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KEY POINTS

- Prolonged strenuous exercise increases plasma concentrations of the hormones epinephrine, growth hormone, cortisol, and glucagon. Insulin is decreased.
- Ingestion of carbohydrate during prolonged exercise blunts these hormone responses and delays fatigue.
- The blunted hormone response may contribute to a delay in both central (brain) and peripheral (muscle) fatigue by helping to spare liver and muscle glycogen, maintain blood glucose, and reduce blood concentrations of free fatty acids, free tryptophan, and ammonia.
- To prevent a fall in blood glucose concentration and to blunt the hormonal response to exercise, every 15-20 min athletes should drink 150-350 ml of a sports drink that contains carbohydrate.

INTRODUCTION

The endocrine (hormonal) system provides for normal bodily functions, including the maintenance of blood glucose levels for optimal health and exercise performance. A decrease in blood glucose during prolonged strenuous exercise can be a major contributor to the onset of fatigue (Davis & Fitts, 1998). The endocrine system attempts to maintain adequate blood glucose levels during exercise by mobilizing other fuels for energy and by stimulating production of glucose from amino acids and other non-carbohydrate sources. Unfortunately, these responses can only delay depletion of the body's carbohydrate stores, and fatigue can occur in spite of large increases in circulating hormones. In fact, as will be described later, there is some evidence suggesting that the dramatic increase in stress hormones that accompany strenuous exercise may actually hasten fatigue.

Ingesting properly formulated carbohydrate drinks can delay fatigue by keeping blood glucose at high levels (Coggan & Coyle, 1987) and perhaps by sparing muscle glycogen stores (Hargreaves, 2000). Interestingly, the increase in stress-related hormones during exercise is also attenuated when carbohydrate drinks are ingested, but whether this has any bearing on the delay of fatigue is uncertain. Therefore, the purpose of this paper is to briefly review how the glucoregulatory hormones (epinephrine, cortisol, insulin, glucagon, and growth hormone) respond to exercise, how carbohydrate feeding alters these responses, and to judge whether there is an association between altered hormone responses and postponement of fatigue.

RESEARCH REVIEW

Hormonal Response To Prolonged Exercise

At the onset of exercise, nerve impulses from motor centers in the brain ("central command"), along with feedback to the brain's hypothalamus from sensory nerves originating in muscle, stimulate or inhibit the release of many hormones. Initial rapid changes in hormone secretion occur in anticipation of the need for metabolic and cardiovascular adjustments necessary to support the increased demands imposed by exercise. These hormonal changes become more dramatic as exercise intensity increases and fatigue develops. Hormonal changes may also occur or intensify to support psychological or emotional factors during intense exercise (Galbo, 1992).

One of the most important signals involved in control of the neuroendocrine system is a decrease in blood glucose concentration. This is demonstrated most clearly in exercise studies involving low-carbohydrate diets, fasting, and glucose

infusion (Kjaer, 1992; Wasserman & Cherrington, 1996). Strenuous prolonged exercise causes predictable decreases in blood glucose and corresponding increases in concentrations of epinephrine (EPI) (Bailey et al., 1993; Burgess et al., 1991a; Francesconi, 1988; Nieman et al., 1995), cortisol (Burgess et al., 1991a; Nieman et al., 1995; Thuma et al., 1995), glucagon (Galbo, 1992; Mitchell et al., 1990; Wasserman & Cherrington, 1996), and growth hormone (GH) (Murray et al., 1995; Nieman et al., 1998; Utter et al., 1999), along with a decrease in insulin (Burgess et al., 1991a,b; Murray et al., 1991, 1995; Utter et al., 1999; Wasserman & Cherrington, 1996). These hormones have a primary role in maintaining a stable concentration of blood glucose and are often referred to as glucoregulatory hormones (Table 1).

The responses of the glucoregulatory hormones to strenuous prolonged exercise (Figure 1) are more pronounced with increasing exercise duration, i.e., as carbohydrate availability becomes limited and fatigue develops. The rather small

changes early in exercise are designed primarily to mobilize extra fuel to meet the increased energy demands of exercise, to shift utilization toward increased fat metabolism, and to maintain blood glucose concentration. The large hormonal changes that occur late in exercise as fatigue develops are caused by the depletion of glycogen in liver and muscle, by the inability to maintain blood glucose concentration due to the fact that liver glucose production cannot keep up with the rate of glucose utilization by skeletal muscles and brain, and by psychological factors related to the increase in effort required to maintain power and impaired mood state.

Effects Of Carbohydrate Ingestion On Hormonal Responses To Exercise

Carbohydrate ingestion immediately before and/or during endurance exercise produces significant alterations in the glucoregulatory hormones. These responses include a blunting of the typical increases in EPI, cortisol, glucagon, and GH, and a smaller decrease in insulin. Insulin may actually increase with carbohydrate administration during low to moderate intensity exercise (Figure 2). This response generally supports the premise that maintenance of plasma glucose is a primary role of these hormones during prolonged exercise.

Ingestion of 30-60 g of carbohydrate per hour is generally sufficient to prevent a drop in blood glucose concentration and to delay fatigue during prolonged exercise (Hargreaves, 2000). Hormone studies using similar feeding protocols typically find that the carbohydrate feedings blunt the glucoregulatory hormone response to exercise. In contrast, when subjects are given only 13 g carbohydrate per hour during nearly 3 h of exercise at 70% VO₂max, there is no effect on various metabolic variables, ratings of perceived exertion, EPI, cortisol, glucagon, insulin, and time to fatigue (Burgess et al., 1991a).

Insulin: When carbohydrate is ingested during exercise, plasma insulin concentrations are typically maintained at resting levels or in some instances increased (Ahlborg & Felig, 1976; Burgess et al., 1991b; Coyle et al., 1983; Davis et al., 1992; Fritzsche et al., 2000; Murray et al., 1991; Nieman et al., 1998).

Epinephrine (EPI): Carbohydrate ingestion blunts the EPI increase during exercise in most studies (Deuster et al., 1992; Fritzsche et al., 2000; Mitchell et al., 1990; Nieman et al., 1998). In one interesting report, increases in EPI were blunted during 122 min of cycling at 62% VO₂max and following 2.5 h of cycling but not running at 75%VO₂max (Utter et al. 1999). It is unclear why this exercise mode-specific response occurred.

TABLE 1. Principal actions of glucoregulatory hormones and some important outcomes of those actions.

HORMONE	GENERAL ACTIONS OF HORMONE	EXPECTED RESULTS OF HORMONE ACTIONS
Insulin	<ul style="list-style-type: none"> ↑ Uptake of Glucose from Blood ↑ Glycogen Synthesis ↑ Uptake of Amino Acids from Blood ↑ Protein Synthesis ↓ Fat Breakdown ↑ Fat Synthesis 	<ul style="list-style-type: none"> ↓ Blood Glucose ↑ Glycogen in Muscle & Liver ↓ Blood Amino Acids ↑ Protein in Tissues ↓ Fatty Acids in Blood ↑ Fat Stress in Tissues
Glucagon	<ul style="list-style-type: none"> ↑ Breakdown of Glycogen in Liver ↑ Production of Glycogen in Liver from Amino Acids and Lactic Acid ↑ Fat Breakdown 	<ul style="list-style-type: none"> ↑ Blood Glucose ↑ Blood Glucose ↑ Fatty Acids in Blood
Epinephrine (EPI)	<ul style="list-style-type: none"> ↑ Breakdown of Glycogen in Liver ↑ Breakdown of Glycogen in Muscles ↑ Fat Breakdown 	<ul style="list-style-type: none"> ↓ Glycogen in Liver; ↑ Blood Glucose ↓ Glycogen in Muscle ↑ Fatty Acids in Blood
Cortisol	<ul style="list-style-type: none"> ↑ Production of Glycogen in Liver from Amino Acids and Lactic Acid ↑ Fat Breakdown ↑ Protein Breakdown 	<ul style="list-style-type: none"> ↑ Blood Glucose ↑ Fatty Acids in Blood ↑ Amino Acids in Blood
Growth Hormone (GH)	<ul style="list-style-type: none"> ↓ Uptake of Glucose from Blood ↑ Uptake of Amino Acids from Blood ↑ Protein Synthesis ↑ Fat Breakdown 	<ul style="list-style-type: none"> ↑ Blood Glucose ↓ Blood Amino Acids ↑ Protein in Tissues ↑ Fatty Acids in Blood

Possible Role Of Glucoregulatory Hormones In The Delay Of Fatigue Associated With Carbohydrate Feedings

The decreased availability of carbohydrate fuel (glycogen and glucose) and the onset of dehydration are the most important limiting factors during endurance exercise, and it is well established that replacing carbohydrate and fluid during exercise by ingesting properly formulated carbohydrate-containing sports drinks will delay fatigue and increase performance. Still, the precise mechanisms responsible for the positive effects of carbohydrate drinks are not fully understood (Davis & Fitts, 1998; Hargreaves, 2000). Coggan and Coyle (1987) suggested that the primary mechanism of delayed fatigue is maintenance of blood glucose and carbohydrate oxidation rates during the latter stages of exercise, at which time muscle glycogen is limited. Carbohydrate ingestion may also spare muscle glycogen in various fiber types during intermittent cycling and running (Hargreaves, 2000). However, it is also possible that the fatigue mechanisms lie within the brain (Davis and Bailey, 1997; Gandevia, 1999). Carbohydrate feedings can enhance brain function and improve one's sense of well being during exercise (Davis, 2000), and most people stop exercising or begin to perform poorly because the effort required to keep going is perceived as too great or that mood has deteriorated too much. This large increase in perception of effort during prolonged exercise almost always precedes an inability of the muscle to produce adequate force or power (Gandevia, 1999). Therefore, the benefits of carbohydrate feedings on delaying fatigue may include a reduced sensation of effort, improved motivation, better mood, and reduced inhibition of central motor drive in the uppermost regions of the brain (Davis, 2000; Gandevia, 1999).

We hypothesize that ingesting carbohydrate during exercise helps maintain blood glucose, thereby reducing the blood concentrations of EPI, glucagon, cortisol, and GH, and increasing insulin. These effects of carbohydrate feeding could delay glycogen depletion in muscle and liver, increase glucose uptake and oxidation in muscle and brain, and lower plasma concentrations of free fatty acids (FFA) and ammonia that may contribute to central fatigue. Although a severe decline in blood glucose (hypoglycemia) at the point of fatigue is a rare occurrence, it is well known that modest decrements in plasma glucose can cause impairments in cognitive function and mood. This can occur even prior to activation of the glucoregulatory hormone response and before traditional symptoms of clinical hypoglycemia develop (De Feo et al., 1988; Jones et al., 1990; Merbis et al., 1996). It should be emphasized that unlike most tissues, including muscle, that rely on multiple sources of energy (e.g., glucose, FFA, amino acids), the brain relies only on glucose for energy.

It is well known that the maintenance of blood glucose for the brain may contribute to lower ratings of perceived exertion often observed under exercise conditions. Utter et al. (1999) recently demonstrated that lower ratings of perceived exertion in subjects consuming carbohydrate drinks were associated with higher carbohydrate oxidation rates, higher blood glucose, higher insulin, and lower cortisol and GH. Lower ratings of perceived exertion have also been observed with glucose infusion during low-intensity exercise (Tabata et al., 1991) and

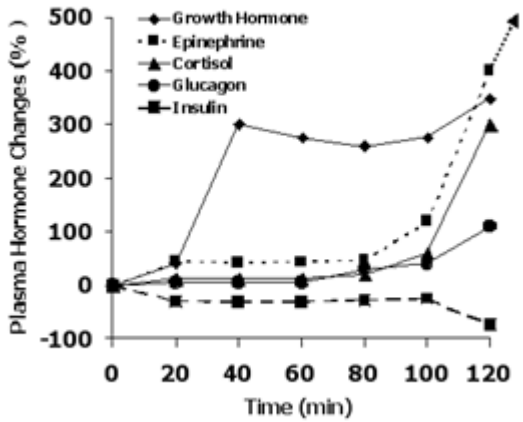


Figure 1
Schematic depiction of changes in plasma glucoregulatory hormone concentrations during 2 h of exercise at 70% VO_2max when athletes do not consume carbohydrate during exercise.

Cortisol: Carbohydrate ingestion during prolonged exercise can also blunt the increase in cortisol concentration during the exercise and for up to several hours thereafter (Nieman et al., 1998; Davis et al., 1989). Utter et al. (1999) showed that cortisol actually decreased following 2.5 h of cycling or running when subjects ingested carbohydrate solutions in comparison to the placebo condition, in which cortisol was maintained at or slightly higher than pre-exercise values. Others have shown similar results during continuous exercise for 2 h (Deuster et al., 1992; Murray et al., 1991, 1995) or following seven 12-min cycling bouts at 70% VO_2peak (Mitchell et al., 1990).

Glucagon and Growth Hormone (GH): The increases in blood glucagon and GH during exercise can be attenuated by carbohydrate feedings. Glucose feedings completely blocked the glucagon response to 4 h of cycling at 30% VO_2max (Ahlborg & Felig, 1976) but did not affect the glucagon response to intermittent cycling at 70% VO_2max (Mitchell et al., 1990). Elevations in plasma GH were blunted following 2.5 h of either cycling or running at 75% VO_2max in subjects given carbohydrate drinks versus a water placebo (Nieman et al., 1998; Utter et al., 1999).

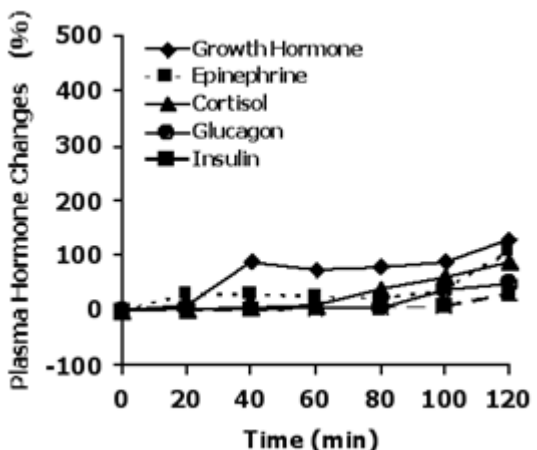


Figure 2
Schematic depiction of changes in plasma glucoregulatory hormone concentrations during 2 h of exercise at 70% VO_2max when athletes ingest 30-60 g of carbohydrates during each hour of exercise.

SUMMARY

with consumption of carbohydrate drinks during prolonged cycling at 70% VO₂max (Burgess et al., 1991b). Other benefits of carbohydrate feedings on CNS function include enhanced mood, motivation, and mental alertness, and sustained neural drive to the muscles during different types of exercise, including exercise that mimics team sports and military operations where optimal mental function is arguably more important than during prolonged cycling or running (Davis, 2000; Lieberman et al., 2002; Nybo, 2003a,b, c; Welsh et al., 2002; Winnick et al., 2005).

The modest decrease in plasma FFA after carbohydrate feedings (resulting from increased insulin and lower EPI, GH, and cortisol) could also help delay central fatigue. How could this work? When the concentration of FFA in blood is reduced, the concentration of free tryptophan also declines. This means that less tryptophan is taken from the blood and converted to serotonin in the brain. Elevated serotonin is thought to promote central fatigue along with a decrease in dopamine (Davis et al., 1992; Davis, 2000).

Carbohydrate feedings also lower blood levels of glucagon and cortisol during exercise, and increase insulin. These changes would be expected to decrease ammonia levels in the blood and the brain during ultra endurance events (Wasserman & Cherrington, 1996); ammonia is toxic to the brain and may also impair muscle metabolism.

Late stages of prolonged exercise are often associated with large increases in gluco-regulatory hormones, which indicate an inability to maintain blood glucose, and these hormonal changes can be an important sign of impending fatigue. The increase in EPI, cortisol, glucagon and GH, along with a reduction in insulin, may contribute to fatigue. Carbohydrate feedings during exercise can blunt these gluco-regulatory hormone responses, and, in part, this may be responsible for delayed onset of fatigue. Every 15-20 min during prolonged exercise, athletes should drink 150-350 ml of a sports drink containing carbohydrate to replace carbohydrate and fluid. This will prevent a fall in blood glucose and will likely delay fatigue. The delay in fatigue under these circumstances may involve both central and peripheral mechanisms.

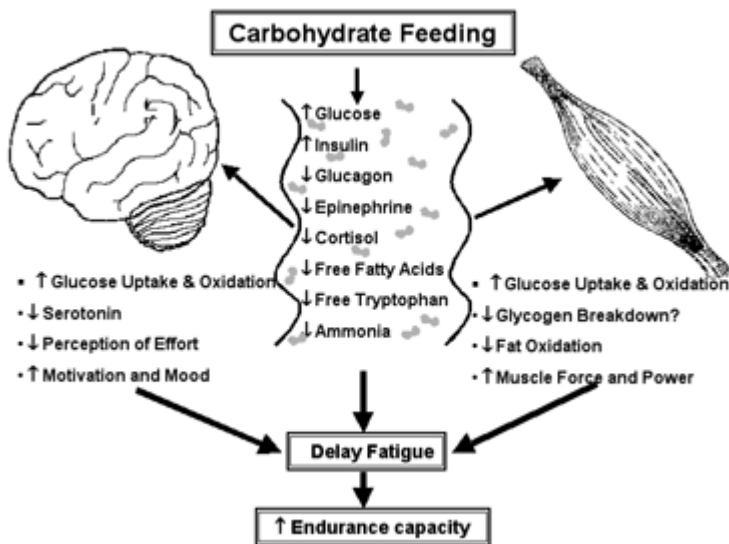


Figure 3
Schematic depiction of how consuming carbohydrate-containing sports drinks during prolonged strenuous exercise might delay fatigue by altering fuels (glucose and fatty acids), hormones, and fatigue-related metabolites (free tryptophan and ammonia) in the blood. These changes in the blood can affect the functions of both the brain and the muscles leading to improved athletic performance.

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