Placebo (PLA) and β-hydroxybutyrate (BHB) trials. Difference between trials with 90% confidence intervals (90%CI) and effect sizes (ES) are also displayed. # significant difference between trials (p < 0.05).

	PLA Mean ± SD	BHB Mean ± SD	BHB-PLA ±90%CI Effect size ±90%CI
4PT Mean Power (W)	355 ± 46	364 ± 58	9 ± 18 ES = 0.19 ± 0.37 <i>Trivial</i>
4PT BHB levels^a (mmol/L)	0.3 ± 0.3	0.6 ± 0.2	0.3 ± 0.1# ES = 1.75 ± 0.50 <i>Large</i>
Submaximal BHB levels^b (mmol/L)	0.3 ± 0.3	0.6 ± 0.3	0.4 ± 0.2# ES = 1.23 ± 0.71 <i>Large</i>
4PT GLU levels^a (mmol/L)	4.6 ± 1.2	4.6 ± 0.9	0.1 ± 0.5 ES = 0.05 ± 0.55 <i>Unclear</i>
Submaximal GLU levels^b (mmol/L)	4.3 ± 0.8	4.1 ± 0.7	-0.2 ± 0.3 ES = -0.24 ± 0.43 <i>Small</i>
4PT lactate levels^a (mmol/L)	7.6 ± 1.7	8.8 ± 3.2	1.1 ± 2.1 ES = 0.60 ± 1.11 <i>Unclear</i>
Submaximal lactate levels^b (mmol/L)	1.6 ± 0.5	1.8 ± 0.7	0.1 ± 0.4 ES = 0.28 ± 0.81 <i>Unclear</i>

^a = taken immediately post 4PT. ^b = taken immediately post submaximal exercise bout (90min). Abbreviations: 4PT= 4 min performance test; BHB= β-hydroxybutyrate; GLU= glucose.

Table 2. Mean values for the measured metabolic variables in the placebo (PLA) and β-hydroxybutyrate salt supplement (BHB) trials. Difference between trials with 90% confidence intervals (90%CI) and effect sizes (ES) are also displayed. # significant difference between trials (p < 0.05).

	PLA Mean ± SD	BHB Mean ± SD	BHB – PLA ±90% CI Effect size ±90% CI
4PT RER	0.96 ± 0.05	1.01 ± 0.07	0.04 ± 0.03# ES = 0.78 ± 0.57 <i>Moderate</i>
Submaximal RER^a	0.85 ± 0.03	0.87 ± 0.05	0.02 ± 0.02 ES = 0.54 ± 0.45 <i>Moderate</i>
4PT VO₂ (L.min⁻¹)	3.88 ± 0.35	3.99 ± 0.49	0.11 ± 0.13 ES = 0.28 ± 0.35 <i>Small</i>
Submaximal VO₂^b (L.min⁻¹)	3.26 ± 0.33	3.19 ± 0.35	-0.07 ± 0.15 ES = -0.20 ± 0.41 <i>Unclear</i>

^a= average taken from the 85-90 min gas sample. ^b= average across all gas samples during the sub maximal bout. Abbreviations: 4PT= 4 min performance test; BHB= β-hydroxybutyrate; PLA= placebo; RER= respiratory exchange ratio.

identified as the intensity where VE/VCO₂ began to rise (Davis 1985). During the 90 min submaximal cycling phase, participants were asked their rating of perceived exertion (RPE) every 15 min (Borg 1982).

Oral β-hydroxybutyrate (BHB) salt supplementation
Twenty minutes prior to the trial, participants ingested either a supplement containing 11.7g of BHB salt (BHB: 30 ml of Ketoforce; Prototype Nutrition, IL, USA) or a taste-matched placebo (PLA: 3g NaCl), diluted with 100 ml of sugar-free lemonade. A second identical dose

of the BHB salt supplement or PLA was ingested at the halfway point (45 min) during the 90 min submaximal cycling phase. The reason for re-ingestion was based on our own unpublished observations, showing that BHB levels peaked 45 min after ingesting the supplement. The 30 ml dose of the supplement was based on the manufacturers instructions.

Blood sampling

Finger-tip blood samples were taken to assess blood glucose and blood BHB levels using a commercially available Freestyle Optium blood glucose and blood ketone monitoring system (Abbot Diabetes Care, Oxon, UK), as used previously (Guimont et al. 2015). Blood lactate was measured using a Lactate Pro 2 Analyser (Arkray KDK, Shiga, Japan) alongside blood glucose and BHB measures at the end of the 90 min submaximal cycling test and 4PT.

Statistical analysis

Data are reported as means \pm SD unless otherwise stated. An excel spreadsheet was used to identify differences between trials for each physiological and performance response (Hopkins 2006). To make inferences about the likely range of the true effect, the uncertainty in the effect was expressed as $\pm 90\%$ confidence interval (CI). Standardised differences in the mean of each measure were used to assess magnitudes of effects and were calculated using Cohen's d and interpreted using thresholds of 0.2, 0.6, 1.2 and 2.0 for *small*, *moderate*, *large* and *very large*, respectively (Hopkins 1997). An effect size (ES) of <0.2 considered *trivial* and the effect was deemed *unclear* if its 90% confidence interval overlapped the thresholds for *small* positive and negative effects. The thresholds used to determine *small* positive and negative effects were an effect size of 0.2, or, where known, the value of the smallest worthwhile change (e.g. 0.3 of the CV = 0.81% for mean power) (Hopkins 2006; Hopkins and Batterham 2006). Normality of the data for all measures was verified visually with histograms and also by the Shapiro-Wilk test. A student's paired t -test was used to compare BHB and PLA for all

measured variables in the Statistical Package for Social Science (V. 24.0, SPSS Inc., Chicago, IL), with an alpha level set at $p < 0.05$.

Results

There were no significant differences ($p = 0.38$), and a trivial effect ($ES = 0.19 \pm 0.37$) between BHB and PLA trials for power output during the 4PT (Table 1).

The BHB salt supplement trial revealed a significant ($p < 0.01$) increase in blood BHB levels during the 4PT, and also during submaximal exercise (Table 1, Figure 2). These differences between trials were associated with large effect sizes (Table 1). The difference in blood lactate concentrations after both the submaximal and

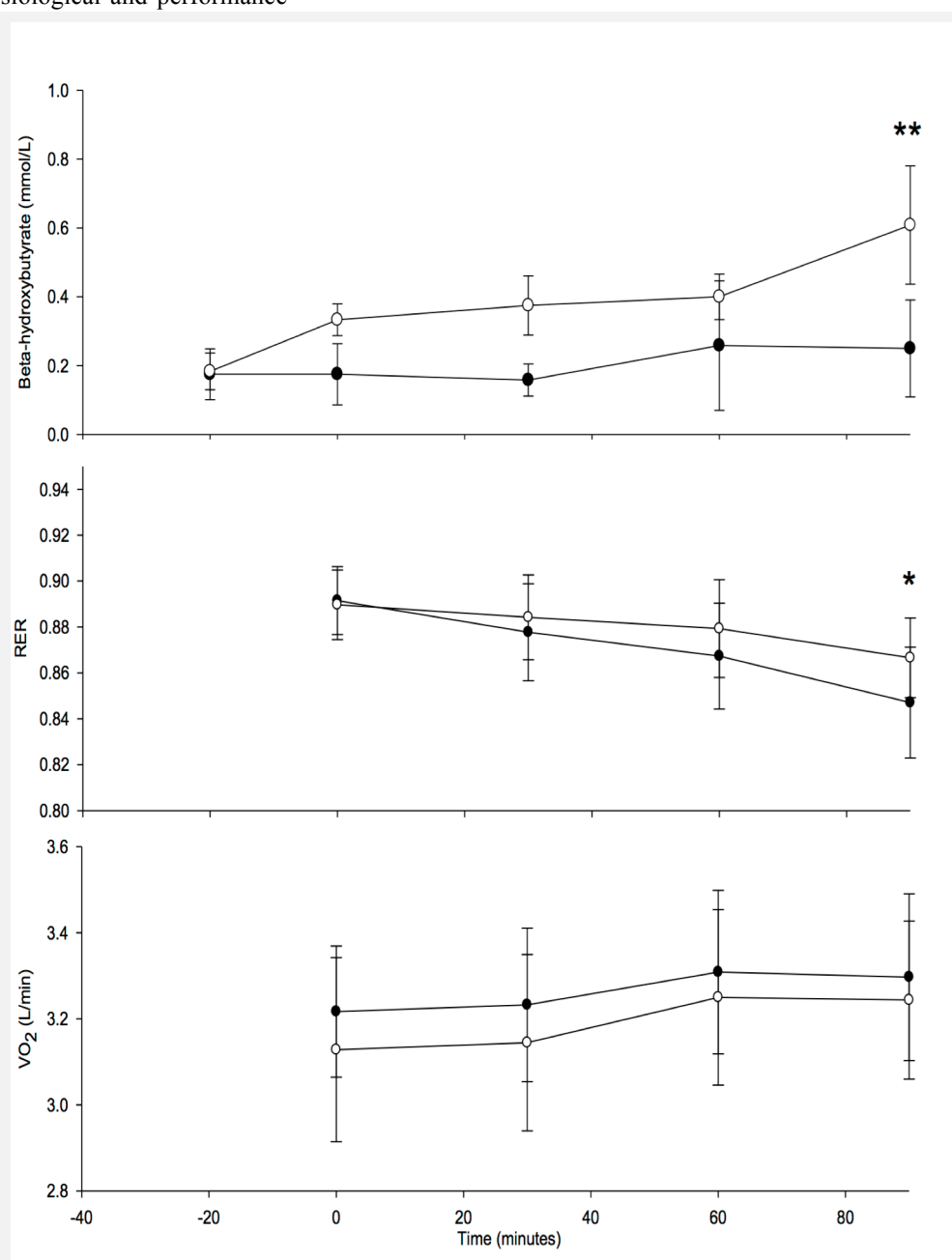


Figure 2. Key physiological measures during submaximal exercise for the placebo (PLA) and β -hydroxybutyrate salt supplement (BHB) trials. Error bars represent 90% confidence intervals. *=small effect, **=moderate effect.

4PT exercise phases were unclear between trials (ES = 0.28 ± 0.81 and 0.60 ± 1.11 , respectively). Differences in average blood glucose during submaximal exercise were small between the BHB trial and placebo trials (ES = -0.24 ± 0.43 , $p = 0.33$), while blood glucose following the 4PT was unclear between trials (ES = 0.05 ± 0.55).

There was a moderate increase in mean RER (ES = 0.54 ± 0.45 , $p = 0.06$) for the BHB trial compared with the PLA trial during the 90 min submaximal exercise phase (Table 2; Figure 2). Similarly, there were moderate increases in mean RER during the 4PT (ES = 0.78 ± 0.57 , $p = 0.03$) in the BHB compared to PLA trial. The average difference in VO₂ between trials during the submaximal phase was unclear (ES = -0.20 ± 0.41). Conversely, there were small (ES = 0.28 ± 0.35) increases in VO₂ observed in the BHB trial compared to the PLA trial during the 4PT.

Ratings of perceived exertion were not significantly different between trials (ES = -0.12 ± 0.33 ; unclear).

Discussion

To our knowledge, this is the first study to examine the effects of an oral β -hydroxybutyrate (BHB) salt supplement on exercise performance in highly-trained cyclists. The main findings were that acute oral BHB salt supplementation resulted in large increases in blood BHB concentrations as well as a moderate increase in the RER, but failed to improve 4-minute all-out cycling performance following 90-minutes of submaximal exercise.

Even though analysis revealed a large increase in blood BHB levels following BHB salt supplementation both during submaximal and maximal exercise, it is possible that the increased BHB concentrations achieved were not great enough to elicit a benefit in performance. BHB values above 2mmol/L have been reported in humans without side effects following ingestion of a ketone ester supplement (Clarke et al. 2012b). However, acute BHB supplementation has the potential to cause gastrointestinal distress, which may counteract any added benefits associated with higher doses. Indeed, it may be possible that chronic ingestion of BHB with a dose that is tolerable may have a greater impact on exercise performance. Average blood BHB concentrations achieved in the current study (0.63 mmol/L) peaked far below the levels required for therapeutic ketosis (≥ 2 mmol/L) (Hashim and VanItallie 2014). Alternatively, research by Johnson and Walton (1972) demonstrated that trained athletes may have an increased tolerance to ketosis during exercise and that low blood ketone concentration values may in fact represent the utilisation of BHB as a fuel.

The increased RER levels, which coincided with the increased BHB concentrations during submaximal exercise, was in contrast to previous research resulting in similar blood BHB levels after adaptation to a ketogenic diet (Lambert et al. 2001; Phinney et al. 1980; Zajac et al. 2014). Phinney et al. (1980) demonstrated lower RER values during exercise following a ketogenic diet (RER = < 0.70) for 6 weeks compared to a pre-diet control condition (RER = 0.76). It has been postulated that BHB supplementation may act as a signal, limiting

glucose and glycogen metabolism (Cahill Jr 1976). Therefore, BHB supplementation may spare glycogen for subsequent high-intensity exercise (Robinson and Williamson 1980). The higher RER and VO₂ in the BHB trial during the 4PT supports this possibility, however due to the fact that muscle glycolysis rates were not measured, these findings remain inconclusive.

A limitation of the current study was the exercise protocol used. The short performance test may have limited our ability to test the capacity of the ketone supplement's glycogen storing capabilities; however, we chose to employ a 4-minute performance test to reflect the characteristics of a typical road race that has a period of sub-maximal cycling, followed by a high-intensity surge in the last kilometers towards the finish line. Indeed, as evidenced by the RER levels in the current study, 90 minutes at VT₂ was likely to lack the intensity and/or duration required to sufficiently reduce glycogen stores and have any effect on the 4PT. This should be considered in future research, along with tighter control on the dietary history of participants leading into the study.

Practical Applications

The present study has shown that BHB salt supplementation increased blood BHB concentrations but did not significantly improve 4-minute maximal cycling performance in highly-trained cyclists. While the current study failed to show any benefit, further research is required, implementing higher dosing regimens of BHB supplementation, perhaps utilizing a chronic dosing protocol or ketone esters. Furthermore, different exercise protocols designed to sufficiently reduce carbohydrate stores should be implemented in future studies before disregarding BHB supplementation as a possible supplement to improve performance.

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Conflict of interest

None.

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