Appetite and blood glucose profiles in humans after glycogen-depleting exercise

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Melanson, Kathleen J., Margriet S. Westerterp-Plantenga, L. Arthur Campfield, and Wim H. M. Saris. Appetite and blood glucose profiles in humans after glycogen-depleting exercise. J. Appl. Physiol. 87(3): 947–954, 1999.—Regulatory functions of glycogen stores and blood glucose on human appetite, particularly relating to exercise, are not fully understood. Ten men (age 20–31 yr) performed glycogen-depleting exercise in an evening, ate a low-carbohydrate dinner, and stayed overnight in the laboratory. The next day, blood glucose was monitored continuously for 517 ± 23 (SE) min. Subjects had access to high-fat and high-carbohydrate foods after baseline glucose and respiratory quotient were determined. In the afternoon, 1 h of moderate exercise was performed. Baseline respiratory quotient was 0.748 ± 0.008, plasma free fatty acids were 677 ± 123 µmol/l, insulin was 4.8 ± 0.5 µU/ml, and leptin was 1.9 ± 0.3 ng/ml. Postabsorptively, 8 of 10 meals were initiated during stability in blood glucose. Postprandially, the association between meal initiation and blood glucose declines became significant ($\chi^2 = 7.82$). During moderate exercise, blood glucose initially decreased but recovered before completion. When the glycogen buffer is depleted, meal initiation can occur during blood glucose stability; the relationship between blood glucose declines and meal initiation reestablishes with refeeding.

glycemic theory; glycogenostatic theory; food intake regulation; hunger; satiety

CARBOHYDRATE METABOLISM has been proposed to be instrumental in food intake regulation, because of its high turnover rate, limited storage, immediate and tight regulation, and critical role as a fuel source for the central nervous system (6, 13). The glucostatic hypothesis postulates that hunger signals are stimulated, at least in part, by changes in glucose utilization rates in both animals (2, 6, 12) and humans (3, 14). As a consequence, changes reflected by declines in blood glucose have been suggested to play a role in short-term food intake regulation and may depend on carbohydrate availability. Day-to-day food intake regulation may depend on carbohydrate stores, as suggested by the glycogenostatic hypothesis (5, 6). This model predicts that individuals consume food to a level that maintains glycogen levels in the body (6). Human studies investigating the glycogenostatic hypothesis have used dietary (22, 24, 25) and/or exercise (23, 29) manipulations to alter glycogen stores. The possible interplay between the glucostatic and glycogenostatic hypotheses has not been examined in humans.

Glycogen stores can be depleted by intensive exercise (10). During the application of such an intensive protocol, the effects of the exercise itself on appetite must be taken into account. Temporary postexercise anorexia, which is dose dependent on the intensity and duration of the exercise (8), has been described in studies in which a test meal was served 10–15 min after exercise (8, 30). However, in studies in which a test meal was offered 50–75 min after exercise, no suppression or increased food intake was observed (9, 28). In these studies, the amount of food consumed was the outcome variable, rather than the duration of postexercise anorexia. Therefore, we chose an approach of observing the spontaneous interval until the next meal after the intensive exercise.

To further investigate the conditions necessary for the coupling of meal initiations and transient declines in blood glucose, we designed a study in which glycogen stores were acutely depleted by exercise, hypothesizing that carbohydrate stores might play a role. Appetite regulation was observed for 24 h, during which blood glucose was monitored continuously for part of the time.

More specifically, we hypothesized that in a state of glycogen depletion, when the body's carbohydrate buffer is removed, disruptions occur in the relationship between patterns of blood glucose and spontaneous meal initiation. On the other hand, changes in blood glucose might occur that are not related to meal initiation. Such changes might occur during exercise in a relatively glycogen-depleted state. Therefore, we also included in the protocol a moderate-exercise session for 1 h. During that period we expected that changes in blood glucose would not be associated with meal initiation and that postexercise anorexia would be observed afterward.

METHODS

Subjects. Ten healthy weight-stable, nonsmoking men recruited from the University community completed this protocol. They all signed informed consents, and the protocol was approved by the Medical Ethics Committee of Maastricht University. As shown in Table 1, subjects were between the ages of 20 and 31 yr and were within the normal range of weight, height, and body mass index. Their average scores on the Herman and Polivy Restraint Questionnaire (7) and the Three Factor Eating Questionnaire (26) were all within the normal range, indicating that the volunteers were not inclined to control their food intake cognitively.

Protocol. The protocol consisted of two visits separated by at least 5 days. The first visit was for a test of maximal aerobic

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capacity and power output (Wmax) on an electrically braked bicycle ergometer (Lode, Groningen, The Netherlands). For this test, volunteers warmed up at 100 W for 5 min and then cycled in 2.5-min increments, increasing by 50 W each time, until volitional exhaustion. Respiratory gases were collected continuously and were analyzed for oxygen and carbon dioxide by a Sensormedics analyzer (Energy Expenditure Unit 2900, Sensormedics, Anaheim, CA). Heart rate was monitored continuously by use of a Polar’s band (Kempele, Finland).

The second visit consisted of a 24-h time-blinded stay in the research center, which is depicted schematically in Fig. 1. It started at 6 PM on the evening before the glucose monitoring, with a glycogen-depleting exercise session on a bicycle ergometer. This exercise protocol has been previously validated to deplete muscle glycogen stores regardless of fitness level (10, 21). The volunteer warmed up for 10 min at 50% of his Wmax and then cycled in 2-min intermittent bouts of 90 and 50% Wmax. When he was unable to cycle at 90% Wmax any longer, the bouts alternated between 80 and 50% Wmax, followed by 70 and 50% Wmax. When he was unable to cycle at 70% Wmax any longer, he was permitted to cool down and shower. After the exercise, the volunteer was told that he could eat whenever he felt hungry enough. Upon this meal request, the volunteer was served a low-carbohydrate (3.4% carbohydrate, 79.7% fat, 16.9% protein) isoenergetic (6 MJ) dinner, designed to maintain energy balance without replenishing carbohydrate stores. These calculations were based on previous studies (21). That night, the volunteer slept in the same bed where the testing was to take place the next day, in a room with no clocks or windows, so that he could remain in time isolation.

Immediately before and after the glycogen-depleting exercise, as well as at the point of the dinner request, and immediately after dinner consumption, the volunteer completed an appetite rating. These ratings consisted of questions on hunger, satiety, desire to eat, and thirst, which volunteers answered by marking 100-mm visual analog scales (VAS). The scales were anchored by such phrases as “not hungry at all” and “extremely hungry.”

The next morning, an 18-gauge, 5-cm Angiocath was placed in a suitable lower arm or antecubital vein of the nondominant arm. The blood withdrawal end of a specially modified, 2.5-m-long double-lumen catheter (MTB Medizintechnik, Amstetten, Germany) was fit into the Angiocath. The catheter was heparinized by pumping sterile heparin-saline solution (500–5,000 U/ml) at a rate of ~25 µl/min through the distal lumen of the catheter to the tip of the cannula. The blood was continuously withdrawn through the proximal lumen of the cannula at a rate of ~25 µl/min. The blood-heparin-saline solution was mixed with a heparinized phosphate buffer, at a 1:10 ratio and was continuously infused into the sample chamber of a glucose analyzer (model 23A, Yellow Springs Instrument, Yellow Springs, OH). Sampling occurred at a rate of 10 times/min, and analog data were amplified, digitized, interfaced (model 1028, Data Translation Interface Board), and displayed continuously on a Macintosh computer monitor (Power PC, Cupertino, CA) by using the program Labview. This monitor was not visible to the subject. Before the insertion of the catheter into the subject, and after the completion of testing, the system was calibrated by using a bag of sterile saline with glucose added to a concentration of ~100 mg/dl. This calibration was done by using the same blood-withdrawal cannula that was used in the subject that day.

An additional 20-gauge, 3.2-cm catheter was placed in the antecubital vein of the other arm for occasional sampling (5–10 times) of insulin, free fatty acids (FFAs), and leptin. This line was kept open with heparinized saline. A 5-ml baseline sample was collected from this catheter into EDTA-containing test tubes and centrifuged for 10 min at 4°C, and plasma aliquots were immediately frozen. Baseline glucose was determined from the continuous line over a minimum of a 30-min accommodation period. During this time, respiratory gases of the subject were analyzed by ventilated-hood indirect calorimetry for the assessment of resting energy expenditure and respiratory quotient (RQ) (Human Biology, Maastricht University, Maastricht, The Netherlands). Throughout the test day, between measurements, volunteers were permitted to read, study, or listen to music.

Before the baseline period, and at random intervals throughout the day, the subject completed VAS ratings of hunger, satiety, and desire to eat as described above. The intervals were randomized so that the volunteer could not determine the passing of time from them. The subject was informed that he could eat and drink ad libitum from an easily accessible cool box containing generous portions of high-carbohydrate and high-fat food and beverage choices. The items were all typical for the Dutch diet (15). The foods consisted of croissants with full-fat margarine and either high-fat cheese (total sandwich: 68.6% fat, 23.2% carbohy-
glucose have been described as rapid (0.41–1.27 mg·dl⁻¹·min⁻¹ for 42–67 min) declines originating from a peak induced by nutrient ingestion (rather than from a stable baseline) (14). Transient and dynamic declines were tallied for each test day, and the number of times that meal initiation occurred in the presence or absence of a decline in blood glucose was quantified.

Postabsorptive refers to the state when all the previously ingested food has been absorbed from the digestive tract, whereas postprandial refers to the state when the digestive tract contains ingested food. Because, in the present protocol, measurements on the test day started at least 10 h after the last nutrient ingestion, the postabsorptive state was defined as the period from the beginning of the testing until the first macronutrient consumption; the postprandial state was defined from the first nutrient consumption until the end of testing.

Comparisons between the results were made by using paired t-tests on the computer software program Statview 2.0 for Macintosh. Associations between changes in blood glucose and meal initiation were tested by using the χ² test for 2 × 2 contingency tables with correction for continuity (16). Multiple-regression analysis was utilized to test relationships between results from both blood sampling and indirect calorimetry and such outcome variables as appetite ratings and food intake. Statistical significance was accepted as P < 0.05. Data presented are means ± SE unless otherwise specified.

RESULTS

As shown in Table 2, the volunteers were moderately to well trained, ranging from recreational tennis players and competitive volleyball players to endurance cyclists and speed skaters. The average duration of the glycogen-depleting exercise was 81 min, ranging from 37 to 126 min. Appetite profiles on the evening of the glycogen-depleting exercise and the following morning are shown in Fig. 2. There were no significant differences in the ratings from before to after the exercise session, although interindividual variability was high. The time interval from the completion of the exercise until the spontaneous meal request for dinner was 76 ± 7 min. Across this time, hunger and desire to eat increased significantly (P = 0.0016 and P = 0.0014) and satiety decreased (P = 0.0367). Thirst did not change significantly (P = 0.138), probably because of the ad libitum access to water. Significant decreases in hunger (P = 0.0001), desire to eat (P = 0.0001), and thirst (P = 0.0004) and increases in satiety (P = 0.0001) were observed from before to after dinner.

The average duration of continuous blood glucose sampling was 517 ± 23 min, ranging from 321 to 606 min. The average volunteer estimation of clock time at the end of the testing was 71 ± 20 min, with all

Table 2. Fitness data of volunteers

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<th>Variable</th>
<th>Mean ± SD</th>
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<td>V̇O₂max, l/min</td>
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<td>V̇O₂max, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Maximum heart rate, beats/min</td>
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<tr>
<td>Maximum power output, W</td>
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<td>282.3–405.0</td>
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<tr>
<td>Maximum power output, W/kg</td>
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<td>Duration of glycogen depletion, min</td>
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<td>37–126</td>
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<td>V̇O₂max, maximal aerobic capacity</td>
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volunteers underestimating the time of day, thus verifying that the subjects were time blinded. Average baseline blood glucose concentrations were 73.4 ± 3.2 mg/dl.

Table 3 depicts the observed responses in the relationship between declines in blood glucose and meal initiation. During the testing day, in the postabsorptive state, 10 meal initiations occurred (1 per subject); 2 occurred in the presence of a transient decline in blood glucose and 8 in the absence of transient declines in blood glucose. A total of two transient blood glucose declines in the postabsorptive state were observed, and both were associated with meal initiation, as mentioned. χ² analysis revealed that, in the postabsorptive state, the synchronization between transient declines in blood glucose and spontaneous meal initiation was not significant (χ² = 0.28, P > 0.50).

In the postprandial state, 15 meals were initiated; 13 were in relation to blood glucose changes: either transient declines (3) or dynamic declines (14). The other two meals were initiated during periods of relative stability in blood glucose. A total of 17 transient and dynamic declines occurred in the postprandial state: 13 were associated with meal initiation, as mentioned, and 4 were not. Collectively, in the postprandial state, the relationship between declines in blood glucose (transient and dynamic) and spontaneous meal initiation was statistically significant (χ² = 7.82, P = 0.010).

Of the six observed postprandial transient declines in blood glucose, five were associated with spontaneous meal initiation. Thus this interdependence was statistically significant (χ² = 4.93, P < 0.050). The 11 observed dynamic declines in blood glucose constituted, on average, a 28.3 ± 2.0% decrease over 60.8 ± 8.3 min, which followed a rise in blood glucose induced by meal ingestion (39.3 ± 3.4% in 60.9 ± 8.2 min). Spontaneous meal initiation occurred during eight (72.7%) of these declines; therefore, dynamic declines in blood glucose were also significantly synchronized with meal initiation (χ² = 5.23, P < 0.050).

Representative glucose curves are depicted in Fig. 3, illustrating occurrences of coupled and uncoupled meal initiation and blood glucose declines. Meal initiation in association with a postabsorptive transient decline is shown in Fig. 3A. In Fig. 3, B–D, it can be seen that postabsorptive blood glucose levels were relatively stable and that meal initiation occurred in the absence of transient declines. Meal initiation after or at the nadirs of dynamic declines occurred for meals 2 and 3 in Fig. 3, C and D.

During the 1-h moderate-intensity exercise, blood glucose declined in all subjects by 23.2 ± 4.3% over the first 25 ± 3 min. This was followed by a rise of 19.8 ± 1.4% in 35 ± 2 min, by exercise completion (Figs. 3, B–D). These changes in blood glucose were not associated with meal initiation, except in one subject, who asked to eat during exercise, near the nadir of his blood glucose. This meal request was denied, but the volunteer initiated a meal 4 min after exercise completion, in association with a rapid decrease in blood glucose, as shown in Fig. 3D.

In all subjects but one, RQ remained below 0.80 throughout the test day, with no significant increases for the group as a whole. The average fasting RQ was 0.748 ± 0.026; after consumption of the first meal, this increased to 0.774 ± 0.071 (P = 0.167), and it again increased to 0.794 ± 0.086 (P = 0.104) after the 1-h moderate-intensity exercise. As shown in Fig. 4, in the volunteers whose RQ remained below 0.80, the change in RQ from baseline to after consumption of the first meal was positively correlated with the decrease in hunger ratings during this time (R = 0.816, P = 0.007). In other words, the more RQ increased, the more hunger decreased.

Significant decreases were observed in FFA levels from before (597 ± 112 µmol/l) to after (317 ± 25 µmol/l) consumption of the first meal (P = 0.037). These levels remained stable at the lower level until the 1-h moderate-intensity exercise session, which induced a significant (P = 0.031) rise in plasma FFAs of 363 ± 101 µmol/l. By the end of the test day, 75 ± 11 min later,

### Table 3. Responses observed in the relationship between blood glucose patterns and meal initiation

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<td>Postprandial transient†</td>
<td>5 (83.3)</td>
<td>1 (16.7)</td>
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<tr>
<td>Postprandial dynamic‡</td>
<td>8 (72.7)</td>
<td>3 (27.3)</td>
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<tr>
<td>Total postprandial§</td>
<td>13 (76.5)</td>
<td>4 (23.5)</td>
<td>17</td>
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<tr>
<th></th>
<th>Yes</th>
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<tr>
<td>Meal Initiation Associated With Declines in Blood Glucose</td>
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Values are no. of responses with percents in parentheses for 10 men. NA, not applicable. *χ² = 0.28, P > 0.50. †χ² = 4.93, P < 0.050. ‡χ² = 5.23, P < 0.050. §χ² = 7.82, P < 0.010.
Fig. 3. A: blood glucose profile of an individual on the test day after glycogen-depleting exercise. Arrow indicates initiation of meal 1, which occurred in association with a transient decline in blood glucose. After minute 62, subject consumed 4 high-carbohydrate sandwiches and 350 ml of carbohydrate drink. B: blood glucose profile of an individual on test day after glycogen-depleting exercise. Solid arrow indicates initiation of meal 1, which occurred in absence of a transient decline in blood glucose. This meal consisted of 4 high-fat sandwiches and 350 ml of high-fat drink. Open arrows demarcate 1-h moderate-intensity exercise session (minutes 346–406). C: blood glucose profile of an individual on test day after glycogen-depleting exercise. Numbered solid arrows indicate initiation of meals 1, 2, and 3, respectively. Meal 1 was initiated in the absence of a transient decline in blood glucose. At this meal, the volunteer consumed 4 high-carbohydrate sandwiches and 350 ml of carbohydrate beverage. After nadirs of next 2 dynamic declines, he consumed 350 ml of carbohydrate beverage each time (meals 2 and 3). Open arrows demarcate 1-h moderate-intensity exercise session (minutes 395–455). D: blood glucose profile of an individual on test day after glycogen-depleting exercise. Numbered solid arrows indicate initiation of meals 1, 2, 3, and 5 (request for meal 4, during exercise, was denied). Meal 1 was initiated in the absence of a transient decline in blood glucose, and meals 2, 3 and 5 were initiated after nadirs of dynamic declines in blood glucose (high-fat sandwiches and carbohydrate beverage). Open arrows demarcate 1-h moderate-intensity exercise session (minutes 332–392).
plasma FFAs dropped by 203 ± 71 µmol/l, although this was not significant (P = 0.121). Baseline insulin levels (4.8 ± 0.5 µU/ml) decreased significantly (P = 0.011) by the time the first meal was initiated (to 3.9 ± 0.5 µU/ml) and showed a significant increase after ingestion of the first meal (to 42.8 ± 6.7 µU/ml; P = 0.002). A nonsignificant (P = 0.142) decrease in insulin concentration (from 27.7 ± 5.3 to 16.5 ± 3.5 µU/ml) was observed from before to after the moderate-exercise bout. Baseline plasma leptin concentrations were 1.90 ± 0.31 ng/ml and showed no significant changes over the course of the day for the group as a whole, although there was considerable intersubject variability.

During the testing day, 2.6 ± 0.4 meals were consumed per volunteer. The first meal was initiated on average at 11:23 AM (± 74 min), which was 151 ± 44 min into the testing. From the baseline VAS rating to the first meal initiation, hunger and desire to eat increased significantly (both P = 0.005) and satiety decreased (P = 0.028). For the seven second meals that were consumed, the average clock time was 1:04 PM (±59 min), resulting in an intermeal interval of 179 ± 32 min. Hunger and desire to eat were significantly lower at the onset of the second meal than of the first meal (P = 0.054 and P = 0.034). Ratings before meal 2 were the same as baseline ratings of hunger (56 ± 8 vs. 57 ± 6) and desire to eat (55 ± 7 vs. 55 ± 5). Appetite ratings did not change significantly across the 1-h moderate-intensity exercise session. However, four subjects initiated food intake 44 ± 14 min afterward. As shown in Table 4, energy intake on the test day averaged 10.3 ± 1.5 MJ, with 50.0 ± 6.8% of the energy coming from carbohydrate (308 ± 39 g), 42.3 ± 8.9% from fat (118 ± 24 g), and 6.9 ± 0.9% from protein (42 ± 6 g).

**DISCUSSION**

In earlier studies with similar experimental conditions but no glycogen depletion (14), postabsorptive transient declines in blood glucose were highly synchronized with spontaneous meal initiation. In the present study, we report that such postabsorptive declines are infrequent in a glycogen-depleted state and that meals are initiated without significant changes in blood glucose. With refeeding, characteristic transient and dynamic declines in blood glucose became apparent and were synchronized with meal initiation. Thus the relationship between meal initiation and transient declines in blood glucose is likely dependent on a glucose buffer, from glycogen stores or postprandially available carbohydrate.

The relationship between transient declines in blood glucose and spontaneous meal initiation has been previously established in rats (2, 12) and humans (3, 14). The question we raised was under which circumstances the relationship may or may not be present. In the present study, two types of disruptions of this coupling have been demonstrated. When the body's carbohydrate buffer is diminished, deprivation-induced feeding may occur in the absence of transient declines in blood glucose. The lack of transient declines in blood glucose in an acute glycogen-depleted state may be due to initially low rates of glucose utilization, as evidenced by high FFA concentrations, low insulin concentrations, and low RQs. The first spontaneous meal of the test day was initiated 151 min into the experiment (11:23 AM), which should be ample time for a transient decline to occur, if there were to be one. Similar studies have observed postabsorptive transient declines associated with spontaneous meal requests, on average, 157 min (11:27 AM) into the study (14). Thus we had sufficient observation time in the postabsorptive state yet observed few transient declines in blood glucose.

It has been proposed (4) that transient declines in blood glucose may occur in relation to the point in time when the liver switches from retaining glucose to releasing glucose. This signal may be detected by peripheral and central nervous system glucoreceptive elements and mapped into meal initiation, as evidenced by studies in vagotomized rats (2). In our glycogen-depleted volunteers, this switch from hepatic glycogenosis to glycogenolysis could not be observed; therefore, this may be another, not necessarily exclusive, possible reason why transient blood glucose declines did not occur postabsorptively in the glycogen-depleted state.

With refeeding, both transient and dynamic declines in blood glucose, characteristic of the postprandial state, were observed and were significantly associated with spontaneous meal initiation in these time-blinded men. This synchronization between blood glucose patterns and feeding, which has been demonstrated in glycogen-replete humans as well (3, 14), is supported by...
in the glycogen-depleted state. Thus, although the present study included a relatively small number of subjects, it adds further evidence to the glucostatic hypothesis and also expands on it, in that sufficient glycogen reserve is necessary for the relationship to operate in the postabsorptive state. It may be relevant to investigate whether this relationship between blood glucose patterns and feeding is also disrupted at the other end of the range of physiological carbohydrate balance, that is, during carbohydrate overfeeding.

Postprandially, decreased FFA levels and increased insulin concentrations provided indirect evidence that glucose utilization rates had increased on refeeding. This would allow more flexibility for blood glucose declines to occur, because of a relative increase in carbohydrate availability, and we have observed that meal initiations are coupled with these declines. The persistently low RQ throughout the day is suggestive of lack of glycogen repletion. This is further supported by the fact that, even across the moderate (50% Wmax) exercise session in the afternoon, rises in FFA concentrations and drops in blood glucose were more exaggerated than would be expected (20). It is likely that the volunteers were mobilizing fat even for this moderate activity, probably due to limited carbohydrate availability.

As hypothesized, the decline and spontaneous recovery in blood glucose across the moderate exercise was not associated with meal requests. This type of dissociation between declines in blood glucose and meal initiation is likely due to other factors involved in the hypophagic response to exercise, such as heightened sympathetic nervous system activity (1) and corticotrophin-releasing hormone (19). This illustrates another situation in which declines in blood glucose and meal initiation may be uncoupled.

In the transition from the postabsorptive to the postprandial state (first meal consumption), it was observed that, even within a relatively narrow range of change in RQ, the more a volunteer shifted toward carbohydrate oxidation, the greater the decrease in his hunger ratings. This interesting relationship was independent of carbohydrate intake. The observation of less hunger with more carbohydrate oxidation has been reported previously (17), suggesting that postprandial carbohydrate metabolism may be involved in the changes of hunger and satiety after a meal and in the body's perception of energy supply (17). Conversely, inhibition of intracellular glucose utilization by 2-deoxy-d-glucose has been shown to stimulate hunger and food intake in humans, supporting a glucoprivic control of food intake in humans (27). Mayer (13) suggested that decreases in glucose utilization rates are associated with increased hunger. In our glycogen-depleted volunteers, increases in carbohydrate oxidation, which occurred on refeeding, were associated with decreases in hunger. Thus our data corroborate former results and show that an inverse relationship between changes in postprandial carbohydrate oxidation and hunger exist in the glycogen-depleted state.

Assuming an average RQ of 0.90 for the evening glycogen-depleting exercise session (21), the total energy expenditure of this session can be estimated as 5.9 ± 6.2 MJ and carbohydrate oxidation as 316 ± 34 g. Therefore, as intended, the dinner consumed after this exercise (6 MJ, 14 g carbohydrate) should have repleted energy without repleting carbohydrate stores. On the testing day, the amount of consumed carbohydrate (308 ± 39 g) approximated the amount expended during exercise. However, although their RQs were low, it can also be assumed that some carbohydrate was being oxidized by carbohydrate-dependent tissues overnight; therefore, for the 24-h testing period, the volunteers were most likely in a negative carbohydrate balance. As mentioned in the introduction, the glucostatic hypothesis predicts that individuals consume carbohydrate to a level that achieves carbohydrate balance. A corollary of this hypothesis is that, if a high-fat diet is consumed, energy must be overconsumed to achieve carbohydrate balance. Given that the volunteers chose relatively high-fat (43%) foods in this study, they overconsumed energy while eating carbohydrate to a level similar to what they had depleted. However, they did not achieve carbohydrate balance within the testing period. Of interest for future research would be to follow the volunteers’ ad libitum food intakes over the following 24 h.

Leptin’s lack of acute response to feeding, or moderate exercise that we observed in our glycogen-depleted volunteers, yet long-term response to positive energy balance over the day, has been reported in glycogen-replete subjects as well (10, 18).

On the evening before the test day, after the volunteers had performed the intense glycogen-depleting exercise, they were free to request a meal whenever they felt hungry enough to eat. This permitted observation of the duration of postexercise anorexia in time-blinded men, which averaged 76 min. This lends understandability to the combination of data in the literature showing that food-intake suppression after exercise is at least partly due to the interval until the next meal (8, 9, 28, 30). In the present study, across the 76-min subject-determined interval, significant increases in hunger and desire to eat and decreases in satiety were observed, thus allowing recovery of postexercise anorexia.

To conclude, in a state of glycogen depletion, postabsorptively, transient declines in blood glucose were infrequent, and meal initiation occurred in the absence of these declines. Postprandially, transient and dynamic declines in blood glucose were synchronized with meal initiation. Thus the relationship between meal initiation and transient declines in blood glucose is dependent on glycogen status (carbohydrate availability). During exercise, changes in blood glucose are not related to meal initiation. Shifts toward carbohydrate oxidation are related to decreased hunger on refeeding in a glycogen-depleted state. The relationship between meal initiation and transient declines in blood glucose, representing a physiological feature of food intake...
regulation, only operates within a normal physiological range of carbohydrate status.

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REFERENCES


