**Title:** Ketone esters and their effects on carbohydrate metabolism during exercise.

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Ketone bodies are metabolites produced by the liver under conditions of low carbohydrate and high fatty acid availability. The ketone body of most abundance is typically beta-hydroxybutyrate (BHB). Physiological scenarios where circulating BHB concentrations are elevated to >1 mmol/L include fasting, exercise, late pregnancy (particularly labor), and very low-carbohydrate diets (1, 2). During scenarios of high BHB concentrations, the brain and muscle can take up and utilize BHB as a fuel (3). In addition, BHB may play a role in signalling via extracellular receptors and inhibiting histone deacetylases (4). BHB therefore produces a wide variety of effects on metabolism and signalling under conditions of low carbohydrate availability.

Ketone supplements are orally ingestible compounds that can raise circulating BHB concentrations without the need to restrict carbohydrate intake. Of the various ketone supplements currently available, the ketone monoester (R)-3-hydroxybutyl (R)-3-hydroxybutyrate, appears to be the most effective at raising plasma BHB concentrations. It has been speculated that ingesting ketone esters alongside carbohydrate during exercise may provide additional fuel and thereby spare glycogen use and enhance performance. To date, however, evidence on glycogen sparing and performance effects of ketone esters during exercise has been equivocal (5-7). This may be, in part, due to the methods of measurement which have focussed on net muscle glycogen utilisation. A more complete understanding of the effects of ketone esters of exercise metabolism would include the potential impact on broader aspects of carbohydrate utilization.

In this issue of the journal, Howard et al. (8) employed dual stable-isotope tracers combined with indirect calorimetry to examine plasma glucose kinetics and exogenous

substrate metabolism with ketone esters ingested during exercise. This allowed assessment of how ingested carbohydrates are handled, and the impact on hepatic carbohydrate metabolism. These methods can overcome some of the limitations of muscle biopsy measures, which are restricted to the site of sampling, providing snapshot data, and potentially introducing artefacts from the sampling procedure. In contrast, the dual-stable isotope method (oral and intravenous infusion of glucose tracers) can provide insight into fluxes, does not require assumptions or extrapolations from a single sample site to other glycogen depots, and can reveal the fate of ingested *versus* endogenous carbohydrates (9).

Ketone ester ingestion raised plasma BHB concentrations to ~1.25 mmol/L at the onset of exercise and suppressed glucose rate of appearance (Ra) from ~7 mg/kg/min to ~6.5 mg/kg/min (equating to a suppression of glucose Ra of ~2 g/h). Since there was no evidence that exogenous glucose oxidation rates were affected to any meaningful extent by ketone ester ingestion (<0.01 g/min difference), it can be assumed that this reduction in glucose Ra primarily represents a reduction in hepatic glucose output. In other words, it is possible that ketone esters may spare liver glycogen stores. The relevance of this reduction, however, should be considered carefully in the context of other strategies. For example, glucose ingestion at a rate of less than 10 g/h can induce a similar suppression of endogenous glucose Ra (10), and a suppression of 2 g/h (reflecting <5% of replete liver glycogen stores) is unlikely to be sufficient to impact performance. However, it may be that optimising the dose and timing of ketone esters could produce more substantial effects of glucose kinetics, since data at rest suggest that BHB concentrations >1.5 mmol/L can suppress endogenous glucose Ra from ~13.5 to ~9.9 g/h (>30% reduction). If this magnitude of

suppression with higher BHB concentrations extends to an exercising context, this could be a physiologically meaningful suppression. The current evidence, however, does not support the idea the ketone esters consistently suppress liver or muscle glycogen utilization to any meaningful degree.

The metabolic impact of ketone esters in this study was, therefore, modest. The impact on performance was negative, whereby both time trial and time-to-exhaustion tests showed a reduction in performance with ketone ester ingestion versus placebo. Since the metabolic effects were relatively small, these are unlikely to explain performance changes with ketone esters in this study. BHB can suppress lipolysis (3), and glycerol and long-chain fatty acid concentrations (as markers of lipolysis) were lower in the present study with ketone ester ingestion (8). Whilst suppressing circulating fatty acid availability can impair endurance performance (11), this seems to be more relevant for more prolonged exercise than that tested in the current study. Other potential mechanisms of impaired performance include gastrointestinal distress and/or acid-base disturbances with ketone esters (7, 12). Increased gastrointestinal symptoms in the current study may have partly explained the performance decrement. This is despite a lack of correlation between gastrointestinal symptoms and the degree of performance decrement, which is perhaps unsurprising given the subjective nature of measuring gastrointestinal distress. The contribution of acidosis remains unknown, since acid-base balance of the blood or muscle was not determined, yet indirect inference from ventilatory data was consistent with greater acidosis in the ketone ester trial (8).

Where next for ketone esters and exercise? The current study makes an important contribution to understanding the acute effects of ketone esters on exercise metabolism with moderate glucose ingestion (30 g/h). However, further work is needed to understand their impact during conditions reflecting sporting scenarios with higher carbohydrate intakes (e.g., >60 g/h) and with glucose-fructose mixtures. It is plausible that ketone esters may interact with these factors, since carbohydrate ingestion dose-dependently affects glucose kinetics (10), and the lactate from fructose ingestion would be competing with the same cell membrane transport proteins as BHB. Nevertheless, attention may be also turning more intensively to longer-term effects of ketone esters and their role as signalling molecules. BHB may stimulate muscle protein synthesis (13), alter catecholamines during exercise (14), and erythropoietin concentrations after exercise (15). These signalling effects of ketone bodies may prove to be more important than their effects as a fuel source for exercise performance and the research landscape in this area appears to provide some exciting opportunities for advancements in understanding.

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