Effect of carbohydrate ingestion on ammonia metabolism during exercise in humans

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Snow, Rodney J., Michael F. Carey, Christos G. Stathis, Mark A. Febbraio, and Mark Hargreaves. Effect of carbohydrate ingestion on ammonia metabolism during exercise in humans. J Appl Physiol 88: 1576–1580, 2000.—The present study was undertaken to examine the effect of carbohydrate ingestion on plasma and muscle ammonia (NH₃ denotes ammonia and ammonium) accumulation during prolonged exercise. Eleven trained men exercised for 2 h at 65% peak pulmonary oxygen consumption while ingesting either 250 ml of an 8% carbohydrate-electrolyte solution every 15 min (CHO) or an equal volume of a sweet placebo. Blood glucose and plasma insulin levels during exercise were higher in CHO, but plasma hypoxanthine was lower after 120 min (1.7 ± 0.3 vs. 2.6 ± 0.1 µmol/l; P < 0.05). Plasma NH₃ levels were similar at rest and after 30 min of exercise in both trials but were lower after 60, 90, and 120 min of exercise in CHO (62 ± 9 vs. 76 ± 9 µmol/l; P < 0.05). Muscle NH₃ levels were similar at rest and after 30 min of exercise but were lower after 120 min of exercise in CHO (1.51 ± 0.21 vs. 2.07 ± 0.23 mmol/kg dry muscle; P < 0.05; n = 5). These data are best explained by carbohydrate ingestion reducing muscle NH₃ production from amino acid degradation, although a small reduction in net AMP catabolism within the contracting muscle may also make a minor contribution to the lower tissue NH₃ levels.

Methods

Subjects. This study was conducted in two parts. Initially, eight endurance-trained men volunteered to exercise and allowed cardiorespiratory and blood samples to be obtained. Subsequently, two of these subjects and a further three subjects volunteered to undertake the same experimental protocol with muscle sampling. The common data obtained for the two subjects participating in both parts of the experi-
Results

Cardiorespiratory data. There were no differences in mean \( \dot{V}O_2 \) (Con: 2.92 ± 0.08, CHO: 2.86 ± 0.09 l/min) and heart rate (Con: 150 ± 3, CHO: 149 ± 1 beats/min) during exercise between the trials. RER was not different at any time point during exercise (data not shown); however, mean RER was higher in CHO (0.87 ± 0.01) than in Con (0.84 ± 0.01; \( P < 0.05 \)), as was the mean rate of carbohydrate oxidation during exercise (1.96 ± 0.07 vs. 1.69 ± 0.10 g/min; \( P < 0.05 \)).

Blood and plasma metabolites. Blood glucose concentrations were similar at rest but were elevated (\( P < 0.05 \)) at all sampling time points during exercise in CHO compared with Con (Table 1). Similarly, plasma insulin concentrations were not different at rest but were higher (\( P < 0.05 \)) after 60 and 120 min of exercise in CHO vs. Con (Table 1). Blood lactate concentrations were not different at rest or during exercise between the trials (Table 1). Plasma NH₃ levels increased (\( P < 0.05 \)) during exercise in both trials from similar resting levels (Fig. 1). Plasma NH₃ concentration was higher (\( P < 0.05 \)) in Con compared with CHO after 60, 90, and 120 min of exercise (Fig. 1). Plasma hypoxanthine concentrations were similar at rest and during most of the exercise period (Table 1). An exercise-induced increase (\( P < 0.05 \)) in plasma hypoxanthine was observed in both trials; however, after 120 min of exercise, the hypoxanthine concentration was lower (\( P < 0.05 \)) in CHO compared with Con (Table 1).

Muscle metabolites. Muscle ATP, ADP, AMP, and TAN contents were not different between the trials (Table 2). Resting muscle PCR was similar in the two treatments, and, in both, the PCR levels were reduced (\( P < 0.05 \)) as a result of exercise. The PCR concentration after 30 min of exercise was higher (\( P < 0.05 \)) in CHO than in Con; however, the small difference after 120 min was not significant (\( P = 0.1 \); Table 2). There was no significant
interaction between treatment and time for muscle IMP (Table 2). There was, however, a significant main effect for time, with IMP concentration at 120 min being higher \((P < 0.05)\) than the resting and 30-min values. Muscle NH\(_3\) at rest was not different between treatments but was increased \((P < 0.05)\) at each subsequent measurement point in Con. In CHO, only at 120 min was muscle NH\(_3\) concentration higher \((P < 0.05)\) than the resting and 30-min levels. The latter two means were not different. Muscle NH\(_3\) concentration after 120 min of exercise was higher \((P < 0.05)\) in Con compared with CHO (Fig. 2).

**DISCUSSION**

The results of the present study indicate that carbohydrate ingestion attenuates muscle and plasma NH\(_3\) accumulation during the latter stages of prolonged submaximal exercise. These data are best explained by carbohydrate ingestion reducing muscle NH\(_3\) production from amino acid degradation. Elevated carbohydrate availability may have also led to a small reduction in net AMP catabolism within the contracting muscle, as reflected by the lower plasma hypoxanthine after 120 min of exercise, suggesting that this source of NH\(_3\) may also make a minor contribution to the lower tissue NH\(_3\) levels.

The major potential sources of NH\(_3\) during submaximal exercise include AMP deamination and amino acid catabolism (19). In the present study, muscle IMP levels were not different between the two trials at any time point, although plasma hypoxanthine after 120 min of exercise was lower with carbohydrate ingestion. This finding suggests that carbohydrate ingestion may have resulted in a better balance between ATP degradation and resynthesis during the latter stages of prolonged exercise. However, the absolute plasma hypoxanthine levels and the magnitude of difference between the trials are relatively small, and thus differences in net AMP deamination are unlikely to account for the lower NH\(_3\) accumulation. Similar conclusions on the role of net AMP deamination during prolonged exercise have been made by other authors (13–15), suggesting that amino acid catabolism is the major source of NH\(_3\) production. Carbohydrate ingestion also appeared to result in a better maintenance of PCr levels during exercise (Table 2), suggesting a small shift from PCr degradation to carbohydrate oxidation for ATP generation.

Previous studies have observed a link between carbohydrate availability and amino acid catabolism during exercise. Davies et al. (4) demonstrated that glucose ingestion attenuated leucine oxidation, as measured by \(^{13}\)CO\(_2\) production from infused \(^{13}\)C-leucine. Sweat urea nitrogen excretion, an indirect marker of protein catabolism, is lower during exercise commenced in a glycogen-loaded state compared with depleted-muscle-glycogen levels (11). Similarly, prior muscle glycogen depletion has been shown to increase net protein degradation during single-leg, knee extension exercise (20). Greater increases in the activity of skeletal muscle branched-chain oxoacid dehydrogenase, the rate-limiting step in branched-chain amino acid oxidation, have been observed during exercise under conditions of reduced carbohydrate availability (20, 22). These results suggest that amino acid catabolism is reduced by increased carbohydrate availability and provide the most plau-

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**Table 1. Plasma glucose, lactate, hypoxanthine, and insulin during 120 min of cycling at \(\sim 65\%\) peak pulmonary oxygen consumption with and without carbohydrate ingestion**

<table>
<thead>
<tr>
<th>Glucose, mmol/l</th>
<th>Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Con</td>
<td>4.5±0.1</td>
</tr>
<tr>
<td>CHO</td>
<td>4.4±0.1</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>0.7±0.1</td>
</tr>
<tr>
<td>CHO</td>
<td>0.7±0.1</td>
</tr>
<tr>
<td>Hypoxanthine, µmol/l</td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>CHO</td>
<td>0.9±0.2</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td></td>
</tr>
<tr>
<td>Con</td>
<td>40±4</td>
</tr>
<tr>
<td>CHO</td>
<td>38±4</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of subjects. Con, without carbohydrate ingestion; CHO, with carbohydrate ingestion. *Different from Con, \(P < 0.05\).

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**Fig. 1. Plasma ammonia and ammonium (NH\(_3\)) during 120 min of cycling at \(\sim 65\%\) peak pulmonary oxygen consumption with (CHO) and without (Con) carbohydrate ingestion. Values are means ± SE; n = 11 subjects. *Different from Con, \(P < 0.05\).**
Different from Con, the degradation of amino acids are purine nucleotide operation of the PNC is a faster rate of NH\textsubscript{3} production compared with CHO. The net effect of a more rapid the other enzymes of the PNC at a faster rate in Con reamination legs of the cycle operate concurrently in contracting skeletal muscle (19), thereby casting doubt over aspartate deamination, via the PNC, as a source of NH\textsubscript{3} production.

The ingestion of carbohydrate during prolonged cycling exercise increases muscle glucose uptake (16), which may account for an increased intramuscular glucose concentration late in exercise when fed carbohydrate (17). Glucose and pyruvate have been shown to inhibit branched-chain oxoacid oxidation in incubated rat diaphragm (2). However, because muscle glucose uptake does not appear to be increased by carbohydrate ingestion until after 20–30 min of exercise (16) and because net muscle glycogen use is unaltered (3, 8), an increase in intramuscular carbohydrate supply may not have been evident until later in the exercise bout. This could account for the observation that plasma and muscle NH\textsubscript{3} levels were attenuated after 60 and 120 min of exercise, respectively, but were similar after 30 min of exercise. It is also possible that an increase in plasma insulin plays a role in the attenuation of ammonia accumulation because it is known to inhibit protein breakdown (6).

The attenuation of muscle NH\textsubscript{3} content observed toward the latter stages of exercise in the carbohydrate ingestion trial may also be partly explained by enhanced alanine production. Alanine is one of the principal nitrogen carriers released from active skeletal muscle (5). In order for alanine to remove free NH\textsubscript{3}, the amino group from glutamate must have also originated from free NH\textsubscript{3}. The major reaction involving the fixation of NH\textsubscript{3} to glutamate is catalyzed by GDH. Although the direction in which the GDH reaction proceeds is unknown, it has been argued that in contracting muscle the reaction favors NH\textsubscript{3} production rather than removal (13). If this is the case, muscle alanine production is not likely to enhance free NH\textsubscript{3} removal. Alternatively, there is the possibility that de novo alanine production from pyruvate and glutamate in the alanine aminotransferase reaction reduces the availability of glutamate for NH\textsubscript{3} production. Carbohydrate ingestion has been shown to elevate muscle alanine content during prolonged submaximal exercise (17), suggesting that muscle alanine production is enhanced with carbo-

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Table 2. Muscle metabolites at rest and after 30 and 120 min of cycling at ~65% peak pulmonary oxygen consumption in CHO and Con trials

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>CHO Rest</th>
<th>CHO 30 min</th>
<th>CHO 120 min</th>
<th>Con Rest</th>
<th>Con 30 min</th>
<th>Con 120 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATP</td>
<td>25.7 ± 1.3</td>
<td>27.3 ± 0.9</td>
<td>24.9 ± 1.0</td>
<td>25.6 ± 1.5</td>
<td>27.7 ± 2.3</td>
<td>25.9 ± 1.6</td>
</tr>
<tr>
<td>ADP</td>
<td>1.93 ± 0.13</td>
<td>2.26 ± 0.19</td>
<td>2.22 ± 0.19</td>
<td>1.95 ± 0.15</td>
<td>2.10 ± 0.23</td>
<td>2.06 ± 0.17</td>
</tr>
<tr>
<td>AMP</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>0.09 ± 0.01</td>
<td>0.07 ± 0.01</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>TAN</td>
<td>27.7 ± 1.4</td>
<td>29.7 ± 1.0</td>
<td>27.3 ± 1.2</td>
<td>27.7 ± 1.5</td>
<td>29.9 ± 2.5</td>
<td>28.2 ± 1.7</td>
</tr>
<tr>
<td>IMP</td>
<td>0.05 ± 0.01</td>
<td>0.06 ± 0.01</td>
<td>0.14 ± 0.01</td>
<td>0.06 ± 0.01</td>
<td>0.07 ± 0.02</td>
<td>0.12 ± 0.04</td>
</tr>
<tr>
<td>PCr</td>
<td>88.0 ± 2.4</td>
<td>67.5 ± 3.4</td>
<td>58.5 ± 2.6</td>
<td>86.3 ± 5.2</td>
<td>79.2 ± 3.0*</td>
<td>68.3 ± 4.2</td>
</tr>
<tr>
<td>Cr</td>
<td>43.6 ± 0.6</td>
<td>62.2 ± 1.4</td>
<td>73.2 ± 4.0</td>
<td>45.4 ± 3.6</td>
<td>52.4 ± 2.3*</td>
<td>62.4 ± 4.1</td>
</tr>
<tr>
<td>Lactate</td>
<td>6.5 ± 0.7</td>
<td>9.7 ± 2.2</td>
<td>7.7 ± 1.5</td>
<td>5.7 ± 1.3</td>
<td>7.0 ± 1.2</td>
<td>9.4 ± 1.8</td>
</tr>
</tbody>
</table>

Values are means ± SE expressed in mmol/kg dry mass; n = 5 subjects. TAN, total adenine nucleotide; PCr, creatine phosphate; Cr, creatine. *Different from Con, P < 0.05.

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Fig. 2. Muscle NH\textsubscript{3} during 120 min of cycling at ~65% peak pulmonary oxygen consumption in CHO and Con trials. Values are means ± SE; n = 5 subjects. dm, Dry mass. *Different from Con, P < 0.05.
hydrate supplementation. In the present study we have no data to support or refute such a mechanism.

In summary, the results of the present study suggest that carbohydrate ingestion attenuates muscle and plasma \( \text{NH}_3 \) accumulation during the latter stages of prolonged submaximal exercise by reducing \( \text{NH}_3 \) production from amino acid degradation.

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