European Journal of Sport Science

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/tejs20

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To cite this article: Hunter L. Paris , Erin C. Sinai , Ren-Jay Shei , Alexandra M. Keller & Timothy D. Mickleborough (2020): The influence of carbohydrate ingestion on peripheral and central fatigue during exercise in hypoxia: A narrative review, European Journal of Sport Science, DOI: 10.1080/17461391.2020.1842512

To link to this article: https://doi.org/10.1080/17461391.2020.1842512

Published online: 22 Nov 2020.

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European Journal of Sport Science, 2020
https://doi.org/10.1080/17461391.2020.1842512

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REVIEW

The influence of carbohydrate ingestion on peripheral and central fatigue during exercise in hypoxia: A narrative review

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Abstract
Hypoxia impairs aerobic performance by accelerating fatiguing processes. These processes may originate from sites either distal (peripheral) or proximal (central) to the neuromuscular junction, though these are not mutually exclusive. Peripheral mechanisms include decrements in muscle glycogen or fluctuations in intramuscular metabolites, whereas central responses commonly refer to reductions in central motor drive elicited by alterations in blood glucose and neurotransmitter concentrations as well as arterial hypoxemia. Hypoxia may accelerate both peripheral and central pathways of fatigue, with the level of hypoxia strongly dictating the degree and primary locus of impairment. As more people journey to hypoxic settings for work and recreation, developing strategies to improve work capacity in these environments becomes increasingly relevant. Given that sea level performance improves with nutritional interventions such as carbohydrate (CHO) ingestion, a similar strategy may prove effective in delaying fatigue in hypoxia, particularly considering how the metabolic pathways enhanced with CHO supplementation overlap the fatiguing pathways upregulated in hypoxia. Many questions regarding the relationship between CHO, hypoxia, and fatigue remain unanswered, including specifics on when to ingest, what to ingest, and how varying altitudes influence supplementation effectiveness. Therefore, the purpose of this narrative review is to examine the peripheral and central mechanisms contributing to fatigue during aerobic exercise at varying degrees of hypoxia and to assess the role of CHO ingestion in attenuating fatigue onset.

Keywords: *Aerobic fitness, nutrition, performance, environmental physiology*

Highlights
- Carbohydrate ingestion may alter fatigue development in hypoxic environments.
- At moderate altitudes, carbohydrate intake may best be used to address peripheral fatigue.
- At extreme altitudes, the efficacy of carbohydrate supplementation likely depends on its capacity to address central fatigue.
- The relationship between carbohydrates, fatigue, and hypoxia is better understood when neurophysiological measures link interventions with outcomes.

Introduction

Fatigue limits work capacity and the rate of fatigue development determines the ability to sustain exercise. Isolating a single physiological factor responsible for fatigue is difficult and current understanding supports a multifaceted etiology in which fatigue stems from peripheral or central loci, and often both concurrently. Hypoxia accelerates the development of fatigue during aerobic exercise, eliciting either reductions in exercise time to exhaustion or a lowering of absolute workload. Like exercise in normoxia, hypoxia-induced fatigue is unlikely to be traced to a single locus as both peripheral and central mechanisms are enhanced depending on hypoxia severity (Taylor, Amann, Duchateau, Meeusen, & Rice, 2016).

In addition to altering fatigue characteristics, hypoxia also influences substrate utilization – prioritizing carbohydrate (CHO) oxidation, particularly

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when absolute exercise intensity is matched between normoxia and hypoxia (Young, Margolis, & Pasiakos, 2019). Therefore, in seeking to mitigate fatigue and improve exercise tolerance in hypoxic environments, bolstering CHO availability through supplementation represents a rational approach. Given that CHO ingestion improves endurance performance at sea level, this strategy may also prove effective in delaying fatigue in hypoxia, particularly considering how the metabolic pathways enhanced with CHO supplementation overlap the fatiguing pathways upregulated in hypoxia (Karelis, Smith, Passe, & Péronnet, 2010; Kent-Braun, Fitts, & Christie, 2012; Taylor et al., 2016). A limited number of studies, however, track performance outcomes following CHO ingestion in hypoxia, and data connecting these performance outcomes with fatiguing processes of peripheral and central origins is scarcer still. Understanding the physiological basis by which fatigue etiology (whether peripheral, central, or a combination of the two) can be influenced by CHO supplementation may be useful in predicting scenarios in which CHO intake has an ergogenic effect. Specifically, if the physiological factors of exercise- and hypoxia-related fatigue are influenced by CHO availability, CHO supplementation may be expected to improve work capacity. Otherwise, CHO ingestion would be unlikely to positively influence performance outcomes in hypoxia.

The aims of this narrative review are: (1) to describe the current understanding of fatigue development in hypoxia, (2) to examine the potential for CHO ingestion to attenuate peripheral and central fatigue development in hypoxia, and (3) to hypothesize on the most likely scenarios for CHO ingestion to influence hypoxia-induced fatigue and thereby stimulate future research. Literature searches were conducted on PubMed and Google Scholar using combinations of keywords and Boolean operators [for example, (exercise OR running OR cycling OR fatigue) AND (hypoxia OR altitude) AND (carbohydrates OR diet)]. Emphasis was placed on rigorously conducted experimental trials, reviews, and meta-analyses. To adhere to reference restrictions, studies were excluded where results overlapped or were redundant between studies. The limited number of studies on this topic, wide disparity in study design, and differences in carbohydrate administration in the existing literature preclude rigorous systematic review and meta-analysis, thus a narrative review format was selected. Due to the small number of studies investigating the interplay between CHO, fatigue, and hypoxia, in cases where primary literature lacks, we summarize available data and, when appropriate, anticipate expected physiological outcomes in light of existing research.

Fatigue

Continual movement results in a progressive reduction in the force generating capacity of skeletal muscle, i.e. fatigue. Whereas fatigue is often considered in light of decrements in performance and exercise inhibition, performance can be unaltered in the midst of fatigue if muscle recruitment is enhanced. Therefore, fatigue may be defined as any transient exercise-induced decrease in muscular force or power output with or without task failure (Gandevia, 2001). Though force production ultimately depends on the contraction of skeletal muscle, disruptions in the ability of the contractile properties to function properly may result from a variety of processes. Commonly, these processes are described in relation to their location, either distal (peripheral) or proximal (central) to the neuromuscular junction.

Peripheral fatigue

Peripheral fatigue originates from mechanisms that occur at, or distal to, the neuromuscular junction (Gandevia, 2001). Causative factors of fatigue within the muscle vary, though research primarily indicates metabolic inhibition of contractile function. Factors such as elevations in H^+, NH_4^+, and P_i concentrations, alteration of Na^+-K^+ pump function, impaired regulation of Ca^{2+} within the myocyte, buildup of K^+ in the transverse-tubular system, exercise-induced muscle damage, and glycogen depletion can all disrupt cross-bridge function in the skeletal muscle (Kent-Braun et al., 2012). These factors do not represent an exhaustive list of metabolites and processes contributing to peripheral fatigue and for further understanding we refer the reader to the review from Kent-Braun, Fitts, and Christie (Kent-Braun et al., 2012).

While exercise per se provokes fatiguing processes within the periphery, whether these mechanisms are responsible for performance decrements depends on the exercise intensity and modality. Peripheral fatigue is most apparent during short-duration (<30 min), high-intensity exercise and exercise with limited muscle recruitment (e.g. single-limb exercise or even cycling compared to running) (Millet & Lepers, 2004).

Instead of picturing autonomous events with a common endpoint (fatigue), one should instead envision these factors collectively diminishing work capacity. Although one individual component may not elicit exercise termination, the accumulation of fatiguing events disrupts cellular processes, resulting in peripheral fatigue and ultimately impairing exercise tolerance. For example, alterations in shortening velocity may occur as a consequence of increases in

H^+ and ADP. This same rise in ADP may simultaneously alter Ca^{2+} handling in the sarcoplasmic reticulum (Kent-Braun et al., 2012). Together, shortening velocity is impacted along with excitation-contraction coupling due to Ca^{2+} disturbances, and force generating capacity is impaired.

Central fatigue

Central fatigue refers to processes proximal to the neuromuscular junction that decrease neural drive to the exercising muscles. Even at rest, limitations in motor unit recruitment occur, but any *additional* impairment in muscle activation from pre- to post-exercise is a metric for central fatigue (Gandevia, 2001). Much like peripheral fatigue, an array of physiological disruptions contribute to the development of central fatigue including: hypoglycemia, fluctuations in circulating neurotransmitter concentrations, arterial hypoxemia, increases in core temperature, and reductions in cortical excitability (Amann, Romer, Subudhi, Pegelow, & Dempsey, 2007; Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2006; Nybo, 2003). For a comprehensive review of mechanisms contributing to central fatigue, we direct the reader to the work by Meeusen and colleagues (Meeusen et al., 2006).

Central fatigue is accelerated in a variety of exercise scenarios without necessarily being the primary impetus for exercise termination. Central fatigue limits performance particularly when exercise is of long-duration (>60 min) and when locomotion causes a large amount of muscular stress (e.g. ultra-marathon running, which would be a combination of both long duration and full-body exercise) (Millet & Lepers, 2004). Like the overlap in peripheral fatigue, mechanisms of central fatigue are not isolated and may occur in conjunction with one another, as well as with fatiguing processes within the periphery.

Fatigue in hypoxia

As elevation increases, ambient barometric pressure decreases thereby lowering the partial pressure of inspired oxygen (P_IO_2) and resulting in hypobaric hypoxia. Although altitude ascent is commonly thought to diminish exercise capacity, decreases in air resistance accompanying reductions in barometric pressure may actually improve exercise lasting <4 min (Amann & Calbet, 2008). For exercise >4 min, however, reductions in P_IO_2 can influence both peripheral and central pathways thereby accelerating fatigue development and creating an environment antagonistic to aerobic performance. As is the case for fatigue in normoxia, the etiology of fatigue in hypoxia depends on exercise modality and intensity. Hypoxia is not an all-or-nothing phenomenon, and when assessing the primary origin of fatigue in hypoxia consideration must also be given to the specific ambient conditions. Although hypoxic training is often referred to as "altitude training" this term can be misleading – tacitly suggesting that either a person is or is not at altitude. We all live at an altitude, but whether that elevation acts as a physiological stressor depends on the severity of altitude and the individual response.

Different levels of altitude elicit varying physiological responses. This is perhaps easiest to appreciate when considering the effort required to exercise at 1000 m (~3300 ft) compared to exercising at 4000 m (~13,000 ft). Severity of altitude may also be understood when considering the shape of the oxyhemoglobin dissociation curve. Once over the shoulder of the curve, even a small reduction in the P_IO_2 (e.g. moving from a moderate altitude to a high altitude) could elicit a large drop in arterial oxygen saturation, indicating that the physiological response to one elevation can differ largely from another, even similar, elevation. Therefore, altitude classifications have been developed to delineate the varying degrees of physiological stress. When discussing hypoxia-induced fatigue we will use the thresholds established by Bartsch and Saltin (Bärtsch & Saltin, 2008): "near sea level" (0–500 m), "low altitude" (500–2000 m), "moderate altitude" (2000–3000 m), "high altitude" (3000–5500 m), and "extreme altitude" (>5500 m). We also note that many studies of hypoxia have employed normobaric hypoxia, in which the fraction of inspired oxygen is experimentally reduced to simulate the severity of hypoxia at a given naturally occurring altitude (i.e. hypobaric hypoxia). While historically experimental studies in hypobaric hypoxia and normobaric hypoxia have been considered equivalent, recent evidence (Millet, Faiss, & Pialoux, 2012a) suggests these stimuli may elicit subtle, but important differences in physiological responses, and thus hypobaric and normobaric hypoxia studies should be compared judiciously. Due to the relatively small number of studies examining fatigue, CHO, and hypoxia, as well as the lack of data specifically regarding fatigue and CHO in normobaric vs hypobaric hypoxia, this narrative review will not discuss potential differences caused by normobaric vs. hypobaric environments. However, we note that future research should be carefully designed to identify what, if any, differences exist between normobaric and hypobaric hypoxia when assessing fatigue and ergogenic aids.

Peripheral fatigue in hypoxia

One method by which peripheral fatigue may be upregulated in hypoxia is through a hastened accumulation of metabolites connected to fatigue. Tissue oxygenation regulates cellular processes during exercise and reductions in P_IO_2 can increase lactate, phosphocreatine hydrolysis, P_i, and ADP (Haseler, Richardson, Videen, & Hogan, 1998). As previously discussed, accumulation of these metabolites impairs excitation-contraction coupling, alters Ca^{2+} regulation in the sarcoplasmic reticulum, and diminishes contractile protein function (Amann & Calbet, 2008). Importantly, elevations in fatigue-related metabolites occur independently of changes in oxygen consumption ($\dot{V}O_2$), demonstrating that changes in P_IO_2 alone are enough to alter metabolic processes and thereby accelerate the rate of peripheral fatigue development (Haseler et al., 1998). Contractile function is also impaired by glycogen depletion and while some have observed a hypoxia-mediated increase in glycogen utilization (Young et al., 2019), others report no difference in carbohydrate oxidation following hypoxic vs. sea level exercise (Griffiths et al., 2019). Differences in elevation, acclimatization, exercise parameters, study population, energy balance, and the muscle type being investigated likely contribute to discrepant findings.

Hypoxia enhances peripheral fatigue, particularly in environments of low or moderate altitude. Previously, Amann et al., (2007) had participants perform a cycling time to exhaustion at ~80% normoxic peak power output. At this intensity and duration (~11 min) performance was primarily limited by peripheral fatigue. When participants completed the same exercise at ~3400 m the time to exhaustion was reduced (~5 min), but the magnitude of peripheral fatigue at exercise termination was comparable to that of normoxia. The authors concluded that this level of peripheral fatigue limited subsequent performance and that moderate hypoxia accelerates fatigue within the periphery thereby reaching this threshold sooner.

Central fatigue in hypoxia

In addition to inducing peripheral mechanisms of fatigue, hypoxia may also accelerate central fatigue development. Although the association between arterial hypoxemia and the central nervous system provides the most apparent relationship between hypoxia and central drive, hypoxia may also influence central fatigue by hastening hypoglycemia as well as altering plasma neurotransmitter concentrations.

Carbohydrate oxidation requires less oxygen per mole of ATP compared with fat oxidation (Hochachka et al., 1991). Therefore, when oxygen becomes limited, CHO oxidation offers a more efficient fuel than oxidation of fats, and individuals may experience hypoxia-induced shifts in substrate oxidation, preferentially oxidizing CHO as a fuel. By prioritizing CHO and increasing the dependency of skeletal muscle on glucose (Brooks et al., 1991) hypoxia could thereby potentiate hypoglycemia and diminish central drive (Nybo, 2003). Additionally, any hypoxia-induced upregulation in sympathetic activity could alter neurotransmitter release and central drive through the cascade of events described by the serotonin fatigue hypothesis (Meeusen et al., 2006). Taken together, hypoxia could accelerate central fatigue development through arterial hypoxemia as well as through hypoxia-induced alterations in nutrient metabolism.

Kayser, Narici, Binzoni, Grassi, & Cerretelli, (1994) demonstrated the influence of hypoxia on central fatigue by having participants cycle to exhaustion at sea level and 5050 m. When exercise was performed at high (nearly extreme) altitude fatigue became more strongly linked with central mechanisms. At the point of exhaustion, hypoxic air was replaced by 100% O_2 and participants were encouraged to continue cycling as long as possible. Supplemental oxygen prolonged exercise time and altered fatigue characteristics such that peripheral mechanisms of fatigue became more prominent and reflected fatigue patterns observed during sea level exercise. Amann et al. (2007) and Millet, Muthalib, Jubeau, Laursen, and Nosaka (2012b) extended these findings by showing that, as the hypoxic environment became progressively more severe (i.e. as elevation continued to rise and arterial hypoxemia intensified), central fatigue contributed a larger role in exercise termination. Taken together, data demonstrate that in moderate hypoxia the periphery remains the dominant location of fatigue and primary influence for exercise termination but at extreme altitudes performance becomes more dependent on central mechanisms (Amann et al., 2007).

Crosstalk in fatigue etiology

Altitude severity and duration of exposure exist alongside exercise modality and exercise intensity in determining fatigue development. We could expect, for example, a hastening of peripheral fatigue during high intensity exercise in moderate hypoxia. When exercise is performed under conditions that amplify both loci of fatigue [e.g. a 90 min run (central) at moderate hypoxia (peripheral)] central and peripheral mechanisms likely coexist and influence one another. For example, we might ask

Table I. Summary of select studies examining the influence of hypoxia* on peripheral or central fatigue

	Elevation (m)	Study	Exercise	Exposure	Primary Locus of Fatigue
Extreme	>7500	Merton (1954)	maximal tetanic contraction of adductor pollicis	ischemia via occlusion of upper arm	peripheral
		Kjær et al. (1999)	cycling to exhaustion 112 W	9 min F_IO_2 0.078 (NH)	central
	7500	Garner et al. (1990)	6 × 6 contractions of tibialis anterior (100% MVC)	40 d ascent 282 mmHg (HH)	central and peripheral
	7000	Millet et al. (2012b)	contraction of elbow to exhaustion (40% MVC)	7.5 min F_IO_2 0.09 (NH)	central
	6500	Garner et al. (1990)	6 × 6 contractions of tibialis anterior (100% MVC)	multi-week ascent to 335 mmHg (HH)	peripheral
	6500	Amann et al. (2007)	cycling to exhaustion (81% normoxic W_{peak})	3 min F_IO_2 0.10 (NH)	central
	6000	Katayama, Amann, Pegelow, Jacques, and Dempsey (2007)	3 × 9 quadriceps contraction (62% MVC)	18 min F_IO_2 0.10–0.11 (NH)	peripheral
		Katayama et al. (2007)	100% MVC	10 min F_IO_2 0.10–0.11 (NH)	no effect of hypoxia on MVC
		Goodall, Ross, and Romer (2010)	quadriceps contractions to exhaustion (60% MVC)	28 min F_IO_2 0.10 (NH)	Central
	5500				
High	5000	Orizio, Esposito, and Veicsteinas (1994)	contraction of elbow flexors (20%, 40%, 60%, 80%, 100% MVC)	6 d ascent, 2 d acclimatization Pyramid Lab, Nepal 412 mmHg (HH)	no effect of hypoxia on MVC or EMG
		Taylor, Bronks, Smith, and Humphries (1997)	cycling 10 min 180 W (77% normoxic HR_{max})	10 min F_IO_2 0.116 (NH)	peripheral
		Millet, Aubert, Favier, Busso, and Benoit (2009)	quadriceps contraction to exhaustion (50% MVC)	15 min F_IO_2 0.11 (NH)	central and peripheral
	4500	Romer et al. (2007)	cycling to exhaustion (92% normoxic W_{peak})	5 min F_IO_2 0.13 (NH)	peripheral
	4000	Goodall et al. (2010)	quadriceps contractions to exhaustion (60% MVC)	33 min F_IO_2 0.13 (NH)	peripheral
	3500	Townsend, Brocherie, Millet, and Girard (2020)	8 × 5-s treadmill sprints	9 min F_IO_2 0.13 (NH)	peripheral
		Millet et al. (2012b)	contraction of elbow to exhaustion (40% MVC)	8 min F_IO_2 0.14 (NH)	peripheral
		Amann et al. (2007)	cycling to exhaustion (81% normoxic W_{peak})	6 min F_IO_2 0.15 (NH)	peripheral
Moderate	3000				
	2500	Goodall et al. (2010)	quadriceps contractions to exhaustion (60% MVC)	37 min F_IO_2 0.16 (NH)	peripheral
	2000	Romer, Haverkamp, Lovering, Pegelow, and Dempsey (2006)	cycling to exhaustion (92% normoxic W_{peak})	10 min F_IO_2 0.16–0.18 (NH)	peripheral

*Elevations calculated from F_IO_2 and available data for testing site elevation and barometric pressure; W_{peak}, peak power output as determined from a maximal incremental exercise test; F_IO_2, fraction of inspired oxygen. NH, normobaric hypoxia, HH, hypobaric hypoxia. Times are approximations based on any pre-exercise wash-in of hypoxic gas and post-exercise measurements while still breathing hypoxic air.

Table II. Summary of select human‡ experimental studies examining the influence of carbohydrate supplementation on exercise performance* in hypoxia of various severities

Exercise duration					
Altitude	0–2 min	2–30 min	30–60 min	60–120 min	> 120 min
Extreme (>5500 m)	*No studies found for extreme altitude*				
High (3000–5500 m)		✓ Consolazio (1969) † ✓Oliver, Golja, and Macdonald (2012)† × Caris, Da Silva, Dos Santos, Tufik, and Dos Santos (2017) # × Bradbury et al. (2020) †		✓ Askew et al. (1987) ^ ✓ Fulco et al. (2005) ^ × Fulco et al. (2007) ^	× Bourrilhon et al. (2010) #
Moderate (2000–3000 m)			× Liao, Mündel, Yang, Wei, and Tsai (2019) ^		× Bourrilhon et al. (2010) #
Low (500–2000 m)			✓ Slivka, Hailes, Cuddy, and Ruby (2008) †	✓ Little et al. (2010) †	

‡For a review on animal studies pertaining to carbohydrate supplementation in hypoxia, please refer to work by Mitchell and Edman (1949); *studies must contain performance outcome compared to placebo or alternative supplementation; a checkmark sign (✓) represents carbohydrate ingestion exerting a positive influence on performance; × represents no influence or a negative influence on performance. Regarding the timing of CHO ingestion relative to performance: †, CHO ingested prior to performance; #, CHO ingested during performance; ^, CHO ingested both prior to and during performance.

whether single limb exercise (peripheral) is altered at extreme altitude (central). At ~6000 m handgrip strength (normally limited by peripheral factors) is reduced, exemplifying how altitude can alter the patterns of fatigue. Maximal typing frequency, however, is unaffected at this same elevation, indicating the importance that exercise intensity has, even within certain environmental conditions and muscle mass recruitment (Rasmussen et al., 2007).

Table I displays the primary locus of fatigue for various elevations and exercise protocols, demonstrating both the general understanding of how altitude influences fatigue, as well as the subtleties of exercise type and intensity existing within this context. In viewing Table I, it is important to distinguish between the primary locus of fatigue and the crosstalk in fatigue development between central and peripheral locations. For example, because moderate hypoxia accelerates peripheral fatigue development, if power output is maintained between normoxia and moderate hypoxia, thresholds of peripheral fatigue will be reached faster in hypoxia. Therefore, when completing a time-trial in moderate hypoxia, power output is necessarily reduced compared to normoxia such that the limitations of peripheral fatigue are not reached until the end of the time-trial. Reductions in power output elicited by hypoxia may be mediated by limiting central drive to the periphery, but because peripheral limitations are directing central output, peripheral mechanisms remain the primary stimulus of fatigue development at moderate altitude. Conversely, at extreme altitude central fatigue dominates and exercise termination will occur prior to reaching peripheral limitations.

Carbohydrate ingestion for the attenuation of fatigue in hypoxia

Each year a growing number of individuals ascend to higher altitudes for recreational and occupational activities where they face potential reductions in work capacity elicited by the hypoxic environment. Developing a strategy to counteract hypoxia-induced fatigue is therefore increasingly relevant.

The importance of CHO as a fuel for exercise has been known since at least the early 1900s (Asmussen, 1971) and numerous investigations have recorded improvements in endurance performance following CHO intake. For a review on CHO supplementation as an ergogenic aid, the work by Coggan & Coyle (1991) remains a flagship article thirty years after publication. As previously mentioned, CHO oxidation provides more ATP for a given amount of oxygen compared to fat and when absolute exercise intensity is maintained, hypoxia elevates the rate of glycolysis compared to sea level activity (Lundby & Van Hall, 2002). Because hypoxia reduces $\dot{V}O_2max$, the greater contribution of CHO in hypoxia could reflect changes in relative exercise intensity when maintaining absolute workload between normoxia and hypoxia. Discussions

continue regarding the merits of using absolute vs. relative intensity when investigating hypoxia-induced alterations in macronutrient oxidation (Griffiths et al., 2019; Young et al., 2019). Practical application likely favours fixing exercise according to energetic demands and absolute intensity (Young et al., 2019), which indicates a hypoxia-mediated increase in CHO use. If ascending to higher altitudes does elevate CHO oxidation, supplementing with additional CHO represents one possible approach to attenuating fatigue in this environment. Indeed, based primarily on the upregulation of CHO oxidation in hypoxia, dietary guidelines for altitude ascension commonly suggest CHO supplementation (Stellingwerff et al., 2019). As shown in Table II, however, studies reporting performance outcomes following CHO supplementation in hypoxia are scarce and conclusions equivocal. If CHO supplementation improves work capacity in hypoxia, the ergogenic benefits could work through a variety of pathways depending once more on exercise specifics. Altitude severity and hypoxic dose (as discussed later) may also dictate the CHO mechanisms of action, potentially delaying both peripheral and central fatigue.

Carbohydrate ingestion & peripheral fatigue in hypoxia

Carbohydrate ingestion can improve exercise capacity otherwise limited by peripheral fatigue [e.g. high intensity exercise ~80% $\dot{V}O_2$max (Jeukendrup, Brouns, Wagenmakers, & Saris, 1997)], demonstrating the potential for CHO supplementation to interact with peripheral pathways. Supplementation may spare endogenous CHO stores, and if ingestion preserves muscle glycogen peripheral fatigue could be diminished. Preservation of glycogen through exogenous supplementation remains speculative, however, and may depend on exercise intensity and duration. Some evidence questions the capacity of CHO intake to spare muscle glycogen altogether (Coggan & Coyle, 1991). Despite conflicting reports, the physiological plausibility of CHO supplementation sparing muscle glycogen remains a putative mechanism by which CHO ingestion may attenuate peripheral fatigue development. Additional pathways by which CHO ingestion could delay peripheral fatigue include alterations of NH_4^+ (Carvalho-Peixoto, Alves, & Cameron, 2007), preservation of membrane excitability and Na^+-K^+-ATPase activity (Stewart et al., 2007), and perhaps retention of sarcoplasmic reticulum function (Xu, Zweier, & Becker, 1995). For a more in-depth understanding of how CHO may influence peripheral (and central) mechanisms at sea level, we recommend the work of Karelis et al. (Karelis et al., 2010).

For exercise at sea level, the ergogenic benefits of CHO on work capacity are well established and evidence suggests CHO supplementation delays peripheral fatigue especially when fatigue etiology is related to conduction of the action potential through the sarcolemma and T-tubules (Stewart et al., 2007).

Inquiry into how *hypoxia* might alter the CHO-peripheral fatigue relationship is an additional question, requiring quantification of fatigue following CHO intake and hypoxic exercise. Data from our laboratory (Paris et al., 2019) demonstrate that while a 1 h run at 65% of sea level $\dot{V}O_2$max elicits peripheral fatigue, neither moderate hypoxia nor CHO supplementation (6% dextrose solution ingested every 15 min) influence peripheral fatigue development. Therefore, though pathways exist whereby CHO supplementation can delay peripheral fatigue in hypoxia, the specific mechanism of fatigue may dictate the efficacy of CHO ingestion.

Carbohydrate ingestion & central fatigue in hypoxia

Carbohydrate intake can influence central drive specifically by preserving blood glucose, affecting neurotransmitter release, and attenuating arterial hypoxemia. Although the ergogenic benefits of CHO intake are frequently attributed to maintaining euglycemia during prolonged exercise (Coggan & Coyle, 1991), by interacting with circulating amino acids, supplementation may also influence neurotransmitter release (Davis et al., 1992). Regarding arterial hypoxemia, CHO ingestion can preserve lung diffusing capacity (Dramise et al., 1975), stimulate ventilation (Charlot, Pichon, Richalet, & Chapelot, 2013), and conserve arterial oxygen content (Charlot et al., 2013), though results lack consistency (Bradbury et al., 2020; Paris et al., 2019).

Under sea level conditions, CHO ingestion was thought to influence performance via central pathways as early as 1936 (Coggan & Coyle, 1991). A 2016 review on CHO and central fatigue, however, concluded that after eighty years of suspecting the crosstalk between CHO intake and central mechanisms, neurophysiological outcome measures depicting the relationship between CHO intake and central drive remain inadequate to definitively link CHO consumption with attenuation of central fatigue (Khong, Selvanayagam, Sidhu, & Yusof, 2017). Still, existing data suggest that central fatigue is delayed particularly when CHO supplementation prevents hypoglycemia (Nybo, 2003; Stewart et al., 2007).

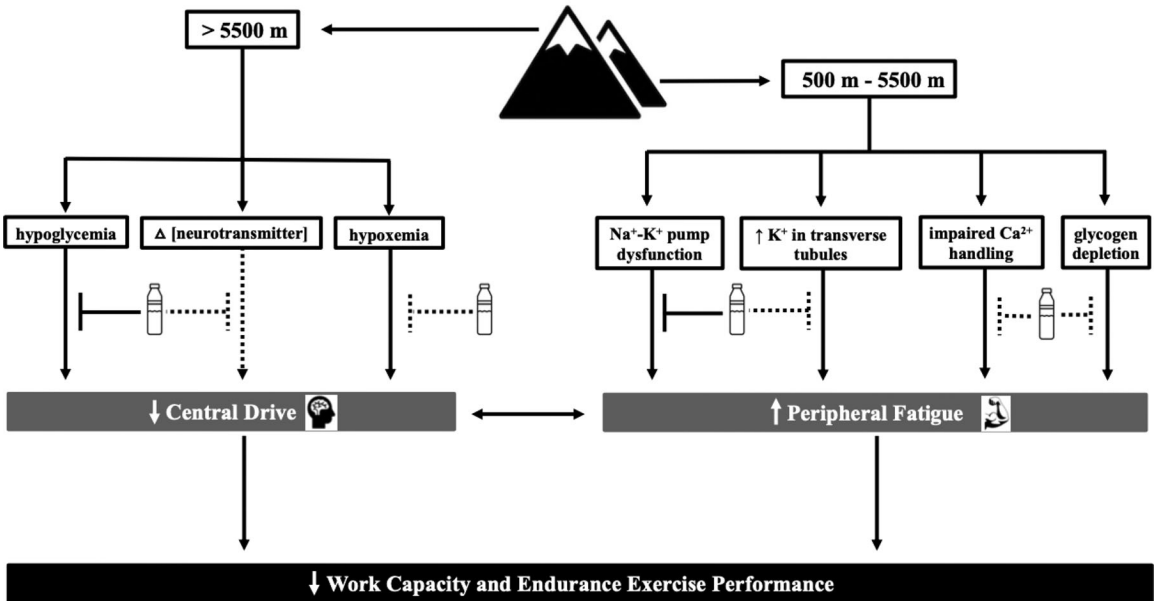

Figure 1. Overview of anticipated connections between exercise- and hypoxia-induced fatigue and attenuation of fatigue via carbohydrate ingestion. Above 5500 m, fatigue is strongly linked with central drive whereas below 5500 m peripheral mechanisms limit exercise performance (depending on the intensity, duration, and type of exercise). Below 5500 m, carbohydrate supplementation during exercise may attenuate fatigue development by preserving membrane excitability and perhaps addressing glycogen depletion. Above 5500 m, CHO ingestion could address central fatigue by delaying hypoglycemia and attenuating arterial hypoxemia. This relationship is further complicated when considering the influence of hypoxic dose on fatigue development and substrate metabolism. Water bottle symbol, carbohydrate supplementation; solid line, well established relation; dashed line, limited or conflicting evidence.

Years of observation support the conclusion that carbohydrate metabolism and aerobic processes find common ground in the central nervous system. In 1940 McFarland and Forbes (1940) reported that, "The functioning of the central nervous system appears to depend upon a continuous and adequate supply of oxygen and glucose. When the concentration of either of these substances in the blood is lowered … there is significant impairment in cerebral function." Here, we see the intersection between CHO and hypoxia on central activation. For CHO to effectively promote central drive though, supplementation must directly address the central mechanisms of fatigue. For example, although CHO ingestion had no effect on the development of central fatigue when running for 1 h at a moderate hypoxia (Paris et al., 2019), arterial oxygen saturation, neurotransmitter precursors, and blood glucose remained unaltered by CHO intake. If CHO is to promote work capacity by delaying central fatigue it must be capable of altering these mechanisms.

Carbohydrates for fatigue in hypoxia – proposed influence

Supplementing with CHO for hypoxia- and exercise-induced fatigue should be considered specifically when exercise is limited by CHO-related phenomena. Thus, in cases where CHO availability is linked to accelerated fatigue development there is a physiological basis for CHO supplementation attenuating fatigue development and perhaps exerting an ergogenic effect. In cases where CHO availability does not influence the mechanisms of exercise limitation, however, we would expect no benefit from CHO ingestion. For example, some evidence demonstrates a failure of glucose supplementation to influence PCr, P_i, ADP, and AMP when ingested every 15 min during 2 h of cycling exercise to exhaustion (Duhamel et al., 2007). Therefore, if fatigue is due primarily to these metabolites we might question the use of CHO as an ergogenic aid.

For CHO ingestion to attenuate fatigue in hypoxia via preservation of peripheral pathways, exercise need be limited by peripheral mechanisms linked with diminished CHO. Short duration exercise at moderate altitude (and perhaps even high altitude) is likely limited by peripheral factors other than CHO availability (Karelis et al., 2010) and we would not anticipate CHO ingestion improving performance under these conditions. Indeed, Bradbury et al. (Bradbury et al., 2020) found no difference in two-mile run performance (~20 min of running following 80 min of walking) when ingesting either CHO or a placebo at high altitude. If this *same* experimental setup were

transferred to extreme altitude, however, where fatigue becomes more limited by central pathways, and if CHO can maintain arterial oxygenation, performance could improve. Similarly, attempting to attenuate central fatigue in hypoxia through CHO ingestion should be considered when common, physiological ground is established between the locus of fatigue in hypoxia and the mechanism addressed through CHO supplementation.

The efficacy of CHO intake depends on the origin of fatigue, which itself is partially contingent upon altitude severity. Figure 1 demonstrates the theorized, mechanistic connections between CHO ingestion and attenuation of fatigue at various elevations. Because moderate hypoxia elevates peripheral fatigue, CHO ingestion will be most effective when addressing peripheral mechanisms. Conversely, due to the relationship between extreme altitude and central fatigue, CHO ingestion will effectively improve performance at extreme altitude by addressing central pathways. If CHO supplementation cannot address the locus of central fatigue (e.g. if it fails to preserve arterial oxygenation), then it will have little influence on performance outcomes in extreme hypoxia. Applying this hypothesis may look as follows: a recent review on nutrition in hypoxia (Stellingwerff et al., 2019) highlighted a lack of studies investigating nutritional interventions for performance at moderate altitude (the elevation of most relevance for individuals training towards sea level performance). We would expect moderate hypoxia to enhance peripheral mechanisms of fatigue. If hypoxia severity, exercise intensity, and exercise duration elicit a fatigue related especially to glycogen depletion or impaired action potential conduction, CHO supplementation should be considered for performance enhancement.

Although direct investigations on the interaction of CHO, fatigue, and hypoxia are limited, some studies have examined the influence of CHO on performance in hypoxia. Table II lists all the studies we identified where CHO ingestion was compared against a placebo or alternative supplement for its ergogenic effects above 500 m. Although data on fatigue is limited, if we consider performance outcomes in these studies, a few themes arise. First, data support CHO supplementation for low-altitude events lasting around 60 min. Given the lower elevation, the mechanisms behind this may reflect those observed when exercising at sea level. Second, despite the numerous ultraendurance events taking place at higher elevations, little is known regarding the efficacy of CHO ingestion under these conditions. Although Bourrilhon et al. (Bourrilhon et al., 2010) found that a CHO-based diet ingested during exercise did not improve ultraendurance climbing performance compared to a protein-based diet, the protein diet still contained 7.6 g kg^{-1} CHO, thus making conclusions for prolonged exercise difficult. On the opposite end of the duration spectrum, no data could be found examining how CHO supplementation might influence fatigue in hypoxia for short duration events. Just as exercise duration could influence CHO efficacy, so too might duration of hypoxic exposure. The relationship between altitude severity and duration of exposure has been referred to as the "hypoxic dose" (Garvican-Lewis, Sharpe, & Gore, 2016; Wilber, Stray-Gundersen, & Levine, 2007). Given that the magnitude of hypoxic dose likely affects physiological adaptations to high altitudes (Garvican-Lewis et al., 2016; Wilber et al., 2007), perhaps hypoxic dose also influences the physiological response to CHO supplementation – where chronic exposure to hypoxia impacts absorption, delivery, and patterns of macronutrient oxidation compared to acute exposure. Lastly, we remain uncertain about the possible influence of CHO on fatigue above 5500 m and can only speculate as to the potential mechanism at these extreme elevations (Figure 1). Ultimately, even given the same elevation and duration of exercise, CHO might influence performance differently. These differences may be explained by nuances such as sex, normobaric vs. hypobaric hypoxia, and energy balance.

Regarding energy state, hypoxia has been shown to alter energy expenditure and cause hypophagia leading to a negative energy balance (Butterfield et al., 1992). Altitude-induced anorexia is partially attributable to alterations in hormones such as ghrelin and insulin, which may then influence substrate metabolism (Debevec, 2017; Macdonald et al., 2009; Matu, Gonzalez, Ispoglou, Duckworth, & Deighton, 2018). While some studies allow for, or even mimic this energy deficit (Bradbury et al., 2020) others attempt to distinguish the effect of hypoxia vs. hypoxia + energy deficit by maintaining energy balance (Brooks et al., 1991). This may partially explain why some people experience performance improvements following CHO ingestion in hypoxia (Fulco et al., 2005) whereas others see no improvements given the same level of hypoxia and the same exercise task (Fulco et al., 2007).

Future directions

Up to now, we have referred to supplementation merely as "CHO ingestion," but logistical considerations abound. For example, the timing of CHO intake is of particular relevance as recent evidence suggests that CHO absorption is compromised at high altitudes (O'Hara et al., 2019). By inhibiting

Table III. Future research directions investigating the influence of carbohydrate ingestion on fatigue development in hypoxia across various themes

Theme	Future research directions
Acclimatization & individualized responses	Do altitude natives differ in fatigue characteristics and responsiveness to carbohydrate supplementation vs. those ascending from sea level? (Fulco et al., 2007) Do women differ in fatigue characteristics and responsiveness to carbohydrate supplementation vs. men? How does duration of altitude exposure change fatigue characteristics and efficacy of carbohydrate ingestion? (Bradbury et al., 2020) How does hypoxia-related energy deficit influence carbohydrate response and should this energy deficit be replicated when using long-term exposure? (Bradbury et al., 2020)
Macronutrient utilization	Is macronutrient metabolism altered in hypoxia when relative exercise intensity is maintained vs. absolute exercise intensity? Are changes in macronutrient metabolism linearly related to ascending altitudes, e.g. as elevation increases does RER change in a stepwise, linear manner? How does an increases reliance on carbohydrate interact with possible reductions in insulin sensitivity to influence carbohydrate supplementation efficacy?
Severity of altitude	How does absorption, utilization, and carbohydrate efficacy change when transitioning through various levels of hypoxia? Does high altitude act as a hybrid of moderate and extreme altitude and influence both central and peripheral equally? (Amann et al., 2007) Is there an individual response to fatigue at altitude, e.g. do some experience accelerations in central fatigue at high, or even moderate, altitudes and does this influence the efficacy of CHO supplementation? In exercise scenarios that alter both peripheral and central pathways of fatigue (e.g. full body exercise, of prolonged duration, at moderate hypoxia), what fatiguing mechanism takes priority?
Content, Dose, and Timing	Does glycemic index alter the influence on fatigue? Application of current recommendations for dosage, as well as exercise duration to hypoxic setting. (Jeukendrup, 2014) Does ingesting carbohydrate in the minutes, hours, or days before hypoxic exposure offer varying influence on hypoxic response vs. carbohydrate ingestion during exercise? (Charlot et al., 2013) How does altitude exposure influence carbohydrate absorption and fatigue responses? (O'Hara et al., 2019)

CHO absorption altitude ascension may prioritize pre-hypoxic CHO loading instead of relying on CHO consumption during exercise. When applying these questions specifically to fatigue, further questions arise. Knowing that insulin regulates neurotransmitter precursors linked with central fatigue (Martin-Du Pan, Mauron, Glaeser, & Wurtman, 1982), how might hypoxia-mediated changes in insulin sensitivity and the insulin-response to CHO ingestion alter neurotransmitter concentrations and central drive? In addition to timing, the type and dosage of CHO exemplify additional areas of uncertainty. Though particulars on CHO supplementation have been established for sea level performance (Jeukendrup, 2014), hypoxia acts as an additional, unique variable and no doubt requires specific research determining how sea level recommendations uphold in hypoxic scenarios. A recent review on dietary recommendations when cycling at higher altitudes (Michalczyk, Czuba, Zydek, Zając, & Langfort, 2016) noted the difficulty in providing precise suggestions to athletes, particularly because of the wide range in elevations cyclists may travel to for training and competition. Therefore, recommendations on intake should also consider hypoxia severity (e.g. Is the physiological response to a glucose solution the same at sea level as in moderate altitude, high altitude, and extreme altitude?).

Finally, further complicating understanding for the role of CHO supplementation on fatiguing pathways in hypoxia, we must recognize that, instead of being an *either-or* phenomenon, fatigue is most likely a *both-and* occurrence, and peripheral mechanisms certainly influence central pathways. In Table III we offer specific questions regarding many of the aforementioned variables (acclimatization, substrate utilization, timing of CHO intake, etc.) which require clarification if CHO ingestion in hypoxia is to be optimized. Many of the more salient questions, such as those regarding absorption, utilization, and carbohydrate efficacy at various levels of hypoxia, are currently under investigation and additional data will

provide a more comprehensive understanding. These questions should be considered in the design of future studies on CHO ingestion, fatigue, and performance in hypoxia.

Conclusions

Work capacity is limited by fatigue originating from peripheral and central mechanisms. Peripheral mechanisms of fatigue include reductions in muscle glycogen as well as alterations in intramuscular metabolites such as NH_4^+, P_i, and K^+, whereas central fatigue is often associated with hypoglycemia, alterations in circulating amino acid concentrations, and arterial hypoxemia. Both peripheral and central pathways can be accelerated by hypoxia, further limiting work capacity.

Due to mechanistic overlaps between fatigue, hypoxia, and CHO oxidation, CHO supplementation has emerged as a potential approach for improving exercise tolerance in hypoxic environments. CHO supplementation should be considered in hypoxic settings specifically when the mechanisms of exercise- and hypoxia-induced fatigue align with CHO availability. At moderate altitudes, where peripheral fatigue dominates, increases in work capacity following CHO ingestion are likely accounted for by preservation of muscle glycogen and membrane excitability. Extreme altitude alters central drive and CHO intake can influence fatigue development under these conditions particularly by maintaining blood glucose. Ultimately, questions remain regarding the interaction between hypoxia, fatigue, and CHO. Future research will characterize the development of peripheral and central fatigue following CHO ingestion and exercise performance across varying degrees of altitude to address whether CHO supplementation contributes to the sweet taste of reaching the top of the mountain.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by National Heart, Lung, and Blood Institute: [grant number T32HL105346].

References

Amann, M., & Calbet, J. A. (2008). Convective oxygen transport and fatigue. *Journal of Applied Physiology*, *104*, 861–870.

Amann, M., Romer, L. M., Subudhi, A. W., Pegelow, D. F., & Dempsey, J. A. (2007). Severity of arterial hypoxaemia affects the relative contributions of peripheral muscle fatigue to exercise performance in healthy humans. *The Journal of Physiology*, *581*, 389–403.

Askew, E. W., Claybaugh, J. W., Hashiro, G. M., Stokes, W. S., Sato, A., & Cucinell, S. A. (1987). *Mauna Kea III: Metabolic effects of dietary carbohydrate supplementation during exercise at 4100 M altitude*. Natick, MA: Army Research Inst of Environmental Medicine.

Asmussen, E. (1971). Muscle metabolism during exercise in man. In B. Pernow (Ed.), *Muscle metabolism during exercise* (pp. 1–11). Boston, MA: Springer.

Bärtsch, P., & Saltin, B. (2008). General introduction to altitude adaptation and mountain sickness. *Scandinavian Journal of Medicine & Science in Sports*, *18*, 1–10.

Bourrilhon, C., Lepers, R., Philippe, M., Van Beers, P., Chennaoui, M., Drogou, C., … Gomez-Merino, D. (2010). Influence of protein – versus carbohydrate-enriched feedings on physiological responses during an ultraendurance climbing race. *Hormone and Metabolic Research*, *42*, 31–37.

Bradbury, K. E., Berryman, C. E., Wilson, M. A., Luippold, A. J., Kenefick, R. W., Young, A. J., & Pasiakos, S. M. (2020). Effects of carbohydrate supplementation on aerobic exercise performance during acute high altitude exposure and after 22 days of acclimatization and energy deficit. *Journal of the International Society of Sports Nutrition*, *17*, 1–5.

Brooks, G., Butterfield, G., Wolfe, R., Groves, B., Mazzeo, R., Sutton, J., … Reeves, J. (1991). Increased dependence on blood glucose after acclimatization to 4300 m. *Journal of Applied Physiology*, *70*, 919–927.

Butterfield, G. E., Gates, J., Fleming, S., Brooks, G. A., Sutton, J. R., & Reeves, J. T. (1992). Increased energy intake minimizes weight loss in men at high altitude. *Journal of Applied Physiology*, *72*, 1741–1748.

Caris, A. V., Da Silva, E. T., Dos Santos, S. A., Tufik, S., & Dos Santos, R. V. T. (2017). Effects of carbohydrate and glutamine supplementation on oral mucosa immunity after strenuous exercise at high altitude: A double-blind randomized trial. *Nutrients*, *9*(692).

Carvalho-Peixoto, J., Alves, R. C., & Cameron, L.-C. (2007). Glutamine and carbohydrate supplements reduce ammonemia increase during endurance field exercise. *Applied Physiology, Nutrition, and Metabolism*, *32*, 1186–1190.

Charlot, K., Pichon, A., Richalet, J.-P., & Chapelot, D. (2013). Effects of a high-carbohydrate versus high-protein meal on acute responses to hypoxia at rest and exercise. *European Journal of Applied Physiology*, *113*, 691–702.

Coggan, A. R., & Coyle, E. F. (1991). Carbohydrate ingestion during prolonged exercise: Effects on metabolism and performance. *Exercise and Sport Sciences Reviews*, *19*, 1–40.

Consolazio, C. F. (1969). Effects of high-carbohydrate diets on performance and clinical symptomatology after rapid ascent to high altitude. *Federation Proceedings*, *28*, 937–943.

Davis, J. M., Bailey, S. P., Woods, J. A., Galiano, F. J., Hamilton, M. T., & Bartoli, W. P. (1992). Effects of carbohydrate feedings on plasma free tryptophan and branched-chain amino acids during prolonged cycling. *European Journal of Applied Physiology and Occupational Physiology*, *65*, 513–519.

Debevec, T. (2017). Hypoxia-related hormonal appetite modulation in humans during rest and exercise: Mini review. *Frontiers in Physiology*, *8*(366).

Dramise, J., Inouye, C., Christensen, B., Fults, R., Canham, J., & Consolazio, C. (1975). Effects of a glucose meal on human pulmonary function at 1600-m and 4300-m altitudes. *Aviation, Space and Environmental Medicine*, *46*, 365–368.

Duhamel, T., Green, H., Stewart, R., Foley, K., Smith, I., & Ouyang, J. (2007). Muscle metabolic, SR Ca(2+)-cycling responses to prolonged cycling, with and without glucose supplementation. *Journal of Applied Physiology*, *103*, 1986–1998.

Fulco, C. S., Kambis, K., Friedlander, A., Rock, P., Muza, S., & Cymerman, A. (2005). Carbohydrate supplementation improves time-trial cycle performance during energy deficit at 4300-m altitude. *Journal of Applied Physiology*, *99*, 867–876.

Fulco, C. S., Zupan, M., Muza, S., Rock, P., Kambis, K., Payn, T., … Cymerman, A. (2007). Carbohydrate supplementation and endurance performance of moderate altitude residents at 4300 m. *International Journal of Sports Medicine*, *28*, 437–443.

Gandevia, S. C. (2001). Spinal and supraspinal factors in human muscle fatigue. *Physiological Reviews*, *81*, 1725–1789.

Garner, S., Sutton, J. R., Burse, R. L., McComas, A. J., Cymerman, A., & Houston, C. (1990). Operation Everest II: Neuromuscular performance under conditions of extreme simulated altitude. *Journal of Applied Physiology*, *68*, 1167–1172.

Garvican-Lewis, L. A., Sharpe, K., & Gore, C. J. (2016). Time for a new metric for hypoxic dose? *Journal of Applied Physiology*, *121*, 352–355.

Goodall, S., Ross, E. Z., & Romer, L. M. (2010). Effect of graded hypoxia on supraspinal contributions to fatigue with unilateral knee-extensor contractions. *Journal of Applied Physiology*, *109*, 1842–1851.

Griffiths, A., Shannon, O. M., Matu, J., King, R., Deighton, K., & O'Hara, J. P. (2019). The effects of environmental hypoxia on substrate utilisation during exercise: A meta-analysis. *Journal of The international Society of Sports Nutrition*, *16*(10).

Haseler, L. J., Richardson, R. S., Videen, J. S., & Hogan, M. C. (1998). Phosphocreatine hydrolysis during submaximal exercise: The effect of FIO_2. *Journal of Applied Physiology*, *85*, 1457–1463.

Hochachka, P., Stanley, C., Matheson, G., McKenzie, D., Allen, P., & Parkhouse, W. (1991). Metabolic and work efficiencies during exercise in Andean natives. *Journal of Applied Physiology*, *70*, 1720–1730.

Jeukendrup, A. (2014). A step towards personalized sports nutrition: Carbohydrate intake during exercise. *Sports Medicine*, *44*, 25–33.

Jeukendrup, A., Brouns, F., Wagenmakers, A., & Saris, W. (1997). Carbohydrate-electrolyte feedings improve 1 h time trial cycling performance. *International Journal of Sports Medicine*, *18*, 125–129.

Karelis, A. D., Smith, J. E. W., Passe, D. H., & Péronnet, F. (2010). Carbohydrate administration and exercise performance. *Sports Medicine*, *40*, 747–763.

Katayama, K., Amann, M., Pegelow, D. F., Jacques, A. J., & Dempsey, J. A. (2007). Effect of arterial oxygenation on quadriceps fatigability during isolated muscle exercise. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *292*, R1279–R1286.

Kayser, B., Narici, M., Binzoni, T., Grassi, B., & Cerretelli, P. (1994). Fatigue and exhaustion in chronic hypobaric hypoxia: Influence of exercising muscle mass. *Journal of Applied Physiology*, *76*, 634–640.

Kent-Braun, J. A., Fitts, R. H., & Christie, A. (2012). Skeletal muscle fatigue. *Comprehensive Physiology*, *2*, 997–1044.

Khong, T., Selvanayagam, V., Sidhu, S., & Yusof, A. (2017). Role of carbohydrate in central fatigue: A systematic review. *Scandinavian Journal of Medicine & Science in Sports*, *27*, 376–384.

Kjær, M., Hanel, B., Worm, L., Perko, G., Lewis, S. F., Sahlin, K., … Secher, N. H. (1999). Cardiovascular and neuroendocrine responses to exercise in hypoxia during impaired neural feedback from muscle. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *277*, R76–R85.

Liao, Y.-H., Mündel, T., Yang, Y.-T., Wei, C.-C., & Tsai, S.-C. (2019). Effects of periodic carbohydrate ingestion on endurance and cognitive performances during a 40-km cycling time-trial under normobaric hypoxia in well-trained triathletes. *Journal of Sports Sciences*, *37*, 1805–1815.

Little, J. P., Chilibeck, P. D., Ciona, D., Forbes, S., Rees, H., Vandenberg, A., & Zello, G. A. (2010). Effect of low-and high-glycemic-index meals on metabolism and performance during high-intensity, intermittent exercise. *International Journal of Sport Nutrition and Exercise Metabolism*, *20*, 447–456.

Lundby, C., & Van Hall, G. (2002). Substrate utilization in sea level residents during exercise in acute hypoxia and after 4 weeks of acclimatization to 4100 m. *Acta Physiologica Scandinavica*, *176*, 195–201.

Macdonald, J. H., Oliver, S. J., Hillyer, K., Sanders, S., Smith, Z., Williams, C., … Chichester, E. (2009). Body composition at high altitude: A randomized placebo-controlled trial of dietary carbohydrate supplementation. *The American Journal of Clinical Nutrition*, *90*, 1193–1202.

Martin-Du Pan, R., Mauron, C., Glaeser, B., & Wurtman, R. (1982). Effect of various oral glucose doses on plasma neutral amino acid levels. *Metabolism*, *31*, 937–943.

Matu, J., Gonzalez, J. T., Ispoglou, T., Duckworth, L., & Deighton, K. (2018). The effects of hypoxia on hunger perceptions, appetite-related hormone concentrations and energy intake: A systematic review and meta-analysis. *Appetite*, *125*, 98–108.

McFarland, R., & Forbes, W. (1940). The effects of variations in the concentration of oxygen and of glucose on dark adaptation. *Journal of General Physiology*, *24*, 69–98.

Meeusen, R., Watson, P., Hasegawa, H., Roelands, B., & Piacentini, M. F. (2006). Central fatigue. *Sports Medicine*, *36*, 881–909.

Merton, P. (1954). Voluntary strength and fatigue. *Journal of Physiology*, *123*(553), 553–564.

Michalczyk, M., Czuba, M., Zydek, G., Zając, A., & Langfort, J. (2016). Dietary recommendations for cyclists during altitude training. *Nutrients*, *8*(377).

Millet, G., Aubert, D., Favier, F., Busso, T., & Benoit, H. (2009). Effect of acute hypoxia on central fatigue during repeated isometric leg contractions. *Scandinavian Journal of Medicine & Science in Sports*, *19*, 695–702.

Millet, G. P., Faiss, R., & Pialoux, V. (2012). Point: Counterpoint: Hypobaric hypoxia induces/does not induce different responses from normobaric hypoxia. *Journal of Applied Physiology*, *112*, 1783–1784.

Millet, G. Y., & Lepers, R. (2004). Alterations of neuromuscular function after prolonged running, cycling and skiing exercises. *Sports Medicine*, *34*, 105–116.

Millet, G. Y., Muthalib, M., Jubeau, M., Laursen, P. B., & Nosaka, K. (2012). Severe hypoxia affects exercise performance independently of afferent feedback and peripheral fatigue. *Journal of Applied Physiology*, *112*, 1335–1344.

Mitchell, H. H., & Edman, M. (1949). *Nutrition and resistance to climatic stress; with particular reference to man*. Quartermaster Food and Container Institute for the Armed Forces: Illinois Univ at Urbana-Champaign.

Nybo, L. (2003). CNS fatigue and prolonged exercise: Effect of glucose supplementation. *Medicine & Science in Sports & Exercise*, *35*, 589–594.

O'Hara, J. P., Duckworth, L., Black, A., Woods, D. R., Mellor, A., Boos, C., … King, R. (2019). Fuel use during exercise at altitude in women with glucose-fructose ingestion. *Medicine & Science in Sports & Exercise*, *51*, 2586–2594.

Oliver, S. J., Golja, P., & Macdonald, J. H. (2012). Carbohydrate supplementation and exercise performance at high altitude: A randomized controlled trial. *High Altitude Medicine & Biology*, *13*, 22–31.

Orizio, C., Esposito, F., & Veicsteinas, A. (1994). Effect of acclimatization to high altitude (5050 m) on motor unit

activation pattern and muscle performance. *Journal of Applied Physiology*, *77*, 2840–2844.

Paris, H. L., Fulton, T. J., Chapman, R. F., Fly, A. D., Koceja, D. M., & Mickleborough, T. D. (2019). Effect of carbohydrate ingestion on central fatigue during prolonged running exercise in moderate hypoxia. *Journal of Applied Physiology*, *126*, 141–151.

Rasmussen, P., Dawson, E. A., Nybo, L., Van Lieshout, J. J., Secher, N. H., & Gjedde, A. (2007). Capillary-oxygenation-level-dependent near-infrared spectrometry in frontal lobe of humans. *Journal of Cerebral Blood Flow & Metabolism*, *27*, 1082–1093.

Romer, L. M., Haverkamp, H. C., Amann, M., Lovering, A. T., Pegelow, D. F., & Dempsey, J. A. (2007). Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *292*, R598–R606.

Romer, L. M., Haverkamp, H. C., Lovering, A. T., Pegelow, D. F., & Dempsey, J. A. (2006). Effect of exercise-induced arterial hypoxemia on quadriceps muscle fatigue in healthy humans. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *290*, R365–R375.

Slivka, D., Hailes, W., Cuddy, J., & Ruby, B. (2008). Caffeine and carbohydrate supplementation during exercise when in negative energy balance: Effects on performance, metabolism, and salivary cortisol. *Applied Physiology, Nutrition, and Metabolism*, *33*, 1079–1085.

Stellingwerff, T., Peeling, P., Garvican-Lewis, L. A., Hall, R., Koivisto, A. E., Heikura, I. A., & Burke, L. M. (2019). Nutrition and altitude: Strategies to enhance adaptation, improve performance and maintain health: A narrative review. *Sports Medicine*, *49*, 169–184.

Stewart, R., Duhamel, T., Foley, K., Ouyang, J., Smith, I., & Green, H. (2007). Protection of muscle membrane excitability during prolonged cycle exercise with glucose supplementation. *Journal of Applied Physiology*, *103*, 331–339.

Taylor, J. L., Amann, M., Duchateau, J., Meeusen, R., & Rice, C. L. (2016). Neural contributions to muscle fatigue: From the brain to the muscle and back again. *Medicine & Science in Sports & Exercise*, *48*, 2294–2306.

Taylor, A., Bronks, R., Smith, P., & Humphries, B. (1997). Myoelectric evidence of peripheral muscle fatigue during exercise in severe hypoxia: Some references to m. Vastus lateralis myosin heavy chain composition. *European Journal of Applied Physiology*, *75*, 151–159.

Townsend, N., Brocherie, F., Millet, G. P., & Girard, O. (2020). Central and peripheral muscle fatigue following repeated-sprint running in moderate and severe hypoxia. *Experimental Physiology.*, Online ahead of print.

Wilber, R. L., Stray-Gundersen, J., & Levine, B. D. (2007). Effect of hypoxic" dose" on physiological responses and sea-level performance. *Medicine & Science in Sports & Exercise*, *39*, 1590–1599.

Xu, K. Y., Zweier, J. L., & Becker, L. C. (1995). Functional coupling between glycolysis and sarcoplasmic reticulum Ca^{2+} transport. *Circulation Research*, *77*, 88–97.

Young, A. J., Margolis, L. M., & Pasiakos, S. M. (2019). Commentary on the effects of hypoxia on energy substrate use during exercise. *Journal of The international Society of Sports Nutrition*, *16*(28).