Ketone Monoester Ingestion Alters Metabolism and Simulated Rugby Performance in Professional Players

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Ketone ingestion can alter metabolism but effects on exercise performance are unclear, particularly with regard to the impact on intermittent-intensity exercise and team-sport performance. Nine professional male rugby union players each completed two trials in a double-blind, randomized, crossover design. Participants ingested either 90 ± 9 g carbohydrate (CHO; 9% solution) or an energy matched solution containing 20 ± 2 g CHO (3% solution) and 590 mg/kg body mass β-hydroxybutyrate monoester (CHO + BHB-ME) before and during a simulated rugby union-specific match-play protocol, including repeated high-intensity, sprint and power-based performance tests. Mean time to complete the sustained high-intensity performance tests was reduced by 0.33 ± 0.41 s (2.1%) with CHO + BHB-ME (15.53 ± 0.52 s) compared with CHO (15.86 ± 0.80 s) placebo (p = .04). Mean time to complete the sprint and power-based performance tests were not different between trials. CHO + BHB-ME resulted in blood BHB concentrations that remained >2 mmol/L during exercise (p < .001). Serum lactate and glycerol concentrations were lower after CHO + BHB-ME than CHO (p < .05). Coingestion of a BHB-ME with CHO can alter fuel metabolism (attenuate circulating lactate and glycogen concentrations) and may improve high-intensity running performance during a simulated rugby match-play protocol, without improving shorter duration sprint and power-based efforts.

Keywords: β-hydroxybutyrate, lactate, glycerol, athletes, team sport, exercise performance

Ketones bodies comprise acetyl-CoA-derived compounds produced by the liver during low carbohydrate (CHO) availability (Cahill, 2006). The principal ketone body is β-hydroxybutyrate (BHB), which displays the highest systemic concentrations and utilization by the brain and skeletal muscle (Cahill, 2006; Mikkelsen et al., 2015). High systemic BHB availability suppresses hepatic glucose production and whole-body glyceral release (Mikkelsen et al., 2015) suggesting sparing of liver glycogen and a suppression of lipolysis. The suppression of lipolysis may act via both direct and indirect (e.g., insulin) mechanisms (Mikkelsen et al., 2015). The metabolic properties of BHB has led to growing interest in methods of raising systemic BHB availability with the putative potential to influence human health and performance.

One of the most effective, practical methods to increase systematic BHB availability without compromising endogenous CHO stores is the oral ingestion of the BHB monoester (BHB-ME), (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (Cox et al., 2016). When compared to CHO ingestion alone, the coinestion of CHO and BHB-ME before and during exercise can potently alter whole-body and skeletal muscle metabolism. BHB-ME-CHO co-ingestion has been shown to increase plasma BHB availability and net intramuscular triglyceride utilization, while suppressing plasma nonesterified fatty acid availability, glycolysis, and net intramuscular glycogen utilization during moderate-intensity exercise (Cox et al., 2016). Although, it should be noted that glycogen sparing has not been reported in all studies (Poffe et al., 2020). Furthermore, an increase in resting skeletal muscle carnitine content and a reduction in blood pH during exercise have also been observed with acute BHB-ME ingestion (Cox et al., 2016; Dearlove et al., 2019; Poffe, Ramaekers, et al., 2021). It is unclear what implications these metabolic responses have for exercise performance, as some of these changes may be beneficial (e.g., increased free carnitine content with potential to buffer acetyl-CoA during high-intensity exercise; Wall et al., 2011), but others detrimental (e.g., reduced blood pH and glycogenolysis potentially impairing high-intensity performance; Poffe et al., 2020; Poffe, Ramaekers, et al., 2021; Poffe, Wyns, et al., 2021; Stellingwerff et al., 2006). BHB-ME ingestion, therefore, produces a relatively unique metabolic milieu, with the potential effects on exercise performance currently unclear.

The evidence to date of ketone body ester ingestion on exercise performance demonstrates positive (Cox et al., 2016), neutral (Evans et al., 2019; Poffe et al., 2020; Poffe, Ramaekers, et al., 2021), and negative (Leckey et al., 2017; Poffe, Wyns, et al., 2021) effects during continuous, endurance-type exercise. Only one study to date has examined the effect of BHB-ME ingestion on intermittent running capacity, using a test originally designed to test soccer performance (Evans & Egan 2018). The addition of ketone ester to CHO ingestion did not influence time-to-exhaustion or 15-m sprint times. However, any potential performance advantage due to the metabolic effects of ketone ester coinestion could have been counteracted by a higher prevalence of gastrointestinal issues with the addition of ketone compared with CHO alone (Evans & Egan 2018). Rugby Union is a team sport characterized by periods of low-speed running interspersed with bouts of high-intensity activity, some of which can be prolonged in duration, and comprise physical contact, and sprinting elements (Austin et al., 2011; Read et al., 2018). The distinct physical demands and characteristics of rugby limit the ability to translate evidence from previous work involving endurance-type exercise, with
some short sprints, to nutritional practices in rugby. It remains unknown whether isocaloric ingestion of ketone ester and CHO influences intermittent exercise performance relevant to team sports, and no study has examined the effects of BHB-ME ingestions in professional rugby players during simulated match play.

Accordingly, the aim of this study was to assess the effect of ketone body ester plus CHO coinestion on simulated rugby union match play performance, compared to isocaloric CHO ingestion alone. It was hypothesized that ketone ester-CHO coinestion would augment simulated rugby union performance, when compared to isocaloric CHO ingestion.

Methods

Participants

Seventeen professional male players (age, 20 ± 1 years; body mass, 97.8 ± 5.3 kg; playing experience 11 ± 4 years) recruited from an English Premiership rugby union club consented to participate. Of the players originally recruited, eight dropped out of the study due to illness or injury, a total of nine participants (five forwards and four backs) completed the study. Experimental procedures were approved by the University of Bath Research Ethics Approval Committee for Health and conducted according to the Declaration of Helsinki.

Experimental Design

The study adopted a double-blind, placebo-controlled, randomized crossover design comprising a preliminary session and two experimental trials, each separated by at least 6 days. Supplements were prepared by an individual unconnected to the study and provided in unmarked containers to those who interacted with participants. Sessions took place during the players’ off-season and on an indoor athletics training facility. One week prior to main trials, participants completed a preliminary session to familiarize them with the protocol (described below). Prior to trials, habitual training was standardized for 1 week. Over the 48 hr preceding the first trial, each participant recorded their diet (estimated record) and replicated this diet before the second trial. Participants refrained from high-intensity exercise, caffeine, and alcohol for 24 hr before sessions. Main trials required participants to complete the match-play protocol ingesting either CHO or an energy matched drink containing CHO and BHB-ME (CHO + BHB-ME) before and at the mid-point of exercise. Performance testing was integrated as part of the validated match-play protocol and included repeat assessment of high-intensity running, sprint and power-based performance.

Simulated Rugby Union Match-Play Protocol

The Bath University Rugby Shuttle Test (BURST) is a rugby union-specific match-play protocol based on physical demands data for elite rugby union (Roberts et al., 2008, 2010). The exercise requirements have been described in detail elsewhere (Roberts et al., 2010). In brief, the protocol involves 16 exercise periods (~5 min each) arranged into 4 × 21-min blocks (Figure 1). Blocks 1 and 3 are followed by 4-min active recovery. A 10-min “half-time” break follows Block 2, comprising 7-min rest and 3-min active recovery. Within each exercise period, participants perform shuttles of walking, cruising, and jogging, interspersed with two bouts of simulated scrumming and rucking, and one bout of mauling. Timing is maintained by verbal instruction from an audio file. A performance test (described below) and 15-m sprint are also completed within each exercise block and on 16 occasions in total.

Figure 1 — A schematic representation of the study protocol. *Contact task order for cycles 1–5.
Power-based performance was assessed during bouts of scrumma-ging using an explosive sled-push (described below) and on 32 occasions. Performance test data are expressed as the mean performance across the BURST protocol. Distance traveled during the BURST (7,078 m) has been validated against match-play demands derived from time–motion analysis (6,418 m), time spent performing contact events (9.9%), is consistent with actual match play (Roberts et al., 2010).

Performance Testing

The high-intensity performance test was designed to replicate a sustained high-intensity exercise bout specific to rugby union competition, and combined aspects of resistance work, sprinting, and agility. Testing required participants to pass through an initial infrared timing gate (Smartspeed, Fusion Sport) and carry one 20-kg tackle bag over 9 m, followed by a second bag over the same distance, pick up a ball, and sprint 14 m before completing an unanticipated rapid change in direction (prompted by a flashing beacon), and then sprint through a final timing gate. Time taken between the timing gates was recorded as the performance test time. Participants had 25 s to return to the start and then perform a single 15-m sprint between two timing gates. There were no significant differences in the time taken to complete the high-intensity performance test and 15-m sprint between two preliminary tests, with a mean coefficient of variation of 1.4% and 1.8%, respectively.

The power-based sled push was performed on a custom-built machine designed to simulate the demands of rugby scrumming. The machine (RJF Design) incorporates a steel frame with a horizontal sled that runs along the frame. Participants adopt a semicrouched position with flexion at the knees and hips and with their shoulders resting against the sled. Participants used an explosive leg drive to push the sled with maximal force through a distance of ~3.5 m. Timing gates (Brower Speed Trap 2) assessed sled movement times with the first set placed 10 cm in front of the sled and then 3 m from the first set. Based on pilot testing, the runner angle was set at an incline of 3°, and additional resistance was provided by loading 100 kg onto the 80 kg sled. There was no significant difference in the time to complete the sled push between two preliminary tests, with a coefficient of variation of 0.6%.

Experimental Trials

Each participant began trials in the morning following a 10 hr overnight fast and having consumed their normal high-CHO breakfast 3 hr before exercise (providing a mean total of 165 g of CHO), and at least 500 ml of water. On arrival, participants provided a urine sample, and were weighed in underwear and shorts using a digital balance scale accurate to 0.05 kg (Avery Ltd.). Thereafter, a resting 500-μl fingertip capillary blood sample was obtained (Softclix Pro, Roche), and subjective ratings of thirst, hunger, and overall gastrointestinal symptoms recorded (scale 1–15). Participants then began a standardized 10-min warm-up that consisted of stretching, jogging, sprinting, one period of the BURST, and baseline performance tests. Participants consumed an initial bolus of test drinks 25 min preexercise, and rated drink pleasantness, and acceptability using a 100 mm scale (Bartoshuk et al., 2004). After a second blood sample, participants then began the BURST. Blood samples and subjective ratings were obtained after each exercise block. Participants received a further half-bolus of test drinks at the midpoint of exercise and provided further ratings. Water was permitted ad libitum during participants’ first trials and then matched in subsequent trials. Body mass was recorded postexercise once participants had removed excess moisture from the skin. Ambient temperature (20 ± 3 °C), and humidity (40% ± 7%), was not different between trials.

Drink Composition

The (R)-3-hydroxybutyl (R)-3-hydroxybutyrate was synthesized at the University of Oxford as a colorless oil comprising ethyl-(R)-3-hydroxybutyrate (~1%) and (R)-1,3-butanediol (~1%), which were the starting materials, (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (94%), 3-betahydroxybutyl 1,3-butanediol monoester (~1%), and di-b-hydroxybutyrate 1,3-butanediol diester (~3%).

Participants received either CHO or CHO with a BHB-ME (CHO + BHB-ME) in equal drink volumes for each trial (629 ± 60 ml in total) divided into an initial preexercise bolus (419 ml) and a smaller mid-exercise bolus (210 ml). Drinks were isocaloric and both made an estimated 16 kJ/kg body mass (BM) available for metabolism (total energy intake 1,528 ± 145 kJ). The ketone monoester was provided at a total dose of 590 mg/kg BM based on pilot data showing that this dosing level induces a sustained moderate ketosis (blood BHB of ~2–3 mmol/L) that was generally well-tolerated and within the physiological response observed during fasting in humans (Clarke et al., 2012). The total amount of CHO ingested was 90 ± 9 g in CHO trials (3% solution) and 20 ± 2 g in CHO + BHB-ME trials (14% solution) and equates to ingestion rates of ~1.1 and ~0.3 g/min, respectively. These intake rates ensured that the CHO trial matched guidance for supporting exercise performance, that is, equal to or above 1 g/min (Jeukendrup, 2004). Some CHO was added to the ketone monoester to enhance drink palatability and given that CHO in the mouth may have a central effect on performance (Carter et al., 2004; Chambers et al., 2009). The CHO content of CHO + BHB-ME was 100% glucose and was achieved by adding a commercially available sports drink (Glacueau, Vitamin Water). The CHO solution included exactly the same volume of this “base drink,” while additional CHO in the form of 35% sucrose and 65% maltodextrin was added as liquid gel (MaxiNutrition, ViperActive) with the primary intention of matching solutions for consistency, texture, and mouthfeel. Given that the raw ketone monoester is bitter in taste, pretesting was conducted to ensure the best possible matching of drinks. To make the taste comparable, CHO was flavored by adding 10 ml/L bitters and CHO + BHB-ME by adding 100 ng/L sweetener (Symrise). Four out of nine participants (44%) correctly guessed the order in which they received test drinks.

Sampling and Analysis

Capillary fingertip blood samples were assessed for blood levels of BHB using a portable analyzer (Abbott Medisense Precision Xtra Advanced Diabetes Monitoring System, Abbott). Blood was collected into serum Microvette 500 collection tubes (Sarstedt Ltd.) and allowed to clot for 15 min at room temperature before being centrifuged at 3,000g for 10 min at 4 °C (Biofuge Primo R, Heraeus). The serum fraction was extracted into 1.5 ml tubes (Eppendorf Ltd.) and frozen at −80 °C. Immunoassays were used to measure serum lactate, glucose, myoglobin, glycerol (Randox), and free fatty acids (Wako Chemical GmbH) in duplicate using an automated spectrophotometer (Cobas Mira, Roche Diagnostics). The coefficient of variation was less than 5% for all parameters. Urine samples were measured for urine specific gravity using a handheld refractometer (Model A300, Atago).
Statistical Analysis

A sample size estimation was performed based on data from Cox et al. (2016), whereby CHO + BHB-ME improved time-trial performance by 411 ± 458 s compared with CHO. Using this effect size ($d = 0.90$), 12 participants should provide greater than 80% power to detect such a difference with a two-tailed $t$ test and an alpha level of .05.

Data that required a single comparison of two means were tested for normality of distribution using the Shapiro–Wilk test. A paired two-tailed $t$ test was used to identify differences between means. A two-way repeated-measures analysis of variance was used to identify differences over time. Where significant interactions were observed, multiple $t$ tests were applied to determine the location of variance, both between treatments at each time point, and between time points within each treatment, relative to baseline, with both methods subject to a Holm–Bonferroni correction (Atkinson, 2001). Statistical tests were conducted using GraphPad Prism (version 8.2.1). The $p$ value was converted into 95% confidence intervals to derive a mechanistic inference about the true value of the effect statistic (Hopkins, 2007). Effects sizes were calculated for performance data using Cohen’s $d$. Data are expressed as mean ± SD in text and mean ± 95% confidence interval in figures. Data for performance tests are presented as the mean overall difference between trials. For all comparisons, $\alpha$ was set at .05.

Results

Exercise Performance

Mean overall time to complete the sustained high-intensity performance test was $0.33 ± 0.41$ s (2.1%) faster with CHO + BHB-ME ($15.53 ± 0.52$ s) compared to the energy matched CHO ($15.86 ± 0.80$ s) placebo ($p = .04$, $dz = 0.80$; Figure 2a). Subsequent 15-m sprint performance was not different between trials ($CHO = 2.57 ± 0.15$, CHO + BHB-ME = $2.56 ± 0.11$ s, $p = .80$). No differences were detected in mean time to complete the power-based sled push between trials ($p = .12$, $dz = 0.58$; Figure 2b). No trial order effects were observed for any of the performance tests ($p ≥ .11$) and no baseline differences were identified for any performance measure ($p = .26–.76$).

$\beta$-Hydroxybutyrate

Presupplementation concentrations of blood BHB were similar between trials (Figure 3a). There was a marked increase in BHB concentrations 20 min after CHO + BHB-ME ($2.53 ± 0.85$ mmol/L) compared with CHO ($0.01 ± 0.03$ mmol/L). Blood BHB concentrations following CHO + BHB-ME remained elevated above CHO throughout the entire trial (treatment: $F = 570$, $p < .001$), with significant differences observed between trials preexercise and at all successive time points (Treatment $×$ Time: $F = 44$, $p < .001$). A second slight increase in BHB concentrations was observed from 40 to 80 min from –2 to –2.6 mmol/L (Figure 3a).

Serum Variables

Glucose concentrations increased from baseline to the end of the warm-up before decreasing over the ensuing 20 min to near presupplementation values. Concentrations then increased over the subsequent 25 min before gradually decreasing (time: $F = 11$, $p < .001$). Glucose concentrations were higher after CHO than CHO + BHB-ME (treatment: $F = 8$, $p < .05$) and were significantly different between trials preexercise ($p = .02$; Figure 3b). Lactate concentrations increased markedly from the onset of exercise and remained relatively stable thereafter (time: $F = 62$, $p < .001$), with significantly lower concentrations after CHO + BHB-ME than CHO (treatment: $F = 10$, $p < .05$; Figure 3c). Serum nonesterified fatty acid concentrations remained near basal levels up to 20 min into exercise and gradually increased thereafter with CHO, but remained at or below preexercise values with CHO + BHB-ME (Figure 3d). Neither the time course nor the magnitude of the response was significantly different between trials, although there was a trend for an interaction (Treatment $×$ Time: $F = 4$, $p = .07$), whereby concentrations were lower 45 min into exercise with CHO + BHB-ME than CHO ($p < .01$). A similar pattern of response was identified for serum glycerol (time: $F = 20$, $p < .001$), although concentrations were significantly lower after CHO + BHB-ME than CHO (treatment: $F = 8$, $p < .05$; Figure 3e). There was a progressive rise in serum myoglobin concentrations throughout the exercise irrespective of trial (time: $F = 19$, $p < .05$; Figure 3f).

Subjective Ratings

Ratings of perceived exertion increased throughout the exercise protocol irrespective of trial (Figure 4a), from initial values of $13 ± 1$ (fairly hard) to $15 ± 2$ (hard). As the time course of response was not different for ratings of gastrointestinal distress as well as drink pleasantness and acceptability, data were...
combined across these time periods. Results showed a trend for gastrointestinal upset to be greater after CHO + BHB-ME (10 ± 2) than CHO (8 ± 1) trials ($T = 2, p = .08$; Figure 4b), while ratings of drink palatability were higher for CHO (47 ± 7) compared with CHO + BHB-ME (21 ± 9) trials ($T = 2, p < .001$).

**Initial Hydration Status and Fluid Balance**

Adequate hydration status was shown by similar pretesting values for urine specific gravity in both trials (CHO = 1.018 ± 0.009, CHO + BHB-ME = 1.021 ± 0.005). Total fluid intake (i.e., prescribed and that consumed ad libitum) was not different between trials (CHO = 1,675 ± 728 ml, CHO + BHB-ME = 1,777 ± 743 ml). There was no significant difference between trials in estimated fluid losses through sweat (CHO = 2,462 ± 563 ml, CHO + BHB-ME = 2,573 ± 642 ml) or for total urine production (CHO = 198 ± 135 ml, CHO + BHB-ME = 226 ± 220 ml). Body mass loss was apparent postexercise (CHO = 984 ± 482 g, CHO + BHB-ME = 1,022 ± 420 g) and equivalent to ~1% dehydration in both trials.

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**Figure 3** — Blood BHB (a), serum glucose (b), serum lactate (c), serum NEFA (d), serum glycerol (e), and serum myoglobin (f) concentrations before and after acute supplementation with CHO ONLY or isocaloric coingestion of CHO + BHB-ME during a simulated rugby union match-play protocol. Values are mean ± 95% CI. *Significant difference between treatments ($p < .05$). **Significant difference between treatments ($p < .001$). ***Significant difference between treatments ($p < .0001$). Asterisks next to figure labels indicate a main effect of treatment. CHO = carbohydrate; CHO only = carbohydrate alone; CHO + BHB-ME = carbohydrate with $β$-hydroxybutyrate monoester; CI = confidence interval.
Discussion

The present study demonstrates that coingestion of ketone body ester with CHO suppresses circulating glycerol and lactate concentrations during exercise, and may improve certain aspects of rugby union performance, when compared with isocaloric CHO ingestion. The data suggest that ingestion of ketone monoester improved simulated rugby union match-play performance, without improving shorter duration sprint and power-based performance. These performance effects were observed in the presence of marginally higher ratings of gastrointestinal distress.

Coingestion of CHO + BHB-ME resulted in blood BHB concentrations remaining above a mean of 2 mmol/L throughout exercise, compared to negligible BHB concentrations with isocaloric CHO ingestion. BHB concentrations above ~1.5 mmol/L can suppress hepatic glucose output and muscle glycogenolysis (Cox et al., 2016; Mikkelsen et al., 2015). Although it should be noted that one recent study reported no difference in plasma lactate concentrations or muscle glycogen breakdown with substantial and sustained increases in BHB concentrations during continuous cycling (Dearlove et al., 2021; Poffe, Ramaekers, et al., 2021). It is therefore possible that circulating BHB concentrations above 1.5 mmol/L combined with intermittent high-intensity exercise is required to detect meaningful metabolic effects. The present study reports marked metabolic effects with BHB-ME plus CHO coingestion, as serum lactate, nonesterified fatty acid, and glycerol concentrations were lower with coingestion of CHO + BHB-ME, compared to isocaloric CHO ingestion alone. Lower glycerol concentrations suggest a suppression of adipose tissue lipolysis.

While lower lactate concentrations could theoretically be due to an increase in lactate clearance rates, a reduction in lactate appearance rate is more likely, as this would be consistent with previous reports (Cox et al., 2016) of a suppression of glycolysis and/or better matching of glycolytic to pyruvate dehydrogenase flux.

The present study demonstrates that coingestion of CHO + BHB-ME may enhance high-intensity intermittent performance, without affecting sprint or power-type performance. It is noteworthy that lactate concentrations were higher in the present study than in many of the other endurance-type studies on ketone supplementation and thus the potential metabolic effects of ketones could be accentuated within our protocol, that is, during high-intensity rugby-related performance. While there was no improvement in very short duration maximal intensity sprints or power-based performance throughout the BURST protocol, there was also no negative impact, and therefore ketone ester-CHO coingestion may represent an effective nutritional strategy for actual match play in professional Rugby Union players.

If lower lactate concentrations reflect a lower rate of glycogenolysis, as has been reported during steady-state exercise (Cox et al., 2016), then the implications of glycogen sparing as a mechanism for performance enhancement in high-intensity exercise is unclear. While the strong association between liver and muscle glycogen depletion with fatigue has led to speculation that sparing of glycogen stores may enhance endurance performance (Bergström et al., 1967; Gonzalez et al., 2016), it is also possible that the inability to access glycogen could impair the capacity for high-intensity exercise (Stellingwerff et al., 2006). Muscle glycogen is the most rapid fuel for adenosine triphosphate resynthesis.

Figure 4 — Rating of perceived exertion (a), gastrointestinal discomfort ratings (b), thirst ratings (c), and hunger ratings (d) during a simulated rugby union match-play protocol following acute ingestion of CHO only or isocaloric coingestion of CHO + BHB-ME. Values are mean ± 95% CI. *Significant difference between treatments (p < .05). CHO = carbohydrate; CHO only = carbohydrate alone; CHO + BHB-ME = carbohydrate with β-hydroxybutyrate monoester; CI = confidence interval.
(Walter et al., 1999), and therefore is the most appropriate fuel for very high-intensity exercise (Gonzalez et al., 2017). Some nutritional strategies that spare glycogen by suppressing glycogenolysis and pyruvate dehydrogenase (PDH) activity, such as low-CHO, high-fat diets, have been shown to impair sprint performance (Stellingwerff et al., 2006). However, other nutritional strategies (e.g., L-carnitine supplementation), have been shown to spare muscle glycogen utilization at moderate exercise intensities (50% $W_{\text{max}}$), but still allow for high rates of glycogenolysis at higher exercise intensities (80% $W_{\text{max}}$; Wall et al., 2011). Whether these responses are translatable to the exercise intensity in the present study, remains to be assessed. Glycogen data are not available in the present study, but prior work has shown that BHB-ME potently suppresses muscle glycogenolysis at 70% $VO_2$ max (Cox et al., 2016), albeit with some inconsistency (Poffle et al., 2020). It is currently unclear whether BHB-ME impairs the ability to access glycogen at very high exercise intensities. The intensity of exercise in the present study is very likely to have exceeded 70% $VO_2$ max based on the blood lactate concentrations indicative of being well above lactate threshold.

An additional explanation for the lower lactate concentrations observed in the present study is a better matching of glycolytic to PDH flux (Stephens et al., 2007). If this is the case, it is currently the most likely explanation for a potential performance enhancement with coingestion of BHB-ME. During high-intensity exercise, the production of acetyl groups from high PDH flux can exceed utilization by the tricarboxylic acid (TCA) cycle, resulting in acetyl-CoA accumulation, depletion of the free CoA pool and, ultimately, inhibition of PDH and TCA flux (Stephens et al., 2007). Skeletal muscle carnitine can act as an acetyl group buffer by forming acetylcarnitine and thereby facilitate better matching of glycolytic, PDH and TCA flux during high-intensity exercise (Stephens et al., 2007; Wall et al., 2011). Acute CHO + BHB-ME coingestion has previously been shown to increase skeletal muscle carnitine content by up to ~50% within 25 min of ingestion (Cox et al., 2016). While this marked increase in muscle carnitine needs confirming, if acute BHB-ME ingestion is able to raise skeletal muscle free carnitine content, this could explain the improvement in performance observed in the present study. Future work will be required to establish whether this is indeed a plausible mechanism by which BHB-ME alters performance.

Any potentially advantageous metabolic effects of BHB-ME ingestion for performance could be negated by other metabolic or nonmetabolic effects, such as a reduction in blood pH and/or an increase in gastrointestinal distress. The precise dose of BHB-ME to produce sufficient circulating BHB concentrations to influence metabolism, while limiting gastrointestinal distress and acidosis requires clarification. In the present study where there was a suggestion of a ~2% (0.3 s) improvement in overall performance, the absolute dose of BHB-ME was ~58 g (590 mg/kg BM), which was coingested with 0.3 g/min of CHO (as a glucose–fructose mixture), compared to 1.1 g/min of CHO alone in the control group. The only previous study to have assessed the effects of ketone body ester ingestion in intermittent running found a neutral effect on time-to-exhaustion when ketone body ester (750 mg/kg BM; 59 g) was ingested in addition to glucose (~1.2 g/min; Evans & Egan 2018). It was noted in that study that there was a greater prevalence of gastrointestinal distress with addition of ketone body ester to glucose ingestion, compared with glucose ingestion alone. This is consistent with other observations of gastrointestinal distress and impaired performance with the addition of acetoacetate diester to CHO ingestion. Therefore, a consistent picture appears to be emerging, whereby the addition of ketone ester ingestion to relatively large CHO intakes may result in sufficient gastrointestinal distress to impair or negate any potentially beneficial performance effects. However, the substitution of ketone ester for CHO intake to result in isocaloric comparisons may explain the lesser prevalence of gastrointestinal complaints in the present study, compared with prior work. It should still be noted that the difference in mean gastrointestinal symptoms score in the present study was two points higher (15-point scale) with CHO + BHB-ME compared to CHO ingestion alone—with two participants reporting more severe gastrointestinal symptoms (scores >12) only with CHO + BHB-ME. Thus, the potential for gastrointestinal distress should be carefully considered if translating these findings into practice.

Some limitations with the present study are worthy of acknowledgment. First, there is potential for the study to be underpowered based on the dropout rate, and having not achieved the desired sample size. This could both inflate any effect size observed and increase the chance of a Type II error. Furthermore, due to the nature of the protocol and the athletes recruited, there is a lack of mechanistic insight and therefore the proposed mechanisms remain speculative. Future work should aim to establish the mechanisms underpinning any potential alterations in metabolism or performance with BHB-ME ingestion during high-intensity intermittent activity.

In summary, the present study demonstrates that coingestion of a BHB-ME with CHO can alter metabolism (reduce circulating lactate and glycerol concentrations) and may improve high-intensity intermittent performance during a rugby simulation protocol in professional players, without altering shorter duration sprint and power-type efforts. Some evidence of gastrointestinal distress was also prevalent. Therefore, Rugby Union players may consider consuming BHB-ME with CHO before and during competition, although individual tolerance should first be tested in training prior to competition due to the potential for gastrointestinal problems.

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