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EDITORIAL

Ketones and inborn errors of metabolism: old friends revisited

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During exercise fat and carbohydrates are the principal substrates that fuel aerobic ATP synthesis in human skeletal muscle. During low-intensity exercise, skeletal muscle relies predominantly on fat-based fuels, thereby sparing the intracellular glycogen stores. During high-intensity exercise, however, there is a shift in fuel selection from fat towards glycolysis and the utilization of glycogen reserves. When glycogen reserves turn low during prolonged intense exercise, but also upon fasting and starvation, ketone bodies such as 3-β-hydroxybutyrate (β-HB) and acetoacetate which are produced by the liver, are increasingly important sources of ATP (Fig. 1).

A paper by Cox and colleagues in *Cell Metabolism* (Cox et al 2016) highlights the benefit of ketone bodies in healthy subjects. Well-trained athletes were supplemented with a synthesized ketone ester ((*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate ketone). This ketone ester led to the reprogramming of skeletal muscle metabolic pathways during exercise and acutely improved cycling performance in these athletes. The ingested ketone ester is converted into β-HB and (*R*)-1,3-butanediol by nonspecific gut esterases, after which the liver converts (*R*)-1,3-butanediol into another molecule of β-HB. Skeletal muscle mono-carboxylate transporters subsequently transport β-HB across the plasma membrane and into the mitochondria. The increased ketone body levels preserve intramuscular glycogen stores and branched-chain amino acids (BCAA) and reduce lactate release during exercise (Fig. 1; Cox et al 2016).

The ketone ester developed by Cox and coworkers may be of great benefit for patients with certain inborn errors of metabolism (IEMs) by serving as an alternative energy source for ATP production (Fig. 1). In addition, patients in which ketone body formation is impaired, such as HMG-CoA synthase deficiency, HMG-CoA lyase deficiency and beta-ketothiolase deficiency, could benefit from this ketone ester. A special IEM that would qualify for ketone ester treatment would be SUCLA deficiency in which the formation of succinate from succinyl-CoA in the TCA cycle is impaired. An increased flux through succinyl-CoA acetoacetate transferase by ketone ester treatment would, at least in theory, increase flux through the TCA cycle.

The idea of treating patients with ketone bodies or ketogenic diets is not new (reviewed in (Scholl-Burgi et al 2015)). In glucose transporter type 1 deficiency (GLUT1) and pyruvate dehydrogenase complex (PDHc) deficiency, ketogenic diets are part of the therapy of choice (Scholl-Burgi et al 2015). Some mitochondrial complex I and II deficiencies could benefit from this ketone ester (Scholl-Burgi et al 2015). A ketogenic diet in patients with glycogen storage disease type III and V significantly improved cardiac remodelling (Valayannopoulos et al 2011) and exercise tolerance (Vorgerd and Zange 2007). Long-term D,L-3-hydroxybutyrate treatment improved cardiac contractility in infants with multiple acyl-CoA dehydrogenase deficiency (Van Hove et al 2003). The newly synthesized ketone ester is preferred over β-HB itself, however, since supplementation of the latter is associated with a substantial load of either acid and/or salt. Also, a ketone drink is easier to adhere to than a ketogenic (high fat, low carbohydrate) diet. As such, this ketone ester could serve as an attractive therapeutic option in

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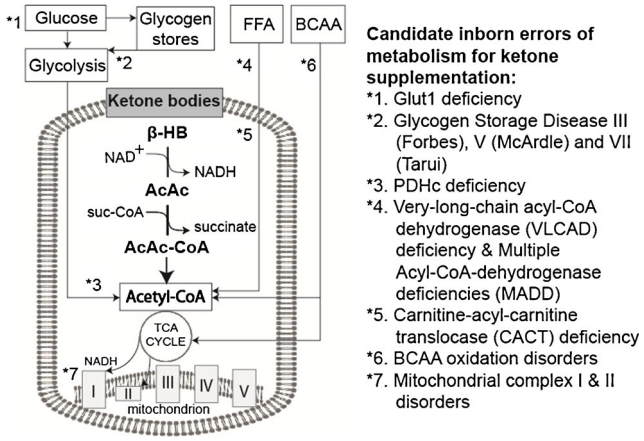

Fig. 1 Schematic representation of ketolysis. The ketone bodies β-hydroxybutyrate (β-HB) and acetoacetate (AcAc) are broken down to acetyl-CoA via aceto-acetyl-CoA (AcAc-CoA). A ketone ester supplement remodelled substrate utilization of intracellular glycogen stores, free-fatty acids (FFA) and branched-chain amino acids (BCAA) oxidation during exercise (Cox et al 2016). A non-exhaustive list of inborn errors of metabolism that may benefit from the therapeutic potential of this ketone ester supplement are listed. Suc-CoA: succinyl-CoA

reducing the clinical symptoms in certain IEMs. Studies to ascertain the presumed beneficial effect of the ketone ester in some IEMs are currently underway.

Compliance with ethical standards

Conflict of interest The authors are not aware of any affiliation, memberships, funding, or financial holdings that may be perceived as affecting the objectivity of this editorial.

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