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Context is key: exogenous ketosis and athletic performance

David J Dearlove, Olivia K Faull and Kieran Clarke

Ketone bodies are energetically efficient metabolic substrates, which are synthesised from lipids during prolonged caloric deprivation. Once considered a simple metabolite to fuel the brain during starvation, ketone bodies are now recognised as having pleiotropic effects on metabolism, including modulating the availability and catabolism of other substrates. The combination of improved energetics and fuel sparing observed during ketosis is pivotal to maintaining energy homeostasis during starvation or fasting. Harnessing these actions may also offer a method to enhance human endurance. Owing to the necessity of depleting carbohydrate stores to induce ketogenesis, exercising during an endogenous ketosis is unlikely to be advantageous. In contrast, the delivery of exogenous ketones creates a novel physiological state, where high circulating ketone concentrations and replete carbohydrate stores are present. Here, we discuss the current understanding of how exogenous ketosis may mimic advantageous aspects of starvation physiology and in doing so, be used to enhance human exercise endurance performance.

Address
The Department of Physiology, Anatomy and Genetics, The University of Oxford, Oxford, UK

Corresponding author:
Dearlove, David J (david.dearlove@dpag.ox.ac.uk)

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Introduction

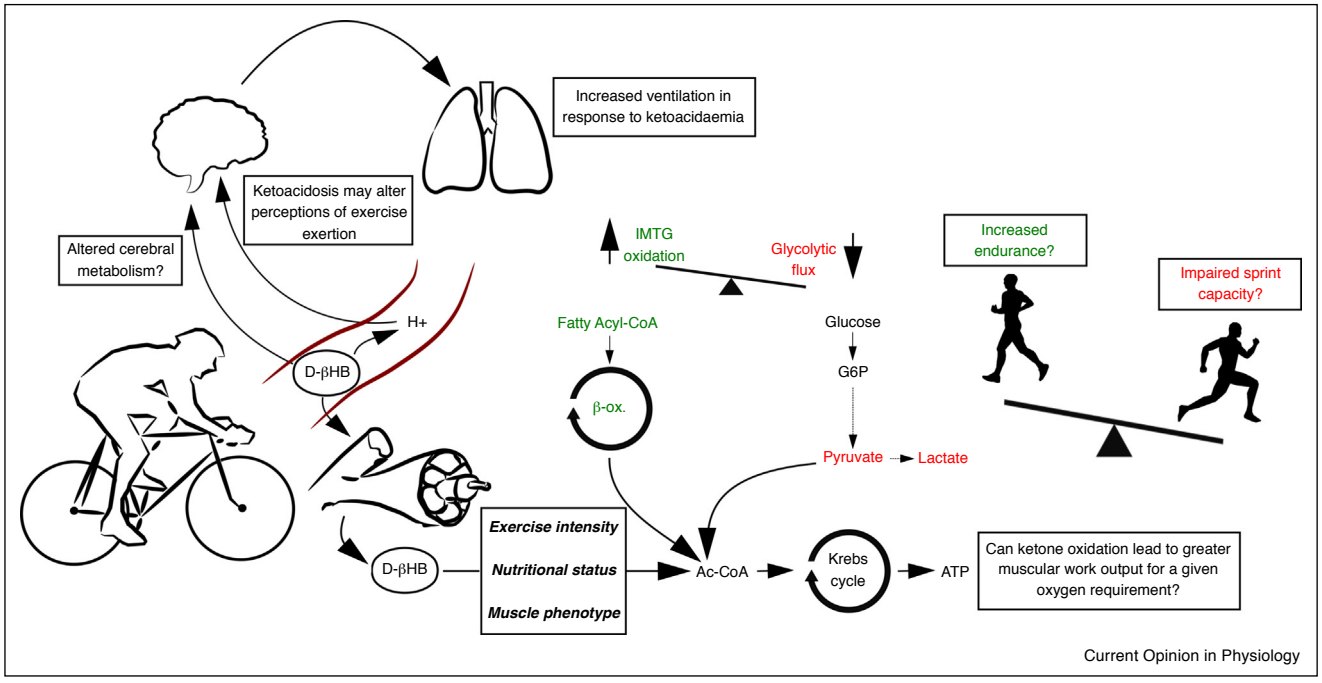
Altering the macronutrient composition of an individual's diet and, therefore, substrate availability, undoubtedly affects exercise performance [1]. Dietary interventions have largely focussed on manipulating the supply and combustion of carbohydrate (CHO) and fat [2,3]. During energetic stress, such as in starvation, exhaustive exercise, or following a CHO restricted diet, the ketone bodies, acetoacetate (AcAc) and D-β-hydroxybutyrate (D-βHB), provide additional metabolic substrates [4]. These lipid-derived molecules are synthesised in large quantities by liver [5], with blood concentrations reaching a physiological ceiling of ~7 mM during prolonged fasting (compared to ~0.1 mM following CHO ingestion) [4]. Ketones provide an alternative oxidisable carbon source to glucose for brain [6] and act as metabolic signals, regulating the use and mobilisation of other fuel substrates [4]. In doing so, ketosis slows the catabolism of finite glycogen and skeletal muscle [6]. Whilst brain takes precedence for the combustion of ketones [7], they can be oxidised by most tissues, including skeletal muscle [8,9]. Ketone oxidation may have thermodynamic advantages over other carbon substrates [10].

The combination of glycogen sparing, improved energetic efficiency and altered substrate metabolism during ketosis could offer a method to enhance human performance [11,12]. However, owing to the necessity of depleting hepatic and intramuscular glycogen stores to induce ketogenesis [4], exercising during an endogenous ketotic state (e.g. through adoption of a ketogenic diet [13]) may be detrimental to performance [14–16]. The advent of ketone supplements offers an alternative approach to elevate blood ketone concentrations, without the need to deplete CHO stores [17,18]. Here, we review how the novel physiological state of exogenous ketosis, characterised by high circulating ketone concentrations and replete glycogen stores, may enhance human endurance.

The ingestion of exogenous ketones alters skeletal muscle metabolism during exercise

During exercise, a perpetual replenishment of the intramuscular adenosine triphosphate (ATP) pool is required for continued muscular contraction. The ATP derived from the combustion of substrates is not equal and depends on a complex interaction between their free energy ($\Delta G'_{ATP}$) and the architecture of metabolic pathways (glycolysis, β-oxidation and in some instances, ketolysis) [11]. Since the work of Balasse and Ferry, we have known that exogenous ketones can be used to fuel exercising muscle [8,9]. By increasing the $\Delta G'_{ATP}$ for ATP synthesis, the oxidation of ketones may be energetically advantageous versus CHO and fat (for review, see Cox and Clark [11]) (Figure 1). In the working rat heart, infusing ketones and glucose versus glucose alone resulted in a 28% greater hydraulic efficiency (J/mol of O_2 consumed), suggesting that ketone oxidation may increase muscular output for a given oxygen requirement [10]. However, this has not been demonstrated in exercising humans. Factors influencing ketone oxidation rates in skeletal muscle may include: the intensity of exercise performed, muscle phenotype (ratio of slow: fast muscle fibres), the nutritional status of the muscle (fed versus fasted) and circulating ketone concentrations.

Figure 1



Known and hypothesised effects of exogenous ketone consumption during exercise. Exercising skeletal muscle readily oxidises ketone bodies. By increasing the $\Delta G'_{ATP}$ for ATP synthesis, ketone oxidation may be thermodynamically advantageous compared to glucose and fat oxidation. Ketone oxidation rates may depend on the intensity of exercise performed, the nutritional status of the muscle (fed versus fasted) and the muscle phenotype. Exercise substrate metabolism is profoundly altered during exogenous ketosis, with increased fat oxidation and decreased glycolytic flux. The preservation of glycogen reserves and potential improvements in energy transduction through ketone oxidation may modestly increase long duration exercise performance. However, high-intensity exercise that relies on rapid glycolytic flux and anaerobic glycolysis may be negatively affected. Whether exogenous ketosis can beneficially alter cerebral metabolism, potentially delaying central fatigue, remains speculative. Exogenous ketosis results in a mild ketoacidaemia, which is compensated for by an increased ventilatory drive. Leg discomfort, anxiety of breathlessness and anxiety of leg discomfort are increased during ketoacidosis. Ac-CoA, acetyl CoA; ATP, adenosine triphosphate; β-ox., β-oxidation; D-βHB, D-β-hydroxybutyrate; H^+, hydrogen ion; IMTG, intramuscular triacylglycerol; G6P, Glucose-6-Phosphate.

Determining this will help to formulate guidelines for the use of exogenous ketones in competition and training.

Exogenous ketones alter skeletal muscle preference for the combustion of other fuels [19••]. Because of its high abundance and energy density, fat is the preferred substrate at rest and low-to-moderate exercise intensities [20]. As intensity increases, however, demand for the rapid resynthesis of ATP necessitates that muscle becomes ever more reliant upon intramuscular glycogen [20]. These stores are low, representing less than 1% of total energy held within the body [6], and are quickly depleted during exhaustive exercise resulting in muscle fatigue [21]. Exogenous ketosis reduces skeletal muscle reliance on intramuscular glycogen, even at typically glycolytic exercise intensities, and instead promotes the oxidation of more abundant intramuscular triacylglycerols [19••]. Having supplemented athletes with a ketone ester before high-intensity exercise (75% maximum power output (W_{Max})), Cox *et al.* found decreased intramuscular glycolytic intermediates, with no change in Krebs cycle intermediates and increased acyl-carnitine species, indicating greater fat and/or ketone oxidation [19••]. The inhibition of glycolysis may have resulted from a restoration of the Randle cycle (glucose-fatty acid cycle), which is typically abrogated during intense or prolonged exercise [22], whereby increased acetyl-CoA and citrate concentrations resulting from ketone and fat oxidation inhibit pyruvate dehydrogenase and phosphofructokinase complexes [23]. Given the well-established link between glycogen availability and endurance exercise capacity [21], the reduced reliance on intramuscular glycogen stores may be advantageous in some contexts (reviewed later). However, not all types of exogenous ketones are equal, and oxidation rates and subsequent metabolic signalling actions may depend on the form consumed.

‘Flavours’ of exogenous ketones

Oral ketone supplements may be delivered as salts (KS) or esters (KE). The effectiveness of these supplements largely depends on their chemical composition. The amount of sodium delivered through KS consumption may be deleterious to health [24], so prolonged

supplementation is undesirable. In humans, serum ketone concentrations following KS ingestion are similar to those seen in post-exercise ketosis (~1 mM) [25,26], well below the physiological ceiling of ~7 mM [4]. This is likely due to the racemic mixture of D-βHB and L-βHB optical enantiomers found in many salt supplements and the limited capacity for salt uptake from the gut [26]. D-βHB is synthesised endogenously in the liver [4]. Conversely, L-βHB is synthesised from Acetoacetyl CoA when it accumulates due to a Krebs cycle bottleneck and is only found in extrahepatic tissues [27]. Only D-βHB is converted into AcAc by the rate limiting enzyme of ketolysis, succinyl-CoA-3-oxaloacid CoA transferase. As such, elevating L-βHB concentrations is unlikely to affect exercise substrate metabolism and, therefore, performance.

KS and KE consumption have opposing effects on blood pH, with the former making blood more alkaline and the latter increasing acidity (ketoacidosis) [26]. In healthy athletes, ingestion of 330 mg kg bw^{-1} of KE (blood D-βHB = 3.7 mM) caused pH and bicarbonate (HCO_3^-) to fall significantly and was compensated for by increased minute ventilation and earlier exercise-induced hyperventilation during an incremental exercise test, with no effect on performance [28]. Whilst both forms of exogenous ketones lower blood glucose, free fatty acids (FFAs) and triglycerides [26], the reported effects of KS on exercise metabolism are inconsistent, and blunted compared to those following KE ingestion [29–31] (Table 1). Notably, KS ingestion does not lower blood lactate during exercise (as observed following KE ingestion [19••,32•]), nor does it appear to affect exercise performance [29–31]. Given the limitations in the delivery and effectiveness of KS, the remainder of this review will focus on KE.

Two KEs have been trialled in rodents and humans, and have been shown to safely, rapidly and reproducibly elevate blood ketone concentrations [17,18]. These compounds are made up of one or more ketone molecules (AcAc or D-βHB) joined with an ester bond to a ketone precursor, such as butanediol or glycerol. Once consumed, the ester bonds are hydrolysed by ubiquitously expressed gut esterases, and the ketones released into the blood stream. Butanediol is processed by the liver to form further D-βHB and AcAc molecules. It is possible to achieve blood ketone concentrations approaching the physiological limit of ~7 mM in a dose dependent fashion, which may remain elevated for several hours after ingestion [26].

In skeletal muscle, circulating ketones are taken up by the monocarboxylate transporter 1 (MCT1) [33]. MCT1 has a low relative affinity for both AcAc and D-βHB (5.5 mM and 10.1 mM, respectively [34]), meaning the rate of ketone uptake is dependent on circulating concentrations. Ketones move across the mitochondrial matrix via the mitochondrial pyruvate carrier (MPC) [35]. The MPC has a very high affinity for AcAc (0.61 mM) compared to D,L-βHB (5.6 mM) [34]. D-βHB is the predominant circulating ketone during an endogenous ketosis [36] and as such, the increased affinity of the MPC for AcAc is logical. However, consuming large quantities of exogenous AcAc and thus perturbing the endogenous ratio of AcAc: D-βHB will saturate the MPC (i.e. the enzyme will work at a constant rate, regardless of increased intracellular AcAc), potentially causing a bottleneck for its oxidation.

βHB is more chemically reduced than AcAc. The relative supply of reducing equivalents to the mitochondrial electron transport chain alters the electrochemical gradient and, therefore, creates a greater $\Delta G'_{ATP}$ for the generation of ATP [37]. Thus, the potential energy transduction benefits achieved through exogenous ketosis could be blunted when an AcAc ester is consumed.

Exogenous ketosis favours long endurance exercise

The utility of exogenous ketones depends on the metabolic demands of the exercise undertaken. As exercise intensity increases, so does reliance upon CHO derived energy sources [20]. As discussed, exogenous ketones alter the normal hierarchy for substrate combustion during exercise by increasing fat oxidation whilst providing an additional, energetically advantageous and readily oxidisable fuel. The subsequent rationing of finite glycogen may be beneficial for long duration exercise. As evidence, Cox *et al.* [19••] found a modest ~2% increase in performance when overnight fasted, highly trained athletes were supplemented with a D-βHB KE plus CHO drink, versus CHO alone before 90 min of bicycle exercise (60 min at 75% W_{Max} followed by a 30 min time trial) (Table 1). However, the inhibition of glycolysis observed during exogenous ketosis may be detrimental to short duration, high-intensity exercise that relies on rapid glycolytic flux and anaerobic glycolysis [20]. Given this, it is likely an exercise intensity/duration threshold exists, where exogenous ketosis moves from being ergogenic to ergolytic. Such a threshold would explain why KE supplementation had no effect on exercise performance during high-intensity intermittent running [32•] or during an incremental ramp test on a static bicycle ergometer [28].

Whilst protocols including steady state exercise following an overnight fast are advantageous for determining the metabolic effects of a dietary intervention, they seldom reflect 'real world' athletic demands. Arguably, just one study has attempted to investigate the effects of exogenous ketosis on exercise performance using a protocol that bears resemblance to sporting competition [38•]; this included standardised pre-race nutrition, self-pacing, and a simulated cycling time trial featuring alternating

Table 1

Summary of studies reporting the acute effects of ketone supplements on exercise substrate metabolism and physical performance

Author (date)	Study design	Participants	Protocol	Form of exogenous ketones an dose (peak [ketone] (mM))	Observed effects on exercise substrate metabolism	Effect on performance
Cox *et al.* 2016 [19••]	Cross over design; KE + CHO versus isocaloric CHO alone	Highly trained athletes ($n = 8$)	1 hour steady-state bicycle exercise at 75% W_{Max} followed by a 30 min time trial for maximum distance	(*R*)-3-hydroxybutyrate-(*R*)-1,3-butanediol; 573 mg kg bm^{-1} (BHB = ~2 mM)	Lower blood lactate, glucose and FFA following KE + CHO ingestion. Metabolomics analysis of skeletal muscle samples revealed that KE ingestion decreased glycolytic intermediates and increased acyl-carnitine species, with no change in Krebs cycle intermediates. Histological analysis showed a preservation in intramuscular glycogen and increased oxidation of intramuscular triacylglycerols.	Significantly improved time trial performance in the KE + CHO condition, with athletes cycling (mean ± SEM) 411 ± 162 m further versus the CHO alone.
O'Malley *et al.* 2017 [30]	Cross over design; KS versus minimal calorie, taste-matched control	Healthy adults ($n = 10$)	Incremental exercise on a static bicycle ergometer (5 min @ 30%, 60% and 80% power at ventilatory threshold) followed by a 150 kJ time trial	0.3 g BHB kg bw^{-1}, 0.01 g potassium kg bw^{-1} and 0.01 sodium kg bw^{-1} (BHB = ~<1 mM)	RER was lower during exercise in the KE versus control condition. Blood glucose was lowered in the KS condition, but there was no difference in blood lactate.	Time to completion was significantly worse in the KS condition (mean ± SD; KS, 711 ± 137 s; control, 665 ± 120 s)
Rodger *et al.*, 2017 [31]	Cross over design; KS versus calorie-free, taste-matched control	Highly trained cyclists ($n = 12$)	90 min at 70% of the second ventilatory threshold followed by a 4 min performance test	11.7 g of BHB salt (BHB = 0.6 mM)	No difference in blood lactate and glucose between conditions. Significant increase in RER during the 4 min performance test in the KS condition.	No difference in 4 min performance test.
Leckey *et al.*, 2017 [34]	Cross over design; KE versus taste-matched control drink (unclear whether this contained calories)	International level cyclists ($n = 8$) and highly trained U23 cyclists ($n = 3$)	31 km time trial performed on a cycling ergometer	1,3-butanediol acetoacetate diester; 250 mg kg bw^{-1} (BHB = ~0.4 mM, AcAc = ~0.5 mM)	KE ingestion caused blood glucose to fall. Post exercise blood lactate concentrations were significantly lower in the KE condition. No difference in RER.	Ketone consumption resulted in a significant reduction in average power output (mean ± SEM; KE, 339 ± 37 W; PLAC, 352 ± 35 W) and significantly worse time to completion. Of note, all participants experienced moderate to severe GI upsets following KE ingestion.
Evans *et al.*, 2018 [29]	Cross over design; KS versus control (plain water)	Trained cyclists ($n = 19$)	Incremental exercise on a static bicycle ergometer (8 min steps at 30%, 40% 50%, 60% 70% and 80% of VO_2 peak)	0.38 g kg bm^{-1} of BHB salts (BHB = ~1.2 mM)	Blood glucose was lower in the KS condition. There was no difference in lactate concentration. RER was significantly higher during exercise following KS ingestion.	Performance was not measured.
Evans and Egan, 2018 [32•]	Cross over design; CHO + KE versus taste-matched CHO alone	Well trained team sports athletes ($n = 11$)	Loughborough intermittent shuttle test (part A, 5 × 15 min intermittent running; part B, shuttle run to exhaustion)	(*R*)-3-hydroxybutyrate-(*R*)-1,3-butanediol; 750 mg kg bm^{-1} (BHB = 2.6 mM)	Blood glucose and lactate concentrations were lower in the KE condition.	No difference in 15 m sprint times or shuttle run time to exhaustion (mean [CI]; KE, 229 [178–280] s; placebo, 267 [199–336] s).

Table 1 (*Continued*)

Author (date)	Study design	Participants	Protocol	Form of exogenous ketones an dose (peak [ketone] (mM))	Observed effects on exercise substrate metabolism	Effect on performance
Dearlove *et al.*, 2019 [28]	Cross over design; KE versus taste-matched calorie free control	Well trained endurance sport athletes ($n = 12$)	Incremental exercise test on static bicycle ergometer (3 min steps, 25 W ramp)	(*R*)-3-hydroxybutyrate-(*R*)-1,3-butanediol; 330 mg kg bw^{-1} (BHB = 3.7 mM)	Falls in blood lactate, glucose and FFA versus control. pH and HCO_3^- lower following KE ingestion. Ventilatory threshold occurred at a significantly lower workload. The workload at the fixed blood lactate level of 4 mM was higher in the KE condition.	No difference. W_{Max} was the same in KE (mean + SEM; 393 ± 22 W) and control (389 ± 20 W).

βHB, β-hydroxybutyrate; CHO, carbohydrate; GI, gastrointestinal; HCO_3^-, bicarbonate; KE, ketone ester; KS, ketone salt; FFA, free fatty acid; RER, respiratory exchange ratio; VO_2, volume of oxygen consumed; W_{Max}, maximum power output.

gradients. Leckey *et al.* found supplementing professional cyclists with an AcAc diester and CHO, versus CHO alone resulted in significantly worse average power and time to completion. These somewhat contradictory performance results compared to those reported by Cox *et al.* [19••] may be accounted for by the exercise protocol employed or the form of KE (AcAc diester versus D-βHB monoester) consumed (as previously discussed). However, as acknowledged by the authors, interpretation is difficult due to the moderate/severe gastrointestinal discomfort suffered by all athletes. Further work is required to elucidate the ergogenic potential of ketone supplementation in intermittent intensity exercise, where beneficial effects on energy transduction and CHO preservation must be weighed against a potentially impaired capacity for high-intensity efforts.

Brain over brawn?

Although largely unconscious, intense exercise requires a high level of cerebral output to coordinate complex movement patterns and muscular contractions. Brain is hungry [39] and has a limited palate [7], and exercise rapidly alters the availability of its preferred substrate: glucose [40]. As a result, central fatigue, that is, fatigue of the central nervous system leading to reduced efferent stimulation of motor units, may occur upon prolonged exhaustive exercise [41]. This complex phenomenon has multiple causes, which are reviewed elsewhere [42]. A pertinent hypothesis, however, is that energy demand exceeds supply, largely resulting from the depletion of glycogen stores held within astrocytes [43]. During exercise, serum concentrations of the monocarboxylic acids (lactate, pyruvate and ketones) are elevated, and are readily taken up by brain for oxidation to supplement glucose [7,44]. Of these, only ketones are known to replace glucose, albeit this switch is slow, taking approximately 6 weeks of starvation [6,7]. Given this, an intriguing hypothesis is that supplementing athletes with nutritional ketones might help delay central fatigue, either by providing an alternative oxidisable substrate and/or sparing the minute cerebral glycogen stores, thus facilitating more prolonged and potentially more coordinated exercise. To date, evidence for this hypothesis is limited. Rats fed a diet including 30% of calories derived from nutritional ketones completed an 8-arm radial maze test following exhaustive exercise 38% faster versus control littermates [45]. In humans, the decline in executive functioning following exhaustive exercise was lessened when athletes were supplemented with ketones and CHO versus CHO alone [32•]. However, given this amounted to an approximate 1% reduction in incorrect answers, the 'real world' relevance of this finding requires further testing.

Any alterations in cognition or behaviour resulting from KE consumption may be derived from the subsequent perturbations to pH (ketoacidosis), rather than ketones

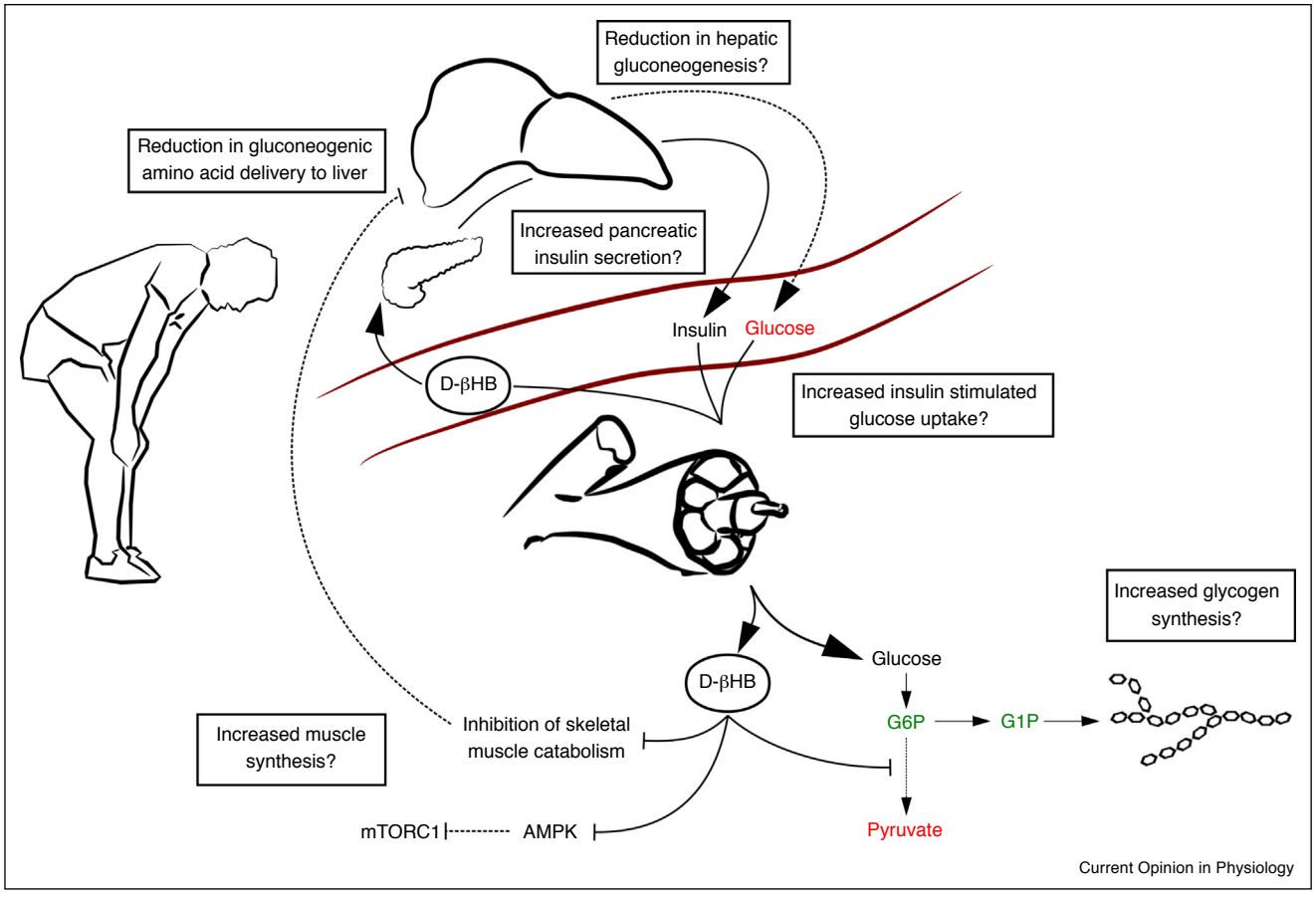
per se. Faull *et al.* [46] demonstrated that elevations in blood hydrogen ion (H^+) concentration resulting from KE ingestion altered aspects of perceived exertion during exercise, increasing perceptions and anxiety of leg discomfort, and anxiety related to breathlessness. This finding suggests an evolutionary purpose to ketoacidaemia, whereby elevated H^+ concentrations provide peripheral feedback during calorie deprivation, increasing anxiety and potentially altering behaviour related to energy expenditure.

Exogenous ketosis may increase post-exercise intramuscular glycogen synthesis and suppress skeletal muscle catabolism

Intramuscular glycogen content is a strong determinant of endurance exercise performance [47]. To enhance glycogen synthesis, current recommendations are to consume 1.0–1.2 g kg^{-1} BW $hour^{-1}$ CHO for 4–6 hours post-exercise [1]. The provision of ketones with gold-standard CHO feeding may further augment glycogen recovery [48,49] (Figure 2). In highly trained athletes, ingesting KE before a 10 mM glucose clamp resulted in a 32% increase in infused glucose (an additional 61 g of glucose delivered over 2 hours) versus a CHO control, leading to a twofold increase in insulin secretion and a 50% increase in glycogen synthesis. It is unclear, however, whether the additional glucose required to maintain a 10 mM blood concentration came from increased glucose uptake (increased rate of disappearance) or reduced hepatic gluconeogenesis (reduced rate of appearance).

Ketones may stimulate insulin secretion [50,51], potentially increasing insulin mediated glucose uptake. However, this effect has not been consistently observed [52–55] and may depend on blood glucose being at high or supraphysiological concentrations [56•]. Alternatively,

Figure 2



Known and hypothesised effects of exogenous ketone consumption during post-exercise recovery. Exogenous ketones cause blood glucose concentrations to fall. This may result from increased insulin stimulated glucose uptake or decreased hepatic gluconeogenesis. Once in the myocyte, glucose may be preferentially directed towards storage due to the inhibitory effects of exogenous ketosis on glycolysis, and a subsequent accumulation of glucose-6-phosphate. Consumption of exogenous ketones following exercise may help preserve muscle mass by suppressing its catabolism and promoting the activation of the anabolic mTOR pathway. AMPK, 5′ AMP-activated protein kinase; D-βHB, D-β-hydroxybutyrate; G1P, Glucose-1-Phosphate; G6P, Glucose-6-Phosphate; mTORC1, mammalian target of rapamycin complex.

the anticatabolic effects of ketones on skeletal muscle [57,58] may have limited the supply of gluconeogenic amino acids to liver, thus reducing hepatic glucose output and facilitating an increase in glucose infusion to maintain a 10 mM blood concentration. The latter mechanism would explain why Vandoorne *et al.* found glycogen synthesis was the same when athletes consumed a fixed mass of CHO (1 g kg^{-1} BW hour^{-1} with 0.3 g kg^{-1} BW hour^{-1} protein) with either a KE or triglyceride containing control drink, despite significantly lower blood glucose concentrations following KE ingestion [59•]. Interestingly, glycogen synthesis was the same even though 5′ adenosine monophosphate-activated protein kinase (AMPK), a potent inhibitor of glycogen synthase [60], was deactivated more quickly following KE ingestion. Once in the myocyte, glucose may be preferentially converted to glycogen due the inhibitory effects of exogenous ketosis on glycolysis causing an accumulation of glucose-6-phosphate, which is an allosteric activator of glycogen synthase [61]. Further work is required to determine the mechanisms for lower blood glucose concentrations during exogenous ketosis and the subsequent effects on glycogen synthesis.

Presumably due to the expedited deactivation of AMPK [60], mammalian target of rapamycin complex 1 (mTORC1) signalling was increased following KE ingestion. The combination of reduced protein catabolism seen during exogenous ketosis [57,58] and potentially increased protein synthesis through mTOR signalling may help maintain muscle mass, which can be challenged by prolonged endurance exercise [62].

Future directions: can the cellular signalling actions of βHB modulate the adaptive response of skeletal muscle to exercise?

Ketones possess an array of cellular signalling functions [63••,64]. βHB inhibits class I histone deacetylases [65], proteins involved in regulating gene expression by deacetylating histone lysine residues, and which may modulate transcriptional activity post-exercise [66]. βHB directly post-translationally modifies histones at lysine residues (lysine β-hydroxybutyrylation) in fasted or diabetic mouse liver, which is associated with activating fasting-related gene networks [67]. βHB is the only endogenous inhibitor of the hydroxycarboxylic acid receptor 2 [68], expressed in white adipose tissue [69] and immune cells [70]. Inhibition results in the suppression of lipolysis [67], creating a negative feedback loop whereby ketones restrict ketogenesis by limiting the supply of FFAs to liver. In addition to these direct signalling functions, βHB may exert indirect effects through its catabolism to ATP by altering the intracellular concentrations of intermediate metabolites, including acetyl-CoA, succinyl-CoA and NAD, which act as substrates for proteins regulating gene expression [63••]. The collective signalling actions of βHB appear to fine-tune metabolism towards increased fat oxidation and fatigue resistance [63••], similar to those sought through endurance exercise training [71]. Further work is required to elucidate the effects of βHB signalling in human skeletal muscle, and whether exogenous ketone supplementation may augment favourable adaptive responses to exercise.

Conclusion

When considering the utility of exogenous ketones to enhance athletic performance, context is key; both in regard to the form of nutritional ketones consumed and their application to athletic disciplines. Whilst ketone salts are readily available, their effects on exercise metabolism are hampered by their racemic formula. Further, given the accompanying sodium load, prolonged consumption may be deleterious to health. The nutritional ketosis achieved through KE consumption alters substrate metabolism in a predictable and potentially advantageous manner. In some contexts, this may be beneficial to athletic performance. When considering the ergogenic potential of exogenous ketosis, it is important to understand the specific metabolic demands of each event. If exercise duration is short and success depends on repeated high-intensity efforts, exogenous ketones may hinder performance. The use of exogenous ketones to improve cognition remains speculative, and changes in bodily perceptions may result from the accompanying acid load rather than altering cerebral substrate metabolism. Finally, exogenous ketosis may aid recovery from exercise by increasing glycogen synthesis and suppressing skeletal muscle catabolism.

Conflict of interest

The intellectual property and patents covering the use of the D-βHB ketone monoester are owned by BTG Ltd, The University of Oxford, the NIH and TdeltaS Ltd. Should royalties ever accrue from these patents, K.C. as a named inventor may receive a share, as determined by the terms of the respective institutions. K.C. is director of TdeltaS Ltd., a spin out company of the University of Oxford, which develops and commercialises products based on the KE. D.D. is an employee and O.K.F. is a former employee of TdeltaS Ltd.

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- • of special interest
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