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Carbohydrate Ingestion during Exercise: Effects on Performance, Training Adaptations and Trainability of the Gut

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Abstract

Carbohydrate feeding has been shown to enhance endurance performance. During exercise of 2 h or more, the delivery of carbohydrates to the muscle is the crucial step and appears to be limited by intestinal absorption. It is therefore important to identify ways to overcome this limitation and study the positive and negative effects of chronic carbohydrate supplementation. There is evidence that intestinal absorption can, at least partly, be overcome by making use of multiple transportable carbohydrates. Ingestion of these carbohydrates may result in higher intestinal absorption rates and has been shown to lead to higher rates of exogenous carbohydrate oxidation which can result in better endurance performance. It also seems possible to increase the absorptive capacity of the intestine by adapting to a high-carbohydrate diet. Carbohydrate supplementation during exercise has been suggested to reduce training adaptations, but at present there is little or no evidence to support this. Despite the fact that it has long been known that carbohydrate supplementation can enhance endurance performance, there are still many unanswered questions. However, there is potential to develop strategies that enhance the delivery of carbohydrates and thereby improve endurance performance.

Introduction

The importance of carbohydrate as a fuel for exercise has been recognized since the early 1920s [1]. In particular, the availability of muscle glycogen has been linked to endurance exercise capacity [2, 3]. Ground breaking

studies in the 1960s investigated the role of high muscle glycogen stores at the onset of exercise (carbo-loading) on exercise performance [2, 4–5], and in the 1980s the interest shifted towards the potential role of carbohydrate ingested just before and during exercise. Although the exact mechanisms are still not entirely elucidated, it is clear that carbohydrate ingestion during exercise can increase exercise capacity and improve exercise performance [for review, see 6–8]. Since the 1980s, studies have used a variety of exercise models to investigate the effects on performance of different feeding regimens, different types of carbohydrate and different amounts of carbohydrate. These studies have revealed the limiting steps for carbohydrate delivery to the working muscle, and this has resulted in new methods to increase this delivery. This review will focus on these recent studies as well as the mechanisms that limit exogenous carbohydrate oxidation during exercise and will discuss practical methods to overcome these limitations in order to improve exercise performance.

Carbohydrate Absorption

Before ingested carbohydrate can be oxidized by the working muscle, it has to be emptied from the stomach, digested (hydrolyzed unless ingested as monosaccharide) and absorbed. It then has to pass through the liver and be taken up by the muscle. Studies have repeatedly shown that gastric emptying is not the main limiting factor to delivery of carbohydrate to the muscle but it is beyond the scope of this paper to discuss the possible limitations and the evidence for and against in any detail. For more information, the reader is directed to other reviews [8, 9]. The most plausible explanation for the limitation to the oxidation of exogenous carbohydrate is that intestinal carbohydrate absorption cannot provide substrate to the working muscle at a high enough rate. This is in contrast to textbook statements which often indicate that the capacity of the intestine to absorb carbohydrate is 'virtually unlimited'. For example, Ferraris et al. [10] state that '. . .capacity for glucose absorption is one or two orders of magnitude higher than daily glucose intakes', while Crane [11] concluded that 'the total daily capacity is 10,211 g of a mixture of glucose and fructose; an amount equivalent to over 22 pounds of sugar and more than 50,000 calories'. The latter would equate to an average absorption of 7.1 g/min. Perhaps more realistic estimates were obtained from studies that used a triple lumen intestinal perfusion technique. Duchman et al. [12], having measured glucose absorption from a 6% glucose-electrolyte solution, estimated whole-body intestinal absorption rates to be in the range of 1.2–1.7 g/min. The measurements were made over a very short (40 cm) section of the gut, and extrapolations to whole-body absorption rates can therefore be problematic, especially because various parts of the gut have different absorptive capacities.

Intestinal sugar transporters are responsible for transporting the monosaccharide carbohydrates glucose, fructose and galactose from the intestinal lumen into the blood. The sodium-dependent glucose transporter (SGLT1) is located in the apical brush border membrane, and is responsible for the transport of glucose and galactose across the luminal membrane. Glucose and galactose are transported along with Na^+ from the lumen into the cytosol. For fructose, there is another transporter protein (GLUT5) that transports the sugar from the lumen into the cytosol, and this process is independent of Na^+. Both these transporters are present in the apical membrane and were discovered and cloned in the 1980s [13–15]. In the basolateral membrane, another transporter (GLUT2) is responsible for transporting the three monosaccharides from the cytosol into the blood. It is generally thought that the transporters on the luminal side are rate limiting. Studies using triple lumen technique or in vitro preparations of the gut may give information about the maximum absorptive capacity of a small section of the intestine, but these findings may be difficult to translate to an in vivo situation [16], particularly in the context of exercise. Perhaps the most insightful information has come from studies that have used stable isotope tracers to measure exogenous carbohydrate oxidation during exercise. When a single monosaccharide carbohydrate is ingested, the oxidation rate of this carbohydrate does not normally exceed 1 g/min [9], perhaps because the SGLT1 transporter may become saturated [17]. When, in addition to glucose, a second monosaccharide that uses a different intestinal transport system, like fructose, was ingested, total carbohydrate oxidation rates were significantly higher. This provides indirect evidence that intestinal transport limits exogenous carbohydrate oxidation [17]. These findings will be discussed in more detail below.

Different Types of Carbohydrate

Isotopic (^{13}C or ^{14}C) labeling techniques have been used to study the efficacy of various ingested carbohydrates. This has provided insights about the time course of oxidation, and also made it possible to compare the oxidation of different carbohydrates. When carbohydrates are ingested from the onset of exercise and at regular intervals thereafter, oxidation of the ingested carbohydrate increases and typically reaches a plateau after 60–90 min. Originally, carbohydrates like glucose, fructose, galactose, sucrose, maltose and glucose polymers were studied. It was found that fructose was oxidized at slightly (4%) lower rates than glucose [18], and galactose oxidation rates were almost 40% lower [18–19]. More recently, it was found that high-molecular-weight glucose polymers were oxidized at similar rates to low-molecular-weight glucose polymer [20]. Therefore, it is unlikely that the rate of intraluminal enzymatic hydrolysis of polysaccharides is limiting. In addition, it was found that trehalose, a disaccharide formed by an α, α_1, 1-glucoside bond between two α-glucose units, and isomaltulose, an isomer of

sucrose, were oxidized at lower rates than maltose and sucrose, respectively [21–22]. For a more complete overview of oxidation rates of different carbohydrates, the reader is referred to recent reviews [7, 23]. Perhaps the most striking finding was that in none of these studies did exogenous carbohydrate oxidation rates exceed 1 g/min (60 g/h) [for detailed review, see 6–8]. The significance of this observation is reflected in various guidelines including those of the American College of Sports Medicine in 2007 which state that athletes should ingest between 30 and 60 g of carbohydrate per hour during prolonged exercise [24].

We suggested that this apparent ceiling of 1 g/min was caused by a limitation in the absorptive capacity of the intestine [7]. As discussed above, glucose is absorbed through the sodium-dependent glucose transporter protein SGLT1. This transport protein in the brush border membrane has a high affinity for glucose and galactose but not for fructose [25]. We hypothesized that the limitation for exogenous carbohydrate oxidation was a saturation of the SGLT1 transporters in the brush border membrane of the intestine which may occur at high rates of glucose ingestion. The evolutionary norm is the ingestion of complex carbohydrate from which absorbable monosaccharide must be liberated by enzymatic hydrolysis: direct loading with ingested monosaccharide is not the condition for which the SGLT1 system evolved. Fructose absorption is not regulated by this mechanism because it is absorbed independently by a sodium-independent transporter GLUT5 [26]. The combined ingestion of these two sugars should therefore result in an increased total delivery of carbohydrates into the circulation and increased oxidation by the muscle. Already in 1995, Shi et al. [27] found evidence that ingestion of carbohydrates that use different intestinal transporters might increase total carbohydrate absorption. In a study by Jentjens et al. [17], evidence was obtained that exogenous carbohydrate absorption was also enhanced. Subjects in this study exercised for 3 h at a moderate intensity in a randomized crossover design, and ingested isoenergetic amounts of either glucose or a glucose:fructose mixture. The oxidation rates in the glucose trials peaked around 0.8 g/min, whereas the oxidation rates with glucose:fructose peaked at 1.26 g/min (see table 1). The studies were extended by studying different carbohydrate mixes such as glucose:sucrose:fructose, glucose:sucrose and maltodextrin:fructose and different ingestion rates [28–34].

These studies indicated that exogenous carbohydrate oxidation rates could be increased to as high as 1.75 g/min if glucose:fructose was ingested at an average rate of 2.4 g/min. However, from a practical point of view the most exciting finding was that a maltodextrin:fructose mix, which is not as sweet as the mixtures discussed above and therefore more palatable, was oxidized at very high rates [31]. Oxidation rates in this study reached 1.5 g/min at an ingestion rate of 1.8 g/min.

It is important to note that in order to benefit from a glucose:fructose mixture, it may be necessary to saturate glucose transporters in the intestine by ingesting sufficient quantities. When carbohydrate is ingested at rates of

Table 1. Summary of the advice for carbohydrate (CHO) intake during endurance events of different durations

Event	CHO required for optimal performance and minimizing negative energy balance	Recommended intake	CHO type	Glucose	Glucose + fructose
<30 min	no CHO required				
30–60 min	very small amounts	mouth rinse	most forms of CHO	●	●
1–2 h	small amounts	up to 30 g/h	most forms of CHO	●	●
2–3 h	moderate amounts	up to 60 g/h	CHO that are rapidly oxidized (glucose, maltodextrin)	○	●
>2.5 h	large amounts	up to 90 g/h	only multiple transportable CHO		●

The amounts recommended and the preferred type and blend of CHO depends on the duration of the event. When the absolute intensity is very low, these figures should be scaled down. A closed circle indicates 'optimal', an open circle indicates 'ok' to use.

0.8 g/min, saturation may not occur, and ingesting part of this carbohydrate as fructose may not result in higher exogenous carbohydrate oxidation rates [35]. However, although glucose was ingested at very low rates in one of the trials (0.54 plus 0.26 g/min of fructose), the oxidation rates for both carbohydrate drinks were the same! This indicates that in some cases glucose:fructose may be an advantage (at high ingestion rates), but there is no disadvantage when it is ingested at low rates.

It is important to note that recent work suggests that combinations of multiple transportable carbohydrates may also provide benefits in terms of gastric emptying and fluid delivery [34, 36, 37]. In one study, it was demonstrated that gastric emptying using the double sampling technique or a ^{13}C-acetate tracer technique was significantly faster with glucose:fructose than with an isoenergetic amount of glucose [37]. Several studies have demonstrated that deuterium appearance in the blood is faster when added to a glucose:fructose solution than to an isoenergetic glucose solution, suggesting faster fluid delivery [34, 36, 37]. It is possible that these effects of glucose:fructose combinations also contribute to the observed performance benefits that will be discussed below.

These studies clearly demonstrate that it is possible to achieve very high exogenous carbohydrate oxidation rates when multiple differentially transportable carbohydrates are ingested.

Exogenous Carbohydrate Availability to Support Endurance Performance

Although studies have consistently shown that carbohydrate can enhance endurance capacity and performance, there have been relatively few attempts to establish a dose-response relationship. The majority of the early studies provided 40–75 g carbohydrate/h and observed performance benefits. Ingesting carbohydrate at a rate >75 g/h did not appear to be any more effective at improving performance than ingesting carbohydrate at a rate of 40–75 g/h. It has been suggested that this is because ingestion of 40–75 g carbohydrate/h already results in optimum carbohydrate availability and ingesting carbohydrate at higher rates may not increase the bioavailability [38]. However, these early studies were not without limitations. In some of these studies, not only was the amount of carbohydrate different but also the composition of the carbohydrates and other ingredients in the drinks, making it difficult to study a true dose response. It is also possible that performance measurements used in some of these studies were not sensitive enough to pick up the small differences in performance that may exist when comparing two different carbohydrate solutions [39]. In a recent review, we concluded that the dose-response relationship was not immediately obvious from the early studies, and that relatively small amounts of carbohydrate can already result in enhanced performance [7]. We also suggested that it is likely that exogenous carbohydrate oxidation rates were positively related to exercise performance, i.e. the more exogenous carbohydrate is available to the working muscle the better the performance. In the last few years, evidence has accumulated in support of such a dose-response relationship and a link between exogenous carbohydrate oxidation and performance. Recently, a well-controlled dose-response study was performed in which 12 cyclists received carbohydrate (glucose) at a rate of 0, 15, 30 and 60 g/h [40] during 2 h of moderate-intensity exercise. This was then followed by a 20-km time trial to measure performance. In this study, a dose-response relationship was observed between carbohydrate intake and exogenous glucose oxidation and between carbohydrate intake and time trial performance.

In another study, subjects ingested 1.5 g/min of glucose:fructose or glucose during 5 h of moderate-intensity exercise, and it was observed that the subjects' ratings of perceived exertion tended to be lower with the mixture of glucose and fructose than with glucose alone, and cyclists were better able to maintain their cadence towards the end of 5-hour cycling [32]. Rowlands et al. [41] also reported reduced fatigue when ingesting a maltodextrin:fructose

mix. It was also demonstrated that a glucose:fructose drink could improve exercise performance [42]. Cyclists exercised for 2 h on a cycle ergometer at 54% VO_{2max}. During the exercise, they ingested either a carbohydrate drink or placebo, and were then asked to perform a time trial that lasted approximately another 60 min. When the subjects ingested a glucose drink (at 1.8 g/min), they improved their power output by 9% (254 vs. 231 W). However, when they ingested glucose:fructose, there was another 8% improvement of the power output over and above the improvement by glucose ingestion (275 vs. 254 W). This is the first study to show that exogenous carbohydrate oxidation rates may be linked to performance and the first study to demonstrate a clear performance benefit with glucose:fructose compared with glucose [42]. These findings were reproduced by Triplett et al. [43] who found very similar performance improvements with glucose:fructose over glucose only. In a study by Stannard et al. [44], subjects were fed galactose, galactose:glucose (1:1) or glucose:fructose (4:1). Although it was not directly measured, based on a study in which galactose oxidation was determined [19], it would be expected that exogenous carbohydrate oxidation from the galactose drink would be lower (galactose is oxidized at significantly lower rates than glucose). Subjects exercise for 2 h at 65% VO_{2max} followed by a self-paced time trial. Galactose ingestion resulted in significantly lower power outputs than the two other drinks, and this would support a link between exogenous carbohydrate oxidation and performance [44].

A large-scale multicentre study by Smith et al. [45] also investigated the relationship between carbohydrate ingestion rate and cycling time trial performance to identify a range of carbohydrate ingestion rates that would enhance performance. In their study, 51 cyclists and triathletes across four research sites completed four exercise sessions consisting of a 2-hour constant load ride at a moderate to high intensity. Twelve different beverages (three at each site) were tested providing participants with 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, and 120 g carbohydrate/h during the constant load ride. A common placebo that was artificially sweetened, colored, and flavored and did not contain carbohydrate was tested at all four sites. The order of the beverage treatments was randomized at each site. Immediately following the constant load ride, participants completed a simulated 20-km time trial as quickly as possible. The ingestion of carbohydrate significantly improved performance and the authors concluded that the greatest performance enhancement was seen at an ingestion rate between 60–80 g carbohydrate/h.

These findings challenge the current American College of Sports Medicine guidelines [46] which suggest that a carbohydrate intake of 30–60 g/h is optimal. Recent evidence seems to indicate that a higher intake of 60–80 g/h is optimal, and that perhaps even higher intakes may be better when multiple transportable carbohydrates are ingested. Recommendations by the authors are summarized in table 1.

Gut Adaptation

Since the absorption of carbohydrate limits exogenous carbohydrate oxidation, and exogenous carbohydrate oxidation seems to be linked to exercise performance, an obvious question is whether it is possible to increase the absorptive capacity of the gut. Anecdotal evidence in athletes would suggest that the gut is trainable and that individuals who regularly consume carbohydrate or have a high daily carbohydrate intake have an increased capacity to empty carbohydrate from the stomach and absorb it. From animal studies it would appear that this is indeed the case. It has been demonstrated that the intestinal carbohydrate transporters can be upregulated by exposing an animal to a high-carbohydrate diet [26, 47]. The mechanisms for this effect are unclear, but interesting animal data indicate a role for the sweet taste family (T1R) of G-protein-coupled receptors and signal transduction molecules such as a-gustducin [48]. Consequently, artificial sweeteners may provide the same responses [49]. The enteroendocrine cell population is the most likely site of nutrient sensing, but data functionally coupling these sensors to similar physiological effects in humans are currently lacking.

To date, there is limited evidence in humans to support or refute this theory. A recent study by Cox et al. [50] investigated whether altering daily carbohydrate intake affects substrate oxidation and in particular exogenous carbohydrate oxidation. It was hypothesized that when exposed to a high-carbohydrate diet for a prolonged period of time (28 days), carbohydrate transporters in the intestine would be upregulated, and this would result in an increase in exogenous carbohydrate oxidation during exercise. In order to study this, the investigators recruited 16 subjects and divided them into a high carbohydrate and a low carbohydrate group. Both groups were fed a diet containing 5 g/kg carbohydrate per day, but the high carbohydrate group received supplements providing an additional 1.5 g/kg carbohydrate per day. Before and after the 28-day period, exogenous carbohydrate oxidation was measured during a 100-min steady-state trial around 70% VO_2 peak. During the exercise bout, the subjects received a 10% glucose solution at 20-min intervals providing almost 2 g of carbohydrate per minute. Exogenous carbohydrate oxidation rates were higher after the high carbohydrate diet, providing evidence that the gut is indeed adaptable and this can be used as a practical method to increase exogenous carbohydrate oxidation. We recently suggested that this may be highly relevant to the endurance athlete and may be a prerequisite for the first person to break the 2 h marathon barrier [51].

Training Adaptation with Low Exogenous Carbohydrate Availability

Carbohydrate supplementation during exercise may not have only positive effects. The positive effects may refer to the acute situation but chronic use

might have negative effects. It has been suggested that carbohydrate ingestion during exercise may limit training adaptations. This idea stems from observations that muscle glycogen stores are related to expression of genes relevant to the adaptation to training. It is generally thought that training adaptations are the result of recurrent changes in gene expression, which occur with every bout of exercise, leading to a change in phenotype such as increases in fatty acid transport and oxidation. For example, a single bout of exercise increases muscle mRNA content of peroxisome proliferator-activated receptor-γ coactivator 1α, a transcriptional regulator of mitochondrial biogenesis.

Chronic glucose ingestion might negatively affect the expression of relevant genes. Glucose ingestion can attenuate the rise in AMP-activated kinase (AMPK) [52], and chronic suppression of AMPK in turn could reduce the increase in citrate synthase activity [53] and reduce muscle glycogen accumulation [54], two well-known training adaptations. Glucose ingestion will suppress lipolysis and reduce the concentration of fatty acids in the plasma, and this possibly attenuate some of the training-induced adaptations. It has been shown that glucose ingestion during exercise may suppress the expression of CPT-1 mRNA, mitochondrial uncoupling protein (UCP3-3) and FAT/CD36 [55]. However, in a carefully conducted study by Akerstrom et al. [56] in which a 10-week leg extension training program was followed by the subjects, glucose ingestion did not alter training adaptations related to substrate metabolism, mitochondrial enzyme activity, glycogen content or performance. Significant increases were observed in citrate synthase activity and β-hydroxyl acyl-CoA dehydrogenase activity after the 10-week training program, but there was no effect of carbohydrate supplementation on these changes. It appears that the effects of glucose ingestion during exercise are distinctly different from those induced by exercising with low glycogen. Performing 50% of all exercise training in a low glycogen condition has been demonstrated to produce marked improvements in markers of oxidative capacity [57–59] compared with training in a glycogen-loaded state all the time.

Practical Implications

When exercise lasts for up to 2 h, a carbohydrate intake up to about 60 g could be recommended. When the exercise lasts 2 h or more, slightly greater amounts of carbohydrate (90 g/h) would be recommended, and these carbohydrates should consist of a mix of multiple transportable carbohydrates, e.g. glucose:fructose or maltodextrin:fructose. The source or form of these carbohydrates may not matter as much as previously thought. It was recently demonstrated that carbohydrates in a beverage were oxidized at similar rates to carbohydrates from a gel (semi-solid) [60]. Also, it was demonstrated that carbohydrates from a bar that contained mostly monosaccharide (in the form of glucose:fructose) could

result in exogenous carbohydrates oxidation that are similar to those seen with a beverage [61]. Exogenous carbohydrate oxidation rates were not different during cycling compared with running [62], and therefore the advice would not be different for these two types of exercise.

In summary, in order to obtain a carbohydrate intake of 90 g/h, athletes could 'mix and match' to fulfill their personal preferences and take into account their tolerance. Of course, these practices have to be tried and tested. Interindividual differences, the effects of gender, habitual diet and nutrient sensing mechanisms all need to be evaluated. Since the gut is so adaptable, it seems wise to have a high carbohydrate intake during training and regularly ingest carbohydrate during exercise. With these strategies, the gut may be trained to absorb and oxidize more carbohydrate, which in turn could result in less gastrointestinal distress and better performance.

References

1 Krogh A, Lindhard J: The relative value of fat and carbohydrate as sources of muscular energy. Biochem J 1920;14:290–363.
2 Bergström J, Hermansen L, Hultman E, Saltin B: Diet, muscle glycogen and physical performance. Acta Physiol Scand 1967;71:140–150.
3 Rodriguez NR, Di Marco NM, Langley S: American College of Sports Medicine position stand. Nutrition and athletic performance. Med Sci Sports Exerc 2009;41:709–731.
4 Hultman E: Physiological role of muscle glycogen in man, with special reference to exercise. Circ Res 1967;10:I-99–I-114.
5 Hultman E, Bergstrom J: Muscle glycogen synthesis in relation to diet studied in normal subjects. Acta Med Scand 1967;182:109–117.
6 Jeukendrup A, Tipton KD: Legal nutritional boosting for cycling. Curr Sports Med Rep 2009;8:186–191.
7 Jeukendrup A: Carbohydrate feeding during exercise. Eur J Sport Sci 2008;8:77–86.
8 Jeukendrup AE: Carbohydrate intake during exercise and performance. Nutrition 2004;20:669–677.
9 Jeukendrup AE, Jentjens R: Oxidation of carbohydrate feedings during prolonged exercise: current thoughts, guidelines and directions for future research. Sports Med 2000;29:407–424.
10 Ferraris RP, Yasharpour S, Lloyd KC, et al: Luminal glucose concentrations in the gut under normal conditions. Am J Physiol 1990;259:G822–G837.
11 Crane RK: The physiology of the intestinal absorption of sugars; in Jeanes A, Hodge J (eds): Physiological Effects of Food Carbohydrates. Washington, American Chemical Society, 1975.
12 Duchman SM, Ryan AJ, Schedl HP, et al: Upper limit for intestinal absorption of a dilute glucose solution in men at rest. Med Sci Sports Exerc 1997;29:482–488.
13 Hediger MA, Coady MJ, Ikeda TS, Wright EM: Expression cloning and cDNA sequencing of the Na^+/glucose co-transporter. Nature 1987;330:379–381.
14 Thorens B, Sarkar HK, Kaback HR, Lodish HF: Cloning and functional expression in bacteria of a novel glucose transporter present in liver, intestine, kidney, and beta-pancreatic islet cells. Cell 1988;55:281–290.
15 Burant CF, Takeda J, Brot-Laroche E, et al: Fructose transporter in human spermatozoa and small intestine is GLUT5. J Biol Chem 1992;267:14523–14526.
16 Gisolfi CV, Summers RW, Schedl HP, et al: Human intestinal water absorption: direct vs. indirect measurements. Am J Physiol 1990;258:G216–G222.

17 Jentjens RL, Moseley L, Waring RH, et al: Oxidation of combined ingestion of glucose and fructose during exercise. J Appl Physiol 2004;96:1277–1284.
18 Burelle Y, Lamoureux MC, Peronnet F, et al: Comparison of exogenous glucose, fructose and galactose oxidation during exercise using 13C-labelling. Br J Nutr 2006;96:56–61.
19 Leijssen DP, Saris WH, Jeukendrup AE, Wagenmakers AJ: Oxidation of exogenous [^{13}C]galactose and [^{13}C]glucose during exercise. J Appl Physiol 1995;79:720–725.
20 Rowlands DS, Wallis GA, Shaw C, et al: Glucose polymer molecular weight does not affect exogenous carbohydrate oxidation. Med Sci Sports Exerc 2005;37:1510–1516.
21 Venables MC, Brouns F, Jeukendrup AE: Oxidation of maltose and trehalose during prolonged moderate-intensity exercise. Med Sci Sports Exerc 2008;40:1653–1659.
22 Achten J, Jentjens RL, Brouns F, Jeukendrup AE: Exogenous oxidation of isomaltulose is lower than that of sucrose during exercise in men. J Nutr 2007;137:1143–1148.
23 Jeukendrup AE: Carbohydrate and exercise performance: the role of multiple transportable carbohydrates. Curr Opin Clin Nutr Metab Care 2010;13:452–457.
24 American College of Sports Medicine, Sawka MN, Burke LM, Eichner ER, et al: American College of Sports Medicine position stand. Exercise and Fluid Replacement. Med Sci Sports Exerc 2007;39:377–390.
25 Kellett GL: The facilitated component of intestinal glucose absorption. J Physiol 2001;531:585–595.
26 Ferraris RP, Diamond J: Regulation of intestinal sugar transport. Physiol Rev 1997;77:257–302.
27 Shi X, Summers RW, Schedl HP, et al: Effects of carbohydrate type and concentration and solution osmolality on water absorption. Med Sci Sports Exerc 1995;27:1607–1615.
28 Jentjens RL, Venables MC, Jeukendrup AE: Oxidation of exogenous glucose, sucrose, and maltose during prolonged cycling exercise. J Appl Physiol 2004;96:1285–1291.
29 Jentjens RL, Achten J, Jeukendrup AE: High oxidation rates from combined carbohydrates ingested during exercise. Med Sci Sports Exerc 2004;36:1551–1558.
30 Jentjens RL, Jeukendrup AE: High rates of exogenous carbohydrate oxidation from a mixture of glucose and fructose ingested during prolonged cycling exercise. Br J Nutr 2005;93:485–492.
31 Wallis GA, Rowlands DS, Shaw C, et al: Oxidation of combined ingestion of maltodextrins and fructose during exercise. Med Sci Sports Exerc 2005;37:426–432.
32 Jeukendrup AE, Moseley L, Mainwaring GI, et al: Exogenous carbohydrate oxidation during ultraendurance exercise. J Appl Physiol 2006;100:1134–1141.
33 Jentjens RL, Shaw C, Birtles T, et al: Oxidation of combined ingestion of glucose and sucrose during exercise. Metabolism 2005;54:610–618.
34 Jentjens RL, Underwood K, Achten J, et al: Exogenous carbohydrate oxidation rates are elevated after combined ingestion of glucose and fructose during exercise in the heat. J Appl Physiol 2006;100:807–816.
35 Hulston CJ, Wallis GA, Jeukendrup AE: Exogenous CHO oxidation with glucose plus fructose intake during exercise. Med Sci Sports Exerc 2009;41:357–363.
36 Currell K, Urch J, Cerri E, et al: Plasma deuterium oxide accumulation following ingestion of different carbohydrate beverages. Appl Physiol Nutr Metab 2008;33:1067–1072.
37 Jeukendrup AE, Moseley L: Multiple transportable carbohydrates enhance gastric emptying and fluid delivery. Scand J Med Sci Sports 2010;20:112–121.
38 Coggan AR, Swanson SC: Nutritional manipulations before and during endurance exercise: effects on performance. Med Sci Sports Exerc 1992;24:S331–S335.
39 Currell K, Jeukendrup AE: Validity, reliability and sensitivity of measures of sporting performance. Sports Med 2008;38:297–316.
40 Smith JW, Zachwieja JJ, Peronnet F, et al: Fuel selection and cycling endurance performance with ingestion of [13C]glucose: evidence for a carbohydrate dose response. J Appl Physiol 2010;108:1520–1529.
41 Rowlands DS, Thorburn MS, Thorp RM, et al: Effect of graded fructose coingestion with maltodextrin on exogenous 14C-fructose and 13C-glucose oxidation efficiency and high-intensity cycling performance. J Appl Physiol 2008;104:1709–1719.

42 Currell K, Jeukendrup AE: Superior endurance performance with ingestion of multiple transportable carbohydrates. Med Sci Sports Exerc 2008;40:275–281.
43 Triplett D, Doyle JA, Rupp JC, Benardot D: An isocaloric glucose-fructose beverage's effect on simulated 100-km cycling performance compared with a glucose-only beverage. Int J Sport Nutr Exerc Metab 2010;20:122–131.
44 Stannard SR, Hawke EJ, Schnell N: The effect of galactose supplementation on endurance cycling performance. Eur J Clin Nutr 2009;63:209–214.
45 Smith JW, Zachwieja JJ, Horswill CA, et al: Evidence of a carbohydrate dose and prolonged exercise performance relationship. Med Sci Sports Exerc 2010;42:84.
46 Joint Position Statement: nutrition and athletic performance. American College of Sports Medicine, American Dietetic Association, and Dietitians of Canada. Med Sci Sports Exerc 2000;32:2130–2145.
47 Ferraris RP: Dietary and developmental regulation of intestinal sugar transport. Biochem J 2001;360:265–276.
48 Dyer J, Daly K, Salmon KS, et al: Intestinal glucose sensing and regulation of intestinal glucose absorption. Biochem Soc Trans 2007;35:1191–1194.
49 Moran AW, Al-Rammahi MA, Arora DK, et al: Expression of Na^+/glucose co-transporter 1 (SGLT1) is enhanced by supplementation of the diet of weaning piglets with artificial sweeteners. Br J Nutr 2010;104:637–646.
50 Cox GR, Clark SA, Cox AJ, et al: Daily training with high carbohydrate availability increases exogenous carbohydrate oxidation during endurance cycling. J Appl Physiol 2010;109:126–134.
51 Stellingwerff T, Jeukendrup AE, Perrey S, et al: Commentaries on viewpoint: the two-hour marathon: who and when? J Appl Physiol 2011;110:278–293.
52 Akerstrom TC, Birk JB, Klein DK, et al: Oral glucose ingestion attenuates exercise-induced activation of 5′-AMP-activated protein kinase in human skeletal muscle. Biochem Biophys Res Commun 2006;342:949–955.
53 Winder WW, Holmes BF, Rubink DS, et al: Activation of AMP-activated protein kinase increases mitochondrial enzymes in skeletal muscle. J Appl Physiol 2000;88:2219–2226.
54 Holmes BF, Kurth-Kraczek EJ, Winder WW: Chronic activation of 5′-AMP-activated protein kinase increases GLUT-4, hexokinase, and glycogen in muscle. J Appl Physiol 1999;87:1990–1995.
55 Civitarese AE, Hesselink MK, Russell AP, et al: Glucose ingestion during exercise blunts exercise-induced gene expression of skeletal muscle fat oxidative genes. Am J Physiol Endocrinol Metab 2005;289:E1023–E1029.
56 Akerstrom TCA, Fischer CP, Plomgaard P, et al: Glucose ingestion during endurance training does not alter adaptation. J Appl Physiol 2009;106:1771–1779.
57 Hulston CJ, Venables MC, Mann CH, et al: Training with low muscle glycogen enhances fat metabolism in well-trained cyclists. Med Sci Sports Exerc 2010;42:2046–2055.
58 Yeo WK, Paton CD, Garnham AP, et al: Skeletal muscle adaptation and performance responses to once a day versus twice every second day endurance training regimens. J Appl Physiol 2008;105:1462–1470.
59 Hansen AK, Fischer CP, Plomgaard P, et al: Skeletal muscle adaptation: training twice every second day vs. training once daily. J Appl Physiol 2005;98:93–99.
60 Pfeiffer B, Stellingwerff T, Zaltas E, Jeukendrup AE: CHO oxidation from a CHO gel compared with a drink during exercise. Med Sci Sports Exerc 2010;42:2038–2045.
61 Pfeiffer B, Stellingwerff T, Zaltas E, Jeukendrup AE: Oxidation of solid versus liquid CHO sources during exercise. Med Sci Sports Exerc 2010;42:2030–2037.
62 Pfeiffer B, Stellingwerff T, Zaltas E, et al: Carbohydrate oxidation from a drink during running compared to cycling exercise. Med Sci Sports Exerc 2011;43:327–334.

Discussion

Dr. McLaughlin: In your presentation, carbohydrate ingestion is expressed in absolute amounts, in grams. Gastrointestinal effects, however, are linked more to concentrations. What volumes are being provided to achieve those intakes, and what is the osmolality of typical solutions?

Dr. Jeukendrup: The osmolality depends partly on the type of carbohydrate provided, but generally the osmolality of these solutions is high, especially when we give glucose and fructose mixes at rates of 1.5–1.8 g/min. We typically use solutions of 10–14% carbohydrate, which are a lot higher than the current recommendations, but similar to what athletes actually do in many endurance events.

Dr. McLaughlin: You comment that the mixture speeds up gastric emptying, but in healthy volunteers at rest, such concentrations will delay gastric emptying significantly. Is something different occurring in the exercising volunteers?

Dr. Jeukendrup: No, you are correct that higher carbohydrate concentrations reduce gastric emptying: These mixes will delay gastric emptying compared to a solution that is 6% carbohydrate. However, when we are talking about higher rates of carbohydrate intake and compare glucose alone with the multiple transportable carbohydrates, the latter will be emptied more quickly.

Dr. McLaughlin: Have you undertaken any measurements of the insulinemic response to these mixed carbohydrate preparations? It is inevitable that if you are increasing the amounts of carbohydrate absorbed in the portal system, insulin secretion is going to be enhanced.

Dr. Jeukendrup: Yes, although the exercise potently suppresses insulin secretion. Even though such prolonged exercise is undertaken at relatively low exercise intensities (typically ~60% VO_{2max}), circulating insulin levels are quite low.

Dr. Spriet: You discussed the Cox study in which well-trained athletes trained for a month with either a high or moderate carbohydrate intake, based on whether they consumed carbohydrates or water during each of their exercise sessions. You concluded that all of the adaptation to the higher carbohydrate intake, which led to an improved ability to oxidize exogenous carbohydrate during exercise, occurred at the level of the gut. However, is there any reason why you would not expect some adaptation to take place at the level of the muscle as well? For example, if training is undertaken for just 2 or 3 weeks, clear increases in GLUT4 expression in the sarcolemma can be demonstrated.

Dr. Jeukendrup: Of course, I can't exclude that possibility, but my interpretation is based principally on the fact that the limitation of total exogenous carbohydrate oxidation capacity is not situated at the muscle level, but in intestinal absorptive capacity.

Dr. Burke: Can I add that there was no change in total muscle GLUT4 concentrations associated with the training and dietary interventions in this study?

Dr. Spriet: But of course, total protein content doesn't necessarily predict transport. You would need to isolate sarcolemmal vesicles and undertake transport studies in these vesicles.

Dr. Hawley: Is the training status from which athletes start important in designing and interpreting these experiments?

Dr. Jeukendrup: I don't think that the training status matters that much. My key message is the gut is the limiting factor, because the absorption capacity is saturable. We

have generally done this study with subjects who are trained enough to be able to exercise for 2 h, but we have also compared relatively untrained with extremely trained and found absolutely no differences.

Dr. van Loon: You measure total carbohydrate oxidation, but are there differences in the metabolic fate of glucose and fructose? What is happening in the liver in particular?

Dr. Jeukendrup: We don't have the actual measurements, but glucose goes through the liver and is simply transported to the muscle to utilize. Fructose is handled differently, being converted mostly to lactate in the liver. It is the lactate that is transported to the muscle for use. You can clearly see much higher plasma lactate levels in any trial where fructose is administered.

Dr. van Loon: Is the lactate being used exclusively by the active muscle or by other tissues?

Dr. Jeukendrup: I would think because of the rate of utilization, it has to be utilized in active muscle.

Dr. Zemel: You commented on several genes, such as UCP3 and others that were downregulated. What is the time course of these experiments?

Dr. Jeukendrup: Usually mRNA abundances are measured, and if I recall from 2 or 3 studies, the downregulation happens almost immediately, and is maintained for a longer period of time.

Dr. Maughan: To return to Dr. McLaughlin's point about concentrations rather than amounts of carbohydrate, I think it's important to recognize that if you give a more concentrated carbohydrate solution, the liquid volume that is emptied from the stomach is reduced, but you still deliver more carbohydrate in total. So carbohydrate delivery to the small intestine is increased, but fluid delivery is decreased. The outcome of achieving very good carbohydrate transport with such hypertonic solutions in the small intestine is to induce water transport in the opposite direction. The initial studies which showed net secretion of water into the small intestine were done with segmental intestinal perfusion. Recently, however, we have done several studies where volunteers drink 10% carbohydrate solutions, and we can actually demonstrate a measurable decrease in plasma volume for the first hour or so after their consumption. So if a subject drinks 500 ml of a high-carbohydrate drink, they will secrete water into their gut lumen and be systemically more dehydrated after the drink than before it.

Dr. Haschke: Doesn't reduced urinary excretion compensate for this?

Dr. Maughan: That will happen later, but in the short term – that is, within 10 or 15 min of ingestion – there is a clear decrease in blood volume. Therefore, I think there are some other processes happening in the gut, and if we consider the practical implications for performance, we need to consider whether dehydration and a reduced circulating plasma volume is a significant issue.

Dr. Jeukendrup: That situation is probably most relevant for solutions containing mainly one type of carbohydrate. If the ingested drink has the multiple transportable carbohydrate mix, you would definitely improve fluid delivery and reduce this type of problem. In our studies, we haven't seen changes in relevant measurements such as plasma osmolality or hematocrit.

Dr. Phillips: With respect to the observation of suppressed gene expression following ingestion of the carbohydrate, is it possible that if subjects are simply able to do more work, they will overcome these effects? This would make it irrelevant in terms of phenotypic adaptation.

Dr. Jeukendrup: This is possible, of course. But sometimes, the exercise that is undertaken is too short to really notice an effect of carbohydrate intake. Some of these studies have used a 1-hour period, where one wouldn't really expect that ingested carbohydrate would make the exercise much easier. It's after 2 or more hours of exercise that we observe those effects.

Dr. Lang: What happens to the non-absorbed glucose? Inhibition of the sodium chloride-glucose cotransport may produce diarrhea. Do these athletes get diarrhea?

Dr. Jeukendrup: I think eventually that the carbohydrate will be absorbed.

Dr. Hoppeler: Is there an evolutionary limit to absorption? Although other animals such as dogs and goats have similar absorption rates, there are some species which can change gut physiology dramatically – such as migratory birds and snakes. There's a possibility that this adaptability is not realized in humans.

Dr. Baar: By contrast, hibernating animals are creatures that aren't using their gut for a long period. Are there any data to show changes in gut transporter function with these animals? It would also be interesting to compare what happens in bears that are vegetarian versus bears that are meat eaters: is there greater dependence in one situation than another?

Dr. Jeukendrup: I don't know that literature very well. But the migratory bird is an extreme example of very rapid regulation – they increase their capacity to take up ingested fat very rapidly.

Dr. Montain: My question has to do more with how this area of research could be applied to enhance adaptation. We have known for quite a while now that exogenous carbohydrate delivered during exercise can produce more power. If an athlete could use strategies every day in training to produce more power, they should get stronger over time. Is there any other aspect of this that could be exploited from your observation?

Dr. Jeukendrup: There is not really enough evidence to draw a really firm conclusion on whether it does or doesn't do anything. It may not do anything except help to maintain the exercise intensity, and I think that should at some stage be beneficial. However, I can't be sure.

Dr. Hawley: One of the things about being an athlete is that you have to stay healthy before you can get fit. What is the evidence for chronic carbohydrate ingestion during exercise having effects on health and the immune system?

Dr. Jeukendrup: We and others have conducted studies which show that markers of the immune system are better maintained when subjects consume carbohydrate during exercise. So, that could be another reason to adopt this approach, but I am not sure how important those markers really are in the overall scheme of preventing illness.

Dr. Maughan: I know your remit was to focus upon carbohydrate, but as the aim is to maximize exogenous substrates, is it timely to look at other nutrient types? A key one that comes to mind is acetate since there seems to be no barrier (at least in dilute solutions) to gastric emptying and absorption. Also, having considered the metabolic fate of fructose, why not consume lactate itself and bypass the need for metabolism in the liver? The gut's carboxylate transporters will rapidly absorb ingested lactate.

Dr. Jeukendrup: The practical problem is how to deliver acetate and lactate in large quantities. Although, in theory, lactate should work really well, tolerance to intake of large amounts of lactate salts hasn't been great in our trials to date. One solution would be to use polylactate, but this has been shown to be difficult to digest and therefore not very useful. Medium-chain triglycerides behave somewhat like carbohydrate, are energy dense,

and according to our tracer studies, are oxidized very rapidly. The problem, again, is that tolerance is limited to small amounts only. We have found that if we give more than 30 g of MCT over a period of 2–3 h, this precipitates GI distress. Yet the delivery of 30 g is not enough to make a significant difference to energy intake, metabolism or performance.

Dr. Baar: Have you studied any anaplerotic amino acids, such as leucine or glutamine?

Dr. Jeukendrup: We have done a bit of work in this area, but there are quite a few studies now that have used studies that use branched-chain amino acids or amino acids in combination with carbohydrate. This has been an area of great discussion in the last few years with studies from Mike Saunders' and John Ivy's groups reporting benefits over carbohydrate. Several other studies, however, which have generally been better designed and incorporated better controls have failed to find these effects.

Dr. Spriet: If we consider alternate fuels such as acetate and lactate, or medium-chain triglycerides, it is frequently forgotten that the amount of energy derived is about half of that from nutritional glucose or long fatty acids. Secondly, it's quite easy to load the system with high concentrations of these things at rest, but during exercise, the biochemical pathways are not set up for this, even with lactate. Biochemistry doesn't favor moving from lactate to pyruvate in muscle under almost all situations, so the tissue is not able to oxidize that much of it.

Dr. Gibala: There are no events on the Olympic program which require exercise time to fatigue. What in your opinion is the best measure of performance?

Dr. Jeukendrup: This really depends on the question that you are trying to answer. The best performance test is the competitive event itself, but then the problem is the lack of a control trial. There is a time and a place to study time to exhaustion, which is relatively easy to do. I think this protocol comes from studies undertaken in animals where there aren't any other options, but it really measures aspects of fatigue. In humans, time to exhaustion depends on the individual's decision of when they have had enough of the exercise task, and there is a huge day to day variation. One does not see such variation in time trials. There is another problem, however, in that we are reliant on the subject's pacing strategies, and differences may be hard to pick up. Overall, I think in situations where you are really looking for a performance answer, you should probably do some form of true performance test such as a time trial. But if you want some measurements to look at the mechanisms at the same time, you could ask participants to do a fixed work load for some period of time then follow with a time trial. This is the protocol we've used the most over the last few years: 1.5–2 h of steady state exercise, followed by a time trial of about 1 h. It seems to be quite sensitive to detect the effects of nutritional manipulations.

Dr. Burke: A comment about measuring performance also serves to criticize our own work as well as that of others. Even though we try to map what is happening to mechanisms and outcomes with such hybrid models of fixed intensity work load and time trials, I still don't think we are really measuring what is important to the performance of elite sport. In many cases, it is not just the total elapsed time of a performance that matters. Rather, it is whether an athlete can respond to challenges that happen during events, such as being able to suddenly increase the tempo in a marathon to sub 3 min/km pace, to surge up a hill, or to sprint to the finish line. If our protocols don't test the athlete's ability to superimpose a very high intensity burst of activity against the background of their general pacing, we probably haven't measured what is really important.

Dr. Jeukendrup: That's why I have always said you have to know what you are looking for when designing the study. If one wants to look at basic mechanisms or metabolic changes, subjects have got to do some kind of steady-state exercise. If we want to look at performance, we have to undertake a performance trial. Ideally, we should completely separate these two domains and try to answer one question at a time rather than trying to answer two or more questions in one overcomplex study.

Dr. Burke: But even if we put a time trial component into a protocol, maybe within that time trial we need to induce some other perturbations?

Dr. Jeukendrup: You could do so, but the next step from that is to ask why we don't study a real race or try to simulate a real race. That would be an even better performance measurement.

Dr. Hawley: I would like to revisit the issue of carbohydrate ingestion and muscle glycogen sparing. Most of us are aware of the original studies showing that there is no glycogen sparing during cycling, although there are some indications of sparing if you look at individual muscle fibers or if the intensity alternates between low and high workloads. We haven't really revisited that question in this context of high carbohydrate doses. My suspicion is that under these conditions if we look at single figures there probably is glycogen sparing. Can you comment on this?

Dr. Jeukendrup: In the studies where we fed carbohydrate at rates of 2.4 g/min, which is not a practically applicable situation in real life, we do observe muscle glycogen sparing. We have only seen that occurring, however, in this set of conditions. At intakes of 1.8 g/min, which is a little bit more realistic but still very high, glycogen sparing is not seen. You really have to push the system to see muscle glycogen sparing.

Dr. Hawley: Perhaps this might apply in an event such as the Tour de France where you are 'hiding' in the peloton for several hours at moderate workloads while ingesting mixed transportable carbohydrates at high rates. Then, as Dr. Burke pointed out, the high intensity bursts will be more effective.

Dr. Jeukendrup: Yes, it's very likely that muscle glycogen synthesis occurs in those recovery periods.

Dr. McLaughlin: A final comment on the human gastrointestinal system. We have about 8 m of small intestine and can lose most of it through surgical accidents or disease. Yet a residual couple of meters of small intestine can become completely adapted to fully absorb all the glucose that is required normally. So, it is clear that the capacity of the human gut for adaptation is absolutely enormous. However, the process is quite slow and can take years. One extra thing that is clear is that the presence of an intact colon is necessary for full adaptation after small bowel resection. We can therefore assume that some signals arise from the large intestine and feed back to the small intestine. Perhaps nutrient detection mechanisms operating within the small intestine are part of this system, and so other agents such as artificial sweeteners may also be able to stimulate these processes. There may also be other components, such as fiber, that the gut microflora acts upon which make an important contribution to adaptation. All these factors need to be taken into account in advancing this model.