CNS Fatigue and Prolonged Exercise: Effect of Glucose Supplementation

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ABSTRACT

NYBO, L. CNS Fatigue and Prolonged Exercise: Effect of Glucose Supplementation. Med. Sci. Sports Exerc., Vol. 35, No. 4, pp. 589–594, 2003. Introduction: Ingestion of carbohydrates during prolonged exercise may improve endurance, whereas an insufficient supply of glucose results in hypoglycemia and fatigue. Fatigue, defined as a loss of force-generating capacity, may develop for a variety of reasons and involve both central and peripheral factors. This study investigated whether CNS activation of the skeletal muscles was affected by prolonged exercise with or without glucose supplementation. Methods: Voluntary force production and central activation ratios, assessed by the twitch interpolation technique, were determined during a 2-min sustained maximal knee extension in eight endurance-trained males in a baseline condition and immediately after 3 h of cycling randomized to be with or without glucose supplementation. Results: The exercise bout without glucose supplementation (placebo trial) reduced the blood glucose concentration from 4.5 ± 0.2 to 3.0 ± 0.2 mM, whereas blood glucose homeostasis was maintained during the glucose trial. The average force during the sustained maximal voluntary muscle contraction was 248 ± 23 N at baseline, 222 ± 20 N in the glucose trial, and 197 ± 21 N in the placebo trial (P < 0.05 between conditions). In the placebo trial, the lowered force production was accompanied by a reduced level of CNS activation compared with the other two conditions (P < 0.05), whereas the central activation ratios were similar in the glucose trial as compared with baseline. Conclusion: Exercise-induced hypoglycemia attenuates CNS activation during a sustained maximal muscle contraction, whereas central activation appears to be unaffected by 3 h of moderately intense exercise in endurance-trained athletes when euglycemia is maintained by carbohydrate ingestion. Key Words: ELECTRICAL STIMULATION, HYPOGLYCEMIA, MAXIMAL VOLUNTARY CONTRACTION, NEUROMUSCULAR ACTIVATION

Dynamic exercise is associated with an enhanced glucose uptake by the active skeletal muscles (28), and blood glucose homeostasis may be threatened if the exercise bout is of long duration (8,9). Carbohydrate supplementation during such conditions can prevent hypoglycemia and increase time to exhaustion (7). The ergogenic effect of glucose supplementation is often ascribed to a higher uptake of blood glucose by the exercising muscles, thereby allowing a sufficient carbohydrate oxidation late in exercise when muscle glycogen levels are low (9). However, failure of the CNS in providing an optimal neural drive to the contracting skeletal muscles may contribute to the development of fatigue during prolonged exercise (24,26). Oxidation of glucose from the bloodstream is under normal circumstances the only energy source for the CNS, and a continuous systemic supply is essential, as glucose storage in neuronal tissue is limited (27). During exercise, the brain may also use circulating lactate as a metabolic fuel, but this appears to be relevant only at high work intensities when the arterial lactate concentration is significantly increased (17) and not during prolonged exercise where the arterial lactate concentration normally remains low (25). During euglycemia, the cerebral metabolic rate of glucose is not limited by endothelial glucose transport (27), but glucose transport across the cerebral capillaries may become rate limiting during hypoglycemia. Thus, the cerebral glucose uptake declines when the arterial glucose concentration falls below a critical point of ~ 3.6 mM (4), and further reductions in the blood glucose concentration are associated with cognitive dysfunction as indicated by impaired performance in neuropsychological tests (1). The effect of exercise-induced hypoglycemia on the ability of the CNS in activating the skeletal muscles has not been evaluated, but the idea that carbohydrate availability for the brain is important in maintaining an adequate neural drive to the muscles is supported by the finding that glucose infusion directly in the carotid artery can delay fatigue in exercising dogs (20).

The aim of this study was to investigate how prolonged exercise with or without glucose supplementation would affect neuromuscular activation. A sustained maximal voluntary muscle contraction (MVC) was therefore performed immediately after 3 h of cycling where subjects either were supplemented with a glucose drink and remained euglycemic or received an artificially sweetened placebo drink and developed hypoglycemia. The relative importance of central and peripheral factors contributing to the development of
fatigue was investigated by superimposing an electrical stimulation on the voluntary contraction and determining the level of CNS activation during the sustained MVC (19).

**METHODS**

**Subjects.** The eight endurance-trained males who participated in the study had a mean (±SE) age of 27 ± 2 yr, height of 182 ± 3 cm, weight of 75 ± 3 kg, and a \( VO_{2}\text{max} \) of 66 ± 2 mL·kg\(^{-1}\)·min\(^{-1}\). The study was approved by the Ethics Committee of Copenhagen and Frederiksberg (KF 01-135/00), and the subjects gave their written informed consent to participate in the experiments. The subjects were, however, not provided with any information about the contents of the two drinks, and they were kept naive to the purpose of the study.

**Experimental protocol.** On two occasions, the subjects cycled on an ergometer (Monark 829E, Varberg, Sweden) for 3 h at a work rate that corresponded to 60% of their predetermined \( VO_{2}\text{max} \) either with or without glucose supplementation. The subjects were asked to abstain from coffee, tea, and other caffeine-containing items for the last 24 h before the experiment, and they were instructed to complete the same training on the day before the experiment (1 h of low-intensity cycling). On the experimental day, the subjects arrived at the laboratory in the morning after an overnight fast. An HR monitor (Polar Electro, Kempele, Finland) was attached to the subject, and a catheter was inserted in a superficial vein on the dorsal side of the hand. Arterialized venous blood samples (heated hand technique, oxygen saturation between 90 and 95%) were obtained at rest and after 1, 2, and 3 h of exercise. Blood samples were stored on ice and analyzed within 30 min on an ABL 615 apparatus (Radiometer, Copenhagen, Denmark). Preexercise MVC was determined as the best of three maximal voluntary isometric contractions with the knee extensors. The 3 h of cycling were then completed at a constant power output of 200 ± 8 W at 90 ± 3 rpm. In one trial (glucose trial), the subjects ingested a 6% glucose polymer (malto-dextrins, Maxim, Geffen, Holland) every 15th minute, whereas in the other trial (placebo trial) the subjects received an equal volume of a noncaloric placebo drink sweetened with cyclamate and saccharine. A total of 200 ± 10 g of carbohydrate was ingested in the glucose trial and the total volume of ingested fluid was 3.3 ± 0.2 L in both trials. The treatment order was randomly assigned and counterbalanced across subjects. HR was monitored and the subject’s RPE (3) was assessed every 20th minute.

**Sustained maximal knee extensions.** Approximately 20 s after the 3 h of cycling, the subjects were seated in a custom-made chair in a standardized position with their knees flexed 90°, and their position secured with straps around the waist and thighs. A sustained maximal isometric knee extension was then performed with the right leg for 2 min, and the subjects were verbally encouraged to make a maximal effort all of the time. The external force of the knee extensor was measured as the changes in voltage detected by a strain gauge dynamometer placed between the ankle and the chair. The dynamometer was calibrated with weights of known mass, voltage changes were converted to force (expressed in N), and the percentage of the preexercise MVC was calculated. Electrical stimulation (EL) was superimposed at 30, 60, 90, and 120 s of the sustained contraction to assess the degree of voluntary activation. The anode (12 × 7 cm) was positioned midway between the superior aspect of the greater trochanter of the right leg and the inferior border of the iliac crest (hip flexed 90°), while the ball-shaped cathode-stimulating electrode (3 cm in diameter) was positioned over the femoral nerve. The electrical stimulus used throughout the protocol was adjusted before exercise based on the peak force during a contraction evoked by a 250-ms train of stimuli delivered at 100 Hz. The stimulus intensity was ~20% higher than that eliciting a maximal twitch, and it was maintained constant across trials. Optimal positioning of the stimulating electrode was also determined before the cycle bout and identical repositioning on subsequent trials was attempted by measuring the distance from the cathode to anatomical landmarks on the subject’s pelvis. The voluntary activation percentage was calculated as MVC divided by the total muscle force, where the total muscle force was the sum of the MVC plus force from the superimposed electrical stimulation. Maximal voluntary force and the level of central activation were also determined in a baseline condition, where the knee extensor protocol was preceded by 15 min of warm-up (cycling at the same workload as in the exercise trials).

**Statistical analysis.** One- and two-way (time-by-trial) repeated measures ANOVA were performed to evaluate differences between and within trials. After a significant \( F \) test, pairwise differences were identified using Tukey’s honest significant difference (HSD) post hoc procedure. The significance level was set at \( P < 0.05 \). Data are presented as means ± SE unless otherwise indicated.

**RESULTS**

The blood glucose concentration was similar at rest on the two experimental days (4.5–4.6 ± 0.2 mmol·L\(^{-1}\)), and this blood glucose level was maintained throughout the 3 h of cycling on the day with glucose supplementation. In contrast, the blood glucose concentration decreased continuously during the trial without glucose supplementation to reach a value of 3.0 ± 0.2 mmol·L\(^{-1}\) at the end of exercise (Fig. 1A). The blood lactate concentration was not different in the two trials, and it remained at 1.2–1.4 mmol·L\(^{-1}\) throughout the cycling exercise (Fig. 1B). The hemoglobin and Na\(^+\) concentrations remained stable during exercise at 9.2 ± 0.2 mmol·L\(^{-1}\) and 139 ± 1 mmol·L\(^{-1}\) in both trials, indicating that hydration status was maintained and equal on the two days. The HR gradually increased from 132 ± 3 beats·min\(^{-1}\) at 20 min to 144 ± 4 beats·min\(^{-1}\) at the end of exercise with a similar response across trials.

The RPE values were similar during the first 2 h of exercise in the two trials. But, during the last hour of cycling the RPE increased to 16 ± 1 in the hypoglycemic trial,
whereas it only reached a value of 13 ± 1 in the euglycemic trial (Fig. 1C).

During the sustained MVC, the average force production was reduced from 222 ± 20 N in the glucose trial to 197 ± 21 N in the placebo trial ($P < 0.05$), and both postexercise values were significantly lower than the baseline value of 248 ± 23 N. Of note, the force was similar at the onset of the maximal contraction in the placebo and glucose trials, and the lower average force production in the placebo trial was mainly the result of an impaired voluntary force production during the last half of the sustained MVC (Fig. 2A). The reduced voluntary force development during the placebo trial was associated with a significantly lower voluntary activation percentage at 60, 90, and 120 s of contraction compared with the other two conditions, whereas the level of central activation was similar in the glucose trial compared with the baseline situation (Fig. 2B). Total muscle force (MVC + EL) did not differ between the placebo and glucose trial (Table 1), and EL nerve stimulation of the relaxed muscle applied 15 s after termination of the sustained MVC elicited a similar force in the placebo trial (102 ± 8 N) as compared to the glucose trial (98 ± 10 N).

DISCUSSION

The present results demonstrate that in endurance-trained subjects the development of hypoglycemia during prolonged exercise was associated with an impaired neuromuscular performance during a sustained contraction, and the lower force production seemed to be somewhat related to
TABLE 1. Voluntary and electrically evoked forces during 2-min maximal isometric knee extension performed after 3 h of cycling randomized to be with or without carbohydrate supplementation.

<table>
<thead>
<tr>
<th></th>
<th>MVC (N)</th>
<th>MVC+EL (N)</th>
<th>Decline in Voluntary Force (%)</th>
<th>Decline in Total Muscle Force (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>529 ± 35</td>
<td>538 ± 34</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>30 s</td>
<td>248 ± 30</td>
<td>278 ± 27</td>
<td>53 ± 4</td>
<td>48 ± 5</td>
</tr>
<tr>
<td>60 s</td>
<td>139 ± 24*</td>
<td>187 ± 21</td>
<td>74 ± 3*</td>
<td>65 ± 4</td>
</tr>
<tr>
<td>90 s</td>
<td>121 ± 23*</td>
<td>176 ± 22</td>
<td>77 ± 3*</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>120 s</td>
<td>108 ± 9*</td>
<td>155 ± 7</td>
<td>80 ± 2*</td>
<td>71 ± 2</td>
</tr>
<tr>
<td><strong>Glucose trial</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preexercise</td>
<td>524 ± 38</td>
<td>535 ± 36</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>30 s</td>
<td>274 ± 32</td>
<td>291 ± 31</td>
<td>47 ± 2</td>
<td>46 ± 3</td>
</tr>
<tr>
<td>60 s</td>
<td>161 ± 18</td>
<td>184 ± 15</td>
<td>69 ± 3</td>
<td>66 ± 3</td>
</tr>
<tr>
<td>90 s</td>
<td>144 ± 19</td>
<td>171 ± 17</td>
<td>72 ± 3</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>120 s</td>
<td>142 ± 18</td>
<td>168 ± 18</td>
<td>72 ± 3</td>
<td>69 ± 3</td>
</tr>
</tbody>
</table>

Values are mean ± SE for eight subjects. * Significantly different from the trial with glucose supplementation (P < 0.05). MVC is the maximal voluntary force while MVC+EL represents the force that was evoked when electrical stimulation was superimposed on the voluntary contraction. The decline in voluntary force and the decline in total muscle force are calculated as 1 − (force during the sustained knee extension/ preexercise force).

“central fatigue.” Thus, the voluntary activation percentage and the average force production were significantly lower during the sustained muscle contraction in the placebo trial as compared with the glucose trial. However, it should be considered that the same muscle force was developed at the onset of the isometric contraction, indicating that hypoglycemia impairs the ability to sustain a high neural drive to the muscles rather than affecting the ability to mobilize maximal force for a limited period of time. In addition to the hypoglycemia-induced CNS fatigue, it appears that the lower force production after the prolonged exercise bouts also involve peripheral fatigue, as the average force was lower in the glucose trial compared with baseline although the level of CNS activation was similar in these two conditions.

The present protocol with 3 h of constant-load cycling in overnight fasting endurance-trained athletes induced a lowering of the blood glucose concentration to 3 mmol·L⁻¹ during the trial without glucose supplementation. The performance effect of ingesting carbohydrates under such conditions is well established (8,9), and the present results support the idea that the beneficial effect of preventing hypoglycemia to some extent is related to the counteraction of central fatigue. It furthermore appears that carbohydrate ingestion is more likely to enhance performance if the exercise bout is of long duration and the subject is overnight fasted (21,29). Thus, nonfasted endurance-trained subjects are able to maintain euglycemia for almost 3 h of exercise during simulated time trials (23), and glucose supplementation seems to have little (14,18) or no (5,6) effect on performance as long as endogenous glucose production is sufficient to maintain blood glucose homeostasis (7). However, hypoglycemia will develop in nonfasted subjects if the exercise bout is of very long duration, and the intensity and mode of exercise as well as the training status of the subjects will determine for how long euglycemia can be maintained without glucose supplementation (16,30). The influence of hypoglycemia on the pattern of force development and CNS activation during the sustained contraction is similar to the effect that previously was observed in response to hyperthermia during a similar MVC protocol (26), and both hypoglycemia and hyperthermia appear to attenuate the ability to sustain a high neural drive to the muscles rather than affecting force mobilization during brief maximal contractions. Furthermore, hyperthermia did not affect force development or central activation during 40-brief MVC interspaced by only 3 s of rest, although hyperthermia markedly reduced the level of CNS activation during a sustained contraction (26). These observations indicate that during exercise conditions associated with central fatigue, the CNS regains the ability to activate the skeletal muscles within a short period of recovery, and it may explain why the voluntary activation percentage was unaffected by hypoglycemia during the initial phase of the postexercise MVC. Depletion of substrates within the CNS and/or alterations in the level of certain neurotransmitters could be one of the mechanisms underlying the decline in central activation during the sustained muscle contraction, but sensory feedback from the contracting muscles could also influence the pattern of CNS activation during the sustained MVC. Thus, sensory feedback may be of minor importance for the activation level during the initial phase of the isometric contraction, whereas it may inhibit motor activation when the contraction is sustained and muscle metabolites accumulate (19). The similar voluntary activation percentage at baseline and after the three hours of cycling with glucose supplementation support the notion that CNS activation during a maximal muscle contraction is unchanged by 3–4 h of moderate-intensity exercise in endurance-trained subjects when they are supplemented with glucose (22). On the other hand, neuromuscular fatigue will develop during ultra-long endurance events even if the athlete ingests glucose (22), and the central component of this fatigue may be influenced by inhibitory feedback signals from the active muscles, arising secondary to glycogen depletion and/or other metabolic changes (19). However, glycogen breakdown is not affected by glucose ingestion during cycling with a constant workload (9). Nevertheless, it cannot be excluded that the reduced muscle activation from the CNS during the trial without glucose supplementation is influenced by an altered feedback from the contracting muscles, as glucose supplementation during prolonged exercise could benefit the metabolic homeostasis in the skeletal muscles via other mechanisms.

The mechanism underlying the hypoglycemia-induced central fatigue could relate to a direct effect of reduced substrate delivery to the brain. Thus, exercise is associated with an activation of large regions of the brain including motor cortex areas as well as regions involved in cardiorespiratory regulation (13), and endothelial glucose transport may become rate limiting for the cerebral metabolic rate of glucose when the arterial glucose concentration falls below a critical point of ~3.6 mM (4). The cerebral cortex is more sensitive to hypoglycemia than other parts of the brain (10), and it seems possible that the central fatigue arising from hypoglycemia may relate to insufficient glucose availability...
in primary and/or secondary motor cortices. A continuous supply of blood glucose to the brain is essential, as glucose storage in neuronal tissue is limited (27), and Ide et al. (17) suggested that central fatigue during strenuous exercise could relate to depletion of brain glycogen stores. Their suggestion is based on the observation that the brain has a large carbohydrate uptake and a reduced oxygen/carbohydrate ratio during recovery from maximal exercise. The fate of the extra glucose and lactate uptake is not known, but replention of brain glycogen stores could be a possibility. Whether brain glycogen or the glucose level in motor cortices is affected by motor activation is not known, but the importance of cerebral carbohydrate availability in preventing central fatigue is underlined by the finding that glucose infusion directly in the carotid artery can delay fatigue in exercising dogs (20). Glucose supplementation could also exert its influence on central fatigue via the serotonergic neurotransmitter system. Thus, prolonged exercise in combination with a low level of blood glucose stimulates the release of free fatty acids (FFA) from adipose tissue, and this will result in an increased plasma concentration of both FFA and free tryptophan, as FFA binds to albumin and displaces some of the albumin-bound tryptophan (11). Tryptophan is the precursor for the synthesis of serotonin (5-hydroxytryptamine), and an increased plasma concentration of free tryptophan is expected to increase the cerebral tryptophan uptake and enhance serotonin production in the brain, because the rate-limiting step in the synthesis of serotonin is the transport of tryptophan into the brain (15). In this way, the serotonin level in the brain is increased during prolonged exercise in rodents (2), and a higher serotonin level could potentially influence the development of central fatigue (24). Glucose ingestion will stimulate the secretion of insulin (28) and blunt the exercise-induced rise in both plasma FFA and free tryptophan, and in this way it may counteract the development of central fatigue by attenuating the rise in brain serotonin (12).

All subjects completed the 3 h of cycling on both days, but an increased difficulty in retaining the required power output toward the end of the cycle bout without glucose supplementation was reflected in the subjects rating of perceived exertion. It is interesting that the RPE score was similar during the first 2–2.5 h of cycling in the two trials but became elevated in the placebo trial when the blood glucose concentration was reduced to ~ 3.5 mM (Fig. 1), because this correspond to the blood glucose level where cerebral glucose uptake begins to decline (4). However, the application of a subjective RPE score as an assessment of fatigue does not allow us to distinguish between central and peripheral factors contributing to the development of fatigue, and further investigations are necessary to establish whether there is a relationship between the impaired central activation during a sustained muscle contraction, the higher RPE during ongoing dynamic exercise, and alterations in the cerebral metabolic rate of glucose.

In summary, exercise-induced hypoglycemia in endurance-trained subjects lowers the average force production during a sustained maximal muscle contraction, and the reduced force development is associated with a diminished activation drive from the CNS. This central fatigue seems to be effectively counteracted when blood glucose homeostasis is maintained, and it is easier for the subjects to retain power output at the end of a prolonged exercise bout when hypoglycemia is prevented via carbohydrate supplementation.

REFERENCES


