Nutrition, the brain and prolonged exercise

PHIL WATSON

School of Sport and Exercise Sciences, Loughborough University, Loughborough, UK

Abstract
Possible peripheral mechanisms of fatigue have been widely documented, including the depletion of muscle glycogen and the loss of body fluids. The notion that the brain may be intimately involved in the fatigue process is not a new one, but recently possible neurobiological mechanisms involved in this response have been investigated. Changes in central neurotransmission occur during exercise that may result in feelings of tiredness, lethargy, and a loss of motivation to continue exercise, contributing to the development of fatigue. There is evidence that manipulation of the neurotransmitters serotonin, dopamine, and noradrenaline, through the administration of pharmacological agents, may delay the onset of fatigue during prolonged exercise, particularly when performing in a warm environment. Supplementation with branched-chain amino acids and tyrosine can influence perceived exertion and some measures of mental performance, but the results of several apparently well-controlled laboratory studies have not demonstrated a positive effect on exercise capacity under temperate conditions. The ergogenic effects of carbohydrate and caffeine are well documented, but often little attention is paid to the central effects of these nutrients. Carbohydrate ingestion has been demonstrated to alter brain activity and cerebral metabolism, factors that may be important in the development of fatigue and the maintenance of skill performance. There is strong evidence for a positive effect of caffeine on exercise performance, with recent data highlighting the role of central adenosine as a mediator of this response.

Keywords: Branched-chain amino acids, carbohydrate, dopamine, neurotransmission, serotonin, tyrosine

Introduction
Textbook views of fatigue occurring during prolonged exercise typically place the primary site of fatigue within the periphery, with the depletion of muscle glycogen and the progressive loss of body fluids cited as key factors. Evidence has accumulated to suggest that events arising entirely within the central nervous system (CNS) can influence the sensation of fatigue and thus affect performance. The notion that the central nervous system is involved in the development of fatigue is not new. Early work conducted by Alessandro Mosso (1904) crudely demonstrated a reduced capacity to perform repeated muscle contractions following a mental effort, and resulted in the development of the term “mental fatigue” (Mosso, 1904). Since this work, many advances have been made to clarify the role of the central nervous system in the development of fatigue, as well as the possible neurobiological mechanisms involved.

Changes in the activity of several central neurotransmitter systems, including serotonin, dopamine, noradrenaline, and adenosine, have been implicated in the development of fatigue during physical activity (Table I). Much of this work has been based on evidence accumulated from studies employing pharmacological agents to alter brain neurotransmission, but the attraction of recent hypotheses is the potential for nutritional manipulation of CNS function to influence mood, the sensation of effort, and/or thermal stress (Table 1). If successful, this has the potential to benefit performance in sporting, occupational, and military settings. Strategies have been employed to manipulate central neurotransmission through changes in diet or supplementation with specific nutrients, including amino acids (branched-chain amino acids, tyrosine), carbohydrates, and caffeine.

The aim of this review is to highlight some of the possible neurobiological mechanisms of fatigue...
and examine whether nutritional interventions are capable of influencing the development of central fatigue during exercise.

Serotonin, branched-chain amino acids, and fatigue

Newsholme and colleagues (Newsholme, Acworth, & Blomstrand, 1987) proposed that the central serotonergic system may play a major role in the aetiology of exercise-induced fatigue. The original “central fatigue hypothesis” was based on evidence that prolonged exercise produced a marked elevation in brain serotonin (5-hydroxytryptamine: 5-HT) in some regions of the brain (Romanowski & Grabiec, 1974). Since increased central serotonergic activity has been associated with subjective sensations of lethargy and tiredness, Newsholme and colleagues (1987) suggested that this response would produce an altered perception of effort, perhaps a differing tolerance of pain/discomfort, and a loss of drive and motivation to continue exercise. This altered sensitivity to fatigue was suggested to result in a reduction in exercise performance (Newsholme et al., 1987).

This response was suggested to provide a link between changes in peripheral substrate availability and the central nervous system, with the shift in substrate mobilization occurring during prolonged exercise directly influencing brain neurotransmitter synthesis. There is a progressive increase in the rate of lipolysis as exercise continues, and circulating free fatty acids compete for binding sites on albumin, ultimately displacing the amino acid tryptophan from this protein carrier. The rate of serotonin synthesis is largely dependent upon the peripheral availability of the essential amino acid tryptophan when it is circulating free, not bound to albumin. An increase in the delivery of tryptophan to the central nervous system will increase serotonergic activity because the rate-limiting enzyme, tryptophan hydroxylase, is not saturated under physiological conditions. Furthermore, free tryptophan and the other large-neutral amino acids share the same carrier in order to pass across the blood–brain barrier, meaning that the plasma concentration ratio of free tryptophan to large-neutral amino acids is thought to be an important determinant of 5-HT synthesis. As the branched-chain amino acids (BCAA) – leucine, isoleucine, and valine – comprise the majority of the large-neutral amino acids found in the blood, the plasma concentration ratio of free tryptophan to BCAA is often referred to.

If a central fatigue mechanism does indeed operate and is mediated by serotonergic neurones, it would be expected that drugs able to affect the activity of these neurones would alter exercise performance. The importance of these pharmacological agents in the treatment of a wide variety of psychiatric disorders means an ever-increasing range of selective serotonergic drugs is being developed, offering a direct approach to study central fatigue mechanisms. Initial findings in humans supported the idea that drugs potentiating the actions of serotonin could reduce exercise performance (Wilson & Maughan, 1992). These findings were supported by early animal investigations showing that drugs that increase brain serotonin release (5-HT agonists) produce a dose-dependent reduction in exercise capacity, while reductions in brain serotonin (5-HT antagonists) have been demonstrated to delay fatigue and prolong exercise time (Bailey, Davis, & Ahlborn, 1992, 1993b). However, further evidence from human pharmacological studies investigating the importance of serotonin in the development of

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Role(s)</th>
<th>Nutritional supplementation</th>
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<tbody>
<tr>
<td>Adenosine</td>
<td>Acts both as a neurotransmitter and a neuromodulator, capable of inhibiting the release of many excitatory neurotransmitters. Dopamine and noradrenaline activity in particular are influenced by adenosine.</td>
<td>Caffeine: ↓ adenosine</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Plays an important role in motivation, memory, reward, and attention. Also involved in motor control and coordination.</td>
<td>Tyrosine: ↑ dopamine</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>Involved in the regulation of attention, arousal, and sleep-wake cycles as well as learning and memory, anxiety, pain, mood, and brain metabolism.</td>
<td>BCAA: ↓ dopamine(?) Tyrosine: ↑ noradrenaline</td>
</tr>
<tr>
<td>Serotonin (5-HT)</td>
<td>Involved in feelings of tiredness and lethargy, sleep, sensory perception, pain, appetite regulation, and thermoregulation. Implicated in many psychiatric disorders.</td>
<td>BCAA: ↓ noradrenaline (?) Tyrosine: ↑ serotonin</td>
</tr>
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Note: BCAA = branched-chain amino acids.
fatigue during prolonged exercise has been somewhat mixed, with most data failing to support the importance of serotonin in the fatigue process (Meeusen, Piacentini, Van den Eynde, Magnus, & De Meirleir, 2001; Pannier, Bouckaert, & Lefebvre, 1995; Strachan, Leiper, & Maughan, 2004).

As free tryptophan largely competes with BCAA for transport across the blood–brain barrier into the central nervous system, reducing the plasma concentration ratio of free tryptophan to BCAA through the provision of exogenous BCAA has been suggested to attenuate the development of central fatigue. Supplementation with BCAA has been suggested to enhance the physical and mental performance of male volunteers competing in either a marathon or a 30-km cross-country race (Blomstrand, Hassmen, Ekblom, & Newsholme, 1991a). While there is some additional evidence that the ingestion of BCAA influences ratings of perceived exertion (Blomstrand, Hassmen, Ek, Ekblom, & Newsholme, 1997) and mental performance (Blomstrand, Hassmen, & Newsholme, 1991b; Hassmen, Blomstrand, Ekblom, & Newsholme, 1994), the results of several apparently well-controlled laboratory studies have not demonstrated a positive effect on exercise capacity or performance. No ergogenic benefit has been reported during prolonged fixed-intensity exercise to exhaustion (Blomstrand, Andersson, Hassmen, Ekblom, & Newsholme, 1995; Blomstrand et al., 1997; Galiano et al., 1991; Struder et al., 1998; van Hall, Raaymakers, Saris, & Wagenmakers, 1995), prolonged time-trial performance (Hassmen et al., 1994; Madsen, MacLean, Kiens, & Christensen, 1996) or incremental exercise (Varnier et al., 1994).

Work by Mittleman and colleagues (1998) has provided some evidence to support a beneficial effect of BCAA ingestion and the apparent role of 5-HT in the fatigue process. A 14% increase in capacity to perform low-intensity (40% \( \dot{V}O_{2\text{max}} \)) exercise in a warm environment was reported following BCAA supplementation. While these data suggest that BCAA may limit central fatigue in the heat, two recent studies have failed to support these findings (Cheuvront et al., 2004; Watson, Shirreffs, & Maughan, 2004). Cheuvront and colleagues (2004) reported that BCAA, when combined with carbohydrate, did not alter physical or mental performance or the physiological response to exercise in the heat. Additionally, ingestion of a BCAA solution before, and during, prolonged exercise in glycogen-depleted individuals did not influence exercise capacity, rectal or skin temperature, heart rate, ratings of perceived exertion or perceived thermal stress despite a four-fold reduction in the plasma concentration ratio of free tryptophan to BCAA (Watson et al., 2004).

During prolonged exercise, the plasma concentration of ammonia (\( \text{NH}_3 \)) increases, largely as a result of the metabolism of BCAA, rather than the deamination of adenosine 5′-phosphate (AMP) to inosine monophosphate (IMP). This response is amplified by the ingestion of BCAA (van Hall et al., 1995; Watson et al., 2004). This increase in ammonia production is one possible explanation for a failure to observe a positive effect of BCAA supplements on physical and mental performance, despite an apparently good rationale for their use. Since \( \text{NH}_3 \) can readily cross the blood–brain barrier, excessive accumulation within the central nervous system may have a profound effect on cerebral function, potentially influencing cerebral blood flow, energy metabolism, synaptic transmission, and the regulation of various neurotransmitter systems. It is also possible that a failure to observe a benefit from BCAA ingestion may arise from a disturbance in catecholaminergic neurotransmission (see section below). The rationale behind BCAA supplementation is to block the uptake of tryptophan, but the possibility that BCAA ingestion will limit the transport of tyrosine into the central nervous system and consequently attenuate central dopamine and noradrenaline synthesis has not been considered.

**Catecholamines, tyrosine, and fatigue**

It is now evident that the response of the central nervous system to exercise involves the interplay of several different neurotransmitter systems (Meeusen, Watson, Hasegawa, Roelands, & Piacentini, 2006) and recently work in this area has looked to explore different transmitter systems and their influence on exercise performance. The catecholaminergic neurotransmitters, dopamine and noradrenaline, are of particular interest, as several agents that act on these systems clearly influence performance and are included on the WADA list of prohibited substances under the stimulant category.

Dopamine and noradrenaline have been implicated in arousal, motivation, reinforcement and reward, the control of motor behaviour, and mechanisms of addiction. Prolonged exercise results in a progressive increase in tissue content of dopamine and its metabolites in a number of cerebral regions (Bailey, Davis, & Ahlborn, 1992, 1993a; Chaoulloff et al., 1987; Heyes, Garnett, & Coates, 1988) and brain microdialysis data have demonstrated an elevation in extracellular dopamine (+28 to 50%) and noradrenaline (+60 to 66%) concentrations during exercise (Gerin & Privat, 1998; Meeusen et al., 1997). Although catecholaminergic neurotransmission is elevated during exercise, a series of animal studies conducted by Bailey and co-workers...
demonstrated that a marked fall in brain tissue dopamine content was apparent at the point of exhaustion (Bailey et al., 1992, 1993b). This finding has led to the suggestion that a depletion of central catecholamines is an important factor in fatigue during strenuous exercise.

The catecholaminergic neurotransmitters are synthesized through a shared metabolic pathway. Central dopamine and noradrenaline synthesis is reliant on the delivery of the non-essential amino acid tyrosine, in a similar manner to serotonin, but the synthesis and turnover of both dopamine and noradrenaline are highly dependent on neuronal discharge activity, with catecholamine synthesis significantly upregulated during arousal and stress. While there is some contention regarding the ability to manipulate central catecholamines through tyrosine supplementation, evidence does suggest that extracellular dopamine concentrations are responsive to increased precursor supply at rest and during conditions of stress (During, Acworth, & Wurtman, 1989). Tyrosine is found in protein-rich dietary sources, including chicken and milk, but unlike tryptophan it is a non-essential large-neutral amino acid (LNAA) that can also be synthesized from phenylalanine in the liver. Cerebral uptake of tyrosine, in a similar manner to serotonin, but the synthesis and turnover of both dopamine and noradrenaline are highly dependent on neuronal discharge activity, with catecholamine synthesis significantly upregulated during arousal and stress.

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Around the 1950s athletes began to realise that stimulants could enhance performance, leading to the widespread use of amphetamines in many endurance events, with a long history of abuse in cycling events in particular (e.g. Kurt Jensen, Tom Simpson, Jan Ullrich). There is good evidence that amphetamine, a potent agent that increases brain dopamine activity, can enhance one’s capacity to perform exercise in a dose-dependent manner (Chandler & Blair, 1980; Gerald, 1978). Amphetamines are a close analogue of dopamine and noradrenaline, which produce a marked elevation in extracellular dopamine concentrations through the stimulation of dopamine release from storage vesicles, inhibition of dopamine re-uptake, and the inhibition of dopamine metabolism. These positive findings have led to the widespread use of amphetamines in many endurance events, with a long history of abuse in cycling events in particular.

Further evidence for a role of dopamine in the development of central fatigue is provided by studies investigating intracranial stimulation of the ventral tegmental area. This region of the brain is dominated by dopaminergic projections, with selective stimulation of this area demonstrated to motivate rats to perform a variety of tasks, and to run ~50% longer when compared with the use of electric shock (Burgess, Davis, Borg, & Buggy, 1991). Taken together, these data clearly support a strong role for central catecholamines in the fatigue process.

Despite the apparent link between fatigue and catecholaminergic neurotransmission, relatively little work has assessed the effects of dopamine and noradrenaline manipulation on exercise capacity in humans. This may relate to the relatively limited number of safe pharmacological agents available to influence central catecholamine concentrations, and the belief that the provision of tyrosine does not markedly alter dopamine and noradrenaline synthesis. Despite an apparently strong rationale, in a recent series of studies Piacentini and colleagues reported no change in performance following the acute administration of a noradrenaline re-uptake inhibitor (Piacentini et al., 2002b), a dual 5-HT and noradrenaline re-uptake inhibitor (Piacentini, Meeusen, Buyse, De Schutter, & De Meirleir, 2002a), or a dual dopamine and noradrenaline re-uptake inhibitor (Piacentini, Meeusen, Buyse, De Schutter, & De Meirleir, 2004) in temperate conditions.

Evidence of an ergogenic benefit of tyrosine supplementation during prolonged exercise is also limited at present. Struder and colleagues (1998) failed to observe any change in the capacity to perform prolonged exercise following the ingestion of a 20 g dose of tyrosine immediately before and during exercise. These data are supported by a recent report showing no effect on time-trial performance following ingestion of a smaller dose of 25 mg/kg (Chinevere, Sawyer, Creer, Conlee, & Parcell, 2002). Additionally, tyrosine supplementation had no measurable effect on endurance, muscle strength or anaerobic power (Sutton, Coll, & Deuster, 2005). Although evidence for an effect of tyrosine on physical performance is limited, stress-related decrements in mood and task performance are reported to be attenuated by tyrosine supplementation (Owasso, Neri, & Lamberth, 1992). Several studies have also indicated that tyrosine ingestion improves stress-induced cognitive and behavioural deficits, in particular working memory, tracking, and stress-sensitive attentional focus tasks (Banderet & Lieberman, 1989; Deijen, Wientjes, Vullings, Cloin, & Langefeld, 1999; Dollins, Krock, Storm, Wurtman, & Lieberman, 1995; Neri et al., 1995; Shurtleff, Thomas, Schrot, Kowalski, & Harford, 1994; Sutton et al., 2005). As many sports are highly dependent on the successful execution of fine and gross motor skills, the possibility that tyrosine ingestion may attenuate the loss in cognitive function that occurs during the later stages of exercise would be desirable, despite no apparent benefit to physical performance.
Part of the apparent lack of consistency in published studies may relate to variations in exercise intensity and duration, but also to the environmental conditions in which exercise was performed. While fatigue during prolonged exercise in temperate conditions is typically associated with the depletion of muscle glycogen stores, it has been suggested that fatigue during prolonged exercise in the heat is mediated by events arising within the central nervous system. There is a strong body of evidence to suggest that hyperthermia exerts a profound effect on several aspects of CNS function, including brain activity, voluntary muscle activation, and motivation to continue exercise (Nielsen & Nybo, 2003). It is possible that this central response may serve as a protective mechanism to limit further heat production from the exercising muscles before serious damage is caused to the body’s tissues.

Recent data strongly suggest that catecholaminergic neurotransmission may act as an important neurobiological mediator of fatigue under conditions of heat stress. While administration of a dopamine/noradrenaline agonist (bupropion) does not appear to influence exercise performance in temperate conditions (Piacentini et al., 2004; Watson et al., 2005), a clear benefit has been reported when exercise was completed in warm environmental conditions. Subjects first completed 60 minutes of fixed intensity exercise at 55% W\text{max}, immediately followed by a time trial lasting approximately 40 minutes, exercise performance in the heat was 9% faster when Bupropion was taken prior to exercise (Watson et al., 2005). Preliminary evidence also suggests that ritalin, a specific dopamine agonist, can also markedly enhance exercise performance in warm, but not temperate, conditions (Roelands et al., 2006).

It is possible that Bupropion and ritalin administration in the heat acts on central neurotransmission to maintain motivation and arousal, enabling individuals to continue to sustain a high power output despite reaching core temperatures normally associated with the cessation of exercise. Individuals attained higher core temperatures during the later stages of exercise when Bupropion and ritalin were administered, and this effort occurred without any apparent change in the participants’ perceived exertion or thermal sensation. It is possible that this drug may enable an individual to dampen or override inhibitory signals arising from the central nervous system to cease exercise due to hyperthermia, allowing a high power output to be maintained. This raises the question of whether the use of these agents, while enhancing exercise performance, increases the risk of developing life-threatening heat illness.

**Caffeine, brain adenosine, and fatigue**

In recent years, the role of central adenosine has been examined through its association with caffeine. The ergogenic effect of caffeine was originally thought to be mediated through an increase in fat oxidation rate and altered metabolic enzyme activity and ion handling within the muscle (Graham, 2001). Subsequent work has largely failed to provide convincing support for these mechanisms, leading to the suggestion that the effects of caffeine supplementation may be largely centrally mediated. Caffeine is a potent adenosine antagonist that freely crosses the blood–brain barrier. The caffeine molecule is structurally similar to that of the neurotransmitter adenosine, meaning it binds to adenosine receptors without activating them, thus producing a marked reduction in central adenosine activity. As such, adenosine acts centrally both as a neurotransmitter and a neuromodulator, capable of inhibiting the release of many excitatory neurotransmitters, with dopamine and noradrenaline activity particularly affected. Increased adenosine within the brain is associated with decreased wakefulness and vigilance and generally lowered motor activity (Cooper, Bloom, & Roth, 2003), with the exact opposite response observed following caffeine ingestion (McLellan et al., 2005).

Unlike many nutritional supplements touted to enhance performance, there is little doubt that caffeine produces an ergogenic effect under most exercise conditions (Graham, 2001). While an optimal dose is still perhaps unclear, evidence suggests that doses as low as 3 mg per kilogram of body mass ingested before exercise can be effective at prolonging exercise time to exhaustion (Pasman, van Baak, Jeukendrup, & de Haan, 1995) and improving race performance (Bridge & Jones, 2006). Similarly, caffeine has been demonstrated to influence several measures of cognitive function, including alertness, concentration, and reaction time, particularly when operating under conditions of stress and fatigue (McLellan et al., 2005). These effects are not only potentially beneficial to the sports performer, but may have application in occupational and military settings where caffeine supplementation has also been widely employed.

Given the widespread use of caffeine by many individuals, it is clear that the level of habitual intake may be an important factor to consider when undertaking caffeine supplementation with the view to enhance performance. Regular exposure to caffeine produces an adaptation to the continual presence of the drug, resulting in an increased expression of adenosine receptors in the central nervous system (Green & Stiles, 1986). This increase in the number of the adenosine receptors...
increases sensitivity to adenosine, with two primary consequences: the stimulatory effects of caffeine are substantially reduced, a response known as tolerance adaptation. Secondly, as these adaptive responses to caffeine make individuals more sensitive to adenosine, a reduction in caffeine intake increases the normal physiological effects of adenosine, resulting in unwelcome withdrawal symptoms in tolerant users (Holtzman et al., 1991).

Despite the many studies investigating the effects of caffeine on performance and the physiological response to exercise, little work has specifically examined the central effect of caffeine ingestion. This was elegantly addressed in a study by Davis et al. (2003), in which exercise capacity was increased following an infusion of caffeine into the brain of rodents. A marked reduction in exercise capacity was apparent when an adenosine agonist was injected centrally, and this response was attenuated when this drug was co-injected with caffeine. These data suggest a role for adenosine in the development of fatigue, perhaps indirectly through the inhibition of excitatory neurotransmitters, including dopamine and noradrenaline.

**Carbohydrate, the brain, and fatigue**

Depletion of substrates within the central nervous system and/or alterations in the level of certain neurotransmitters are potential mechanisms underlying the decline in central activation during sustained muscle contraction. Maintenance of blood glucose concentration is important for the continuation of endurance exercise at a given exercise intensity. Supplementation of carbohydrate results in a greater uptake of blood glucose by the exercising muscles, thereby preserving a high rate of carbohydrate oxidation late in exercise when muscle glycogen concentrations are low (Coyle, 1992). The beneficial effect of glucose supplementation during prolonged exercise could also relate to increased (or maintained) substrate delivery for the brain.

Exercise-induced hypoglycaemia has been reported to reduce brain glucose uptake and overall cerebral metabolic rate (Nybo, Moller, Pedersen, Nielsen, & Secher, 2003), and is associated with a marked reduction in voluntary activation during sustained muscular contractions (Nybo, 2003). This reduction in CNS activation was abolished when euglycaemia was maintained. Carbohydrate ingestion also attenuated losses of mental function observed following high-intensity intermittent exercise, mimicking that encountered during many team sports, with improvements in time to volitional exhaustion, maintenance of sprint performance, and vertical jump height being observed (Winnick et al., 2005). Recent work has also focused on the effects of carbohydrate supplementation on measures of CNS fatigue, assessed largely through the performance of skills-based tasks and psychological inventories. Ingestion of carbohydrate before and during exercise has been reported to attenuate losses in the performance of whole-body motor skills tasks (Welsh, Davis, Burke, & Williams, 2002; Winnick et al., 2005). Animal studies suggest that glucose plays an important role in the regulation of central neurotransmission, and alterations in extracellular glucose concentrations have been demonstrated to have a marked influence on 5-HT release and re-uptake during exercise and recovery (Bequet, Gomez-Morino, Berthelot, & Guezennec, 2002).

Carbohydrate feeding suppresses lipolysis, consequently lowering the circulating concentration of plasma free fatty acids. Recognizing this, Davis et al. (1992) suggested carbohydrate ingestion as a means of reducing cerebral tryptophan uptake. A five- to seven-fold increase in the plasma concentration ratio of free tryptophan to BCAA was reported under placebo conditions. Supplementation with a 6% or 12% carbohydrate solution attenuated the increase in plasma free fatty acids and free tryptophan, reducing the plasma concentration ratio of free tryptophan to BCAA in a dose-dependent manner. Exercise capacity during carbohydrate trials was increased over the placebo, suggesting that carbohydrate ingestion is an effective means of delaying the onset of central fatigue, but it is difficult to separate the contribution of central factors from the widely reported benefits of carbohydrate at attenuating peripheral fatigue. As many amino acid studies administered BCAA in combination with carbohydrate, this practice may have masked any potential performance effect.

In addition to changes in circulating blood glucose, the possibility that the depletion of brain glycogen may be important to the development of fatigue during strenuous exercise has recently been explored. The store of glycogen found in the brain is typically overlooked due to its small size (0.5–1.5 g), but as this is a dynamic store with a high rate of turnover, any disturbance could have a marked influence on neuronal function. A fall in the cerebral oxygen to carbohydrate uptake ratio, determined using arterial–venous difference across the brain, has been reported following exhaustive exercise (Dalsgaard, Ide, Cai, Quistorff, & Secher, 2002). This suggests that glucose and lactate are being taken up by the brain in excess of oxygen, possibly to replenish brain glycogen stores or contribute to the de novo synthesis of neurotransmitters (Nybo & Secher, 2004). A reduction in brain glycogen has also been implicated in the homeostatic drive to sleep (Kong et al., 2002), supporting a possible role in the fatigue process.
A novel approach to the study of the central effect of CHO supplementation was recently presented by Carter and colleagues (Carter et al., 2004a). Failure to observe a benefit of glucose infusion on time trial performance (Carter et al., 2004b), prompted this group to suggest an alternative mechanism for the ergogenic effect of CHO centred around the activation of CHO receptors found in the mouth. Carter et al. reported a 3% (PLA 61.4 ± 1.6 min; CHO 59.6 ± 1.5 min) increase in performance following the rinsing of a maltodextrin solution around the mouth before and during exercise. No solution was actually ingested during the protocol, suggesting that this performance benefit may have been mediated through direct communication between receptors present in the mouth and the brain. This concept is supported by work investigating brain activity following the ingestion of a bolus of glucose (Liu et al., 2000). Ingestion of glucose has been demonstrated to result in a marked increase in brain activation around the hypothalamus, occurring immediately after ingestion. A second spike in activity was also observed 10 minutes following ingestion, presumably occurring as the substrate enters the circulation. These findings are very novel and suggest an interesting mechanism of action. Further investigation of CHO receptors in the mouth is certainly warranted.

**Fluids, cerebral circulation, and fatigue**

Prolonged exercise in a warm environment results in a significant loss of hypotonic fluid, in the form of sweat secreted on to the skin surface, to assist in the dissipation of heat. Little research has investigated the effects of exercise-induced dehydration on the brain, but evidence suggests that alertness, concentration, and performance of cognitive tasks are reduced at relatively mild levels of dehydration (Maughan, 2003). These findings suggest a disturbance in brain function with dehydration, although the underlying neurobiological mechanism for this response is not clear at present.

Exercise in a warm environment requires not only an increase in blood flow to the active muscles, but also a marked elevation in skin blood flow to facilitate heat loss. This alteration in blood flow results in competition between the muscle, skin, and other areas of the body for a limited cardiac output, with hepatic and renal blood flow typically reduced to compensate. Cerebral blood flow is increased during exercise, but a progressive decline as exercise continues has been reported with hyperthermia compared with exercising under control conditions (Nybo & Nielsen, 2001). The consequence of this response is not clear at present, but it does not appear to influence cerebral metabolic rate.

Plasma hyperosmolality, resulting from exercise in the heat, causes a shift of fluids from interstitial and intracellular spaces to defend blood volume, thus helping to maintain blood flow to the working muscle and skin (Nose, Mack, Shi, & Nadel, 1988). It is also clear that an elevation in extracellular osmolality can exert a marked influence on brain volume. The net movement of fluid across the blood–brain barrier, and shrinkage of the barrier's structural endothelial cells, may also result in a transient opening of the tight junctions of the blood–brain barrier, causing increased exchange of substances between the periphery and the central nervous system. The relative impermeability of the blood–brain barrier helps to maintain a stable environment for the brain by regulating exchange between the central nervous system and the extracerebral environment. As the blood–brain barrier plays a vital role in the regulation of exchange between the central nervous system and the peripheral circulation, either acute or chronic changes in the permeability of this barrier may alter the entry or exit of species likely to alter brain function and may influence exercise performance.

There is some evidence that prolonged exercise may lead to increased permeability of the blood–brain barrier. Animal studies have established that the blood–brain barrier can be widely disrupted following 30 min of forced swimming exercise (Sharma, Cervos-Navarro, & Dey, 1991). Additionally, a recent human study reported an increase in circulating serum S100β, a proposed peripheral marker of blood–brain barrier permeability, following prolonged exercise in a warm environment. This response was abolished by the ingestion of water in a volume sufficient to maintain euhydration during exercise (Watson, Black, Clark, & Maughan, 2006). At present, the functional consequences of changes in blood–brain barrier permeability during exercise are not clear, but marked change in permeability during exercise may modify the transport kinetics of neurotransmitter precursors and other metabolites or allow the accumulation of unwanted substances in the central nervous system.

**Conclusions**

In his classic text, *The Physiology of Muscular Exercise*, Francis Bainbridge (1919) stated, “It has long been recognised that the main seat of fatigue after muscular exercise is the central nervous system... There appear, however, to be two types of fatigue, one arising entirely within the central nervous system, the other in which fatigue of the muscles themselves is superadded or sends signals to the nervous system”. Evidence has since accumulated to support this hypothesis, with changes in central
neurotransmission, cerebral metabolism, and blood flow all potentially involved in the fatigue process. It is clear that a considerable amount of work is still required to elucidate the exact role and the relative contribution of these factors to the development of fatigue during exercise.

An attraction of the brain neurotransmission hypothesis of central fatigue is the possibility that the activity of central neurotransmitters can be manipulated through changes to diet and nutritional supplements. Any pharmacological or nutritional strategies that have the potential to improve exercise performance by delaying the onset of fatigue are likely to be exploited by athletes. Although this is an exciting prospect, caution should perhaps be exercised given that central regulation of effort and drive to continue an activity is likely to be in place to protect the body from harm. It is possible that methods of manipulating central fatigue may enable an individual to dampen or override inhibitory signals arising from the central nervous system to cease exercise, allowing higher power outputs to be maintained or exercise to be continued for longer than would have otherwise been possible. The danger of this situation was apparent during the 1967 Tour de France cycle race, where the British cyclist Tom Simpson collapsed and died from heat-related illness on the Mont Ventoux climb after taking amphetamines to enhance his performance.

References


