The gastroenteroinsular response to glucose ingestion during postexercise recovery

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1Division of Metabolism and Endocrinology, School of Medicine, The Queen’s University of Belfast, Belfast, N. Ireland; 2Schwartz Center for Metabolism and Nutrition, 4Departments of Medicine, 4Physiology, and 5Nutrition, Case Western Reserve University School of Medicine, Cleveland, OH; and 6National Coaching and Training Center, University of Limerick, Limerick, Ireland

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O’Connor, Aine M., Suresh Pola, Blathnaid M. Ward, Davina Fillmore, Keith D. Buchanan, and John P. Kirwan. The gastroenteroinsular response to glucose ingestion during postexercise recovery. Am J Physiol Endocrinol Metab 290: E1155–E1161, 2006.—This study examined gastrointestinal hormone and peptide responses when glucose was ingested after prolonged exercise. Six endurance-trained male athletes ran on a treadmill for 2 h at 60% \( V_O_2_{max} \). Immediately after the run, the athletes consumed 75 g of glucose in 250 ml of water (ExGLU) or flavored water as a placebo control (ExPL). On a separate visit, the athletes rested for 2 h and then consumed glucose (ConGLU). During the first 60 min of recovery from exercise alone (ExPL), plasma vasoactive intestinal peptide (VIP), gastrin, and glucagon-like peptide-1 (GLP-1) all increased significantly, whereas glucose, insulin, and gastric inhibitory polypeptide (GIP) were unchanged from the immediate postexercise value. When glucose was ingested after exercise (ExGLU), glucose, insulin, VIP, gastrin, GLP-1, and GIP were all increased (P < 0.01). However, when glucose was ingested after resting for 2 h (ConGLU), VIP levels were unaffected, although glucose, insulin, gastrin, GLP-1, and GIP levels increased (P < 0.05). The plasma glucose response was greater (P < 0.03) and the plasma insulin response lower (P < 0.004) during ExGLU compared with ConGLU. There was a significantly higher (P < 0.01) VIP response during the initial period of recovery in ExGLU than there was with both ExPL and ConGLU. Plasma VIP showed a modest negative correlation with circulating glucose (r = −0.35, P < 0.03) and insulin (r = −0.37, P < 0.03) during the ExGLU recovery period. In summary, when glucose is ingested after prolonged exercise, there is mild insulin resistance and a corresponding rapid transitory increase in plasma VIP. These data suggest that VIP may play an important glucoregulatory role when glucose is ingested during the immediate postexercise recovery period.

The immediate postexercise period appears to be associated with mild reversible insulin resistance, which is characterized by an attenuated insulin response and an increased glucose response to oral glucose (10, 21, 25, 27, 33, 37, 43). The physiological basis for the increased glucose response has been shown to be partly a function of greater release of glucose from the splanchic tissues (20, 30, 39). Gut peptides and hormones of the enteroinsular axis may also play an important functional role in fuel homeostasis and contribute to maintaining a balance between energy utilization and mobilization. The metabolic role of peptides from the enteroinsular axis, including vasoactive intestinal peptide (VIP), gastric inhibitory polypeptide (GIP; also called glucose-dependent insulinoctropic polypeptide), and glucagon-like peptide-1 (GLP-1), are known. However, the response of these peptides during recovery from exercise and the role they may play after glucose ingestion in the immediate postexercise period is less clear.

VIP is secreted by the central (CNS) and peripheral (including enteric) nervous systems in response to duodenal acidification, gastric distention, and meal consumption (6, 40). Its actions include relaxation of smooth muscle (both vascular and nonvascular), mediating gut motility via relaxation and vasodilatation, inhibition of gastric acid secretion, stimulation of intestinal secretions, and regulation of pancreatic release of insulin and glucagon (28, 38). Plasma VIP concentrations have been known to increase during strenuous exercise, suggesting a possible metabolic role for this peptide. Exercise-mediated increases in VIP are thought to act through reperfusion of splanchnic blood flow (29, 36). VIP has been described as a “hormone of need” in that its secretion is increased during starvation and exercise and is associated with increases in glycogenolysis, lipolysis, and hepatic gluconeogenesis (16, 31). Increased VIP levels do not correlate, however, with low blood glucose levels (36). VIP levels decrease after glucose ingestion at rest, and the rise in VIP during strenuous exercise is attenuated with concurrent glucose ingestion (29, 35). Little is known, however, regarding VIP release when glucose is ingested after exercise.

The release of insulinoctropic hormones GIP and GLP-1 from the gut may play an important role in the regulation of glucose metabolism both during and after exercise. GIP is released from the K cells of the duodenum and jejunum in response to oral nutrients. GIP inhibits both gastric acid secretion and gut motility while stimulating insulin secretion (13). GLP-1 is released from the L cells of the ileum and colon, as well as from the CNS. Also stimulated by oral nutrients, GLP-1 secretion is mediated by vagal stimulation, GIP, aceylcholine, and neuromedin C. GLP-1 functions to enhance glucose disposal after nutrient ingestion by not only stimulating insulin secretion but also inhibiting glucagon secretion, inhibiting food intake, and stimulating pancreatic islet neogenesis and proliferation (28). Both GIP and GLP-1 play important roles in mediating postprandial insulin secretion (42, 44) and may also play a role in insulin-independent glucose metabolism.

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REGULATORY PEPTIDES AND GLUCOSE INGESTION

disposal (9, 19, 23). GIP concentrations do not change after exercise, although the effects of concomitant or postglucose ingestion on GIP secretion in the acute setting are not known (22). Furthermore, the effects of exercise on GIP and GLP-1 and the effects of GIP and GLP-1 on insulin and glucose metabolism postexercise have not been investigated.

Gastrin, secreted mostly by the G cells of the gastric antrum and duodenum, is a potent secretagogue for gastric acid, and its release is stimulated by luminal contents, humoral and neural influences, adrenaline, exercise, and an oral water load (3, 4, 7, 28, 29). Although gastrin concentrations rise during exercise, glucose ingestion during exercise does not increase gastrin secretion, and gastrin levels plateau 15 min postexercise (29). Few studies have been performed to examine the effects of glucose ingestion after exercise on gastrin release and its relationship to insulin and glucose metabolism.

The purpose of the present study was to determine the regulatory hormone/peptide responses to glucose ingestion immediately after prolonged exercise to increase our understanding of metabolism during recovery in competitive athletes. In particular, we were interested in hormones/peptides of the enteroinsular axis: VIP, gastrin, GIP, and GLP-1. We hypothesized that increases in VIP would be suppressed in response to glucose ingestion postexercise, gastrin would increase with ingestion of any fluid, and GIP and GLP-1 levels would increase with glucose ingestion postexercise to result in an insulinotropic effect in these athletes.

METHODS

Subjects

Six healthy, endurance-trained, male runners volunteered to participate in the study. Subject characteristics are presented in Table 1. Written informed consent was obtained from each subject in accordance with the guidelines for the protection of human subjects at the National Coaching and Training Center, University of Limerick and The Queen’s University of Belfast. Initial screening included a physical examination, blood chemistry, and a resting electrocardiogram. Each subject completed an incremental treadmill test to determine maximal oxygen consumption (V\(\text{O}_2\) \text{max}). Oxygen and carbon dioxide concentrations were analyzed by a fully automated online system (Ametek OCM-2; Thermox Instruments, Pittsburgh, PA). Heart rate was monitored and recorded at 5-s intervals using a Polar Sport Tester (Polar, Kempele, Finland). Height was measured to the nearest 1.0 cm, without the subjects wearing shoes. Body mass was measured to the nearest 0.1 kg with the subjects wearing shorts. All subjects were experienced, competitive middle- and long-distance runners and were training an average of ~50 miles/wk at the time of the study.

Experimental Design

Each subject performed three trials separated by at least 10 days. This was a randomized, double-blind, placebo-controlled study. For 2 days before each trial, subjects were instructed to eat a diet that consisted of 55% carbohydrate, 30% fat, and 15% protein and were requested to forego training in the 24-h period preceding each trial. Subjects were provided with a standardized 674 kcal meal and 500 ml of water to ensure hydration 2 h before each trial, and all trials were completed in the mid-to-late afternoon.

Exercise trial. After obtaining the baseline blood sample, subjects began a 120-min run at 60% V\(\text{O}_2\) \text{max} on a motorized treadmill (Quinton Q65, Seattle, WA) at 0% grade. Serial bloods were collected at 30-min intervals during the run, and heart rate and V\(\text{O}_2\) were also recorded at 30-min intervals. Immediately upon finishing, the subjects were given a 250-ml placebo drink [placebo ingestion after exercise (ExPL)], which included 15 ml of a carbohydrate-free flavoring solution (Diet Quosh; C & C, Dublin, Ireland). Serial blood samples were collected at 5, 10, 20, 30, 45, and 60 min after ingesting the drink.

Exercise-glucose trial. Baseline blood was obtained before exercise. The subjects then performed the same exercise bout as described for ExPL. Immediately after the run, a drink containing 75 g of glucose (Polycal, Cow & Gate, Trowbridge, UK) in 250 ml of water containing 15 ml of Diet Quosh was consumed within 2 min [glucose ingestion after exercise (ExGlu)]. Subjects were monitored for an additional 60 min, similar to ExPL. Blood samples were collected at 5, 10, 20, 30, 45, and 60 min after drinking. Both drinks were similar in appearance and taste, with a pH of 4.2.

Resting glucose trial. After obtaining baseline blood samples, subjects rested for 120 min, equivalent to the length of the exercise sessions. Additional blood samples were drawn at 30, 60, 90, and 120 min after the resting period. Subjects were then provided with a drink [glucose ingestion after rest (ConGlu)] containing 75 g of glucose in 250 ml water containing 15 ml of Diet Quosh. The drink was consumed within 2 min, and the subjects remained supine for another 60 min, during which blood samples were obtained at 5, 10, 20, 30, 45, and 60 min.

Blood Analyses

Baseline, exercise, and recovery blood samples were obtained from an indwelling catheter flushed with saline. Blood samples for hormone analysis were collected in lithium-heparin tubes containing Trasylol (2,500 kallikrein units per 10 ml of blood). Samples for metabolite measurement were collected in tubes containing 5% perchloric acid. Samples were centrifuged and stored at −20°C until subsequent analysis. Hemoglobin and hematocrit concentrations were determined from blood samples obtained immediately before and after exercise, as previously described (45). Changes in plasma volume were estimated according to Dill and Costill (11). Plasma insulin, VIP, GIP, gastrin, and GLP-1 were measured by specific and sensitive radioimmunoassays, as previously described (1, 32). The sensitivity of these assays was 0.5 ng/l for insulin, 10 ng/l for VIP, 15 ng/l for GIP, 10 ng/l for gastrin, and 30 ng/l for GLP-1. The interassay coefficient of variation was 11.5% for insulin, 7.5% for VIP, 10% for GIP, 7.4% for gastrin, and 11% for GLP-1. The intra-assay coefficient of variation was 7.8% for insulin, 5.3% for VIP, 8% for GIP, 4.6% for gastrin, and 8% for GLP-1. Blood glucose, lactate, and β-hydroxybutyrate were measured by enzymatic fluorimetric continuous flow assay (1).

Statistical Analysis

All values are expressed as means ± SE. A repeated-measures analysis of variance for a crossover study was used to determine significant main effects and interactions. Post hoc tests were performed to identify specific mean differences and at which time points they occurred. The data were analyzed using the Statview II statistical package (Abacus Concepts, Berkeley, CA). The α-level for statistical significance was set at the \(P < 0.05\) level of confidence for all variables.

### Table 1. Descriptive characteristics of the subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Means ± SE</th>
<th>Range</th>
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<tbody>
<tr>
<td>Age, yr</td>
<td>35.5 ± 5.0</td>
<td>19–50</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174.7 ± 1.4</td>
<td>169–179</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>67.0 ± 2.6</td>
<td>57–78</td>
</tr>
<tr>
<td>V(\text{O}_2) \text{max}, ml/min lkg (^{-1})</td>
<td>62.8 ± 2.6</td>
<td>54.5–70.2</td>
</tr>
<tr>
<td>Training mileage, miles/wk</td>
<td>52.5 ± 8.3</td>
<td>30–80</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 6). V\(\text{O}_2\) \text{max} = maximal oxygen consumption.

Exercise (Fig. 1). Glucose levels during both exercise trials were greater than during the ConGLU trials. Insulin levels were not appreciably altered during recovery in the ExPL trial, and levels remained similar to the resting control trial. When glucose was ingested after exercise, there was a rapid surge in plasma glucose that was sustained throughout the 60-min period of recovery. As expected, a similar surge was observed when glucose was ingested during the resting control trial, but values were significantly lower at 5 (P < 0.03) and 10 min (P < 0.02) than they were with the ExGLU trial. Glucose levels were not appreciably altered during recovery in the ExPL trial, and levels were significantly lower than in either of the two trials that involved glucose ingestion.

Mean resting lactate levels were within the normal expected range and were similar for the first 120 min of each trial (Table 2). Blood lactate levels were unaffected by exercise in these athletes. Likewise, during recovery from exercise, lactate levels remained unchanged and were not altered by glucose ingestion. Resting β-hydroxybutyrate levels were also within the normal range and were similar for all three trials (Table 2). During recovery from exercise, levels were increased (P < 0.0001), and the elevation appeared to be independent of glucose ingestion. In support of this observation, glucose ingestion during the resting control trial did not elicit any change in β-hydroxybutyrate levels.

### Hormone/Peptide Responses

As expected, resting plasma insulin levels were normal in these athletes and were similar for all three trials (Fig. 2). Exercise induced a suppression of insulin that was evident after 30 min of running, and these levels remained suppressed throughout the 2-h bouts. During the recovery period, insulin increased in response to the ingestion of glucose. During the ExGLU trial, insulin levels increased throughout the 60-min recovery period. However, the insulin response to glucose ingestion during recovery was lower than it was in the ConGLU trial. Insulin levels remained suppressed during the ExPL trial.

Resting plasma VIP concentrations were similar before all three experiments (Fig. 3). Exercise resulted in an increase in VIP, and the elevation was evident after ~90 min of running. During the 60-min recovery period, VIP levels continued to rise with a peak at ~10 min postexercise. Glucose ingestion postexercise elicited a greater peak increase in VIP than with the ExPL trial (P < 0.001). However, glucose ingestion in the absence of exercise (ConGLU) did not alter plasma VIP.

Resting GIP concentrations were also similar before each experimental trial (Table 3). Although GIP concentrations did not vary significantly between trials, the GIP concentration at 120 min was lower than the respective baseline concentrations for all three

### RESULTS

**Exercise**

The total running time was 120 min for each exercise trial. The average VO₂ during exercise was 41.2 ± 2.2 and 40.0 ± 2.1 ml·kg⁻¹·min⁻¹ for the ExGLU and ExPL trials, respectively. These means were not statistically different and represent ~60% of VO₂max. The mean heart rates during each exercise trial were 142 ± 3 and 142 ± 6 beats/min. Plasma volume changes were greater during the exercise trials (ExGLU, −4.8 ± 1.3; ExPL, −3.1 ± 1.9%) than they were during the resting trial (1.2 ± 1.1%). Substrate and hormone responses were not corrected for plasma volume shifts because the subjects consumed the fluids immediately after exercise, which, together with the cessation of exercise, would have initiated a reversal of the fluid shift arising from the exercise bout.

**Substrate Responses**

Plasma glucose levels were similar at baseline for each of the three trials and remained relatively unchanged during exercise (Fig. 1). Glucose levels during both exercise trials remained similar to the resting control trial. When glucose was ingested after exercise, there was a rapid surge in plasma glucose that was sustained throughout the 60-min period of recovery. As expected, a similar surge was observed when glucose was ingested during the resting control trial, but values were significantly lower at 5 (P < 0.03) and 10 min (P < 0.02) than they were with the ExGLU trial. Glucose levels were not appreciably altered during recovery in the ExPL trial, and levels were significantly lower than in either of the two trials that involved glucose ingestion.

Mean resting lactate levels were within the normal expected range and were similar for the first 120 min of each trial (Table 2). Blood lactate levels were unaffected by exercise in these athletes. Likewise, during recovery from exercise, lactate levels remained unchanged and were not altered by glucose ingestion. Resting β-hydroxybutyrate levels were also within the normal range and were similar for all three trials (Table 2). During recovery from exercise, levels were increased (P < 0.0001), and the elevation appeared to be independent of glucose ingestion. In support of this observation, glucose ingestion during the resting control trial did not elicit any change in β-hydroxybutyrate levels.

**Table 2. Mean results of lactate and β-hydroxybutyrate, measured throughout each trial**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Trial</th>
<th>Exercise (min)</th>
<th>Recovery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Rest 30 60 90</td>
<td>120 5 10 20 30 45 60</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>ExGLU</td>
<td>0.9±0.1 1.0±0.1 1.1±0.2</td>
<td>1.1±0.2 0.9±0.2 0.9±0.1 0.9±0.1 1.1±0.2 1.0±0.1</td>
</tr>
<tr>
<td></td>
<td>ExPL</td>
<td>1.1±0.1 0.8±0.1 0.8±0.1 0.7±0.1 0.8±0.2</td>
<td>0.8±0.2 0.8±0.1 0.1±0.2 0.8±0.1 1.0±0.3 1.1±0.4</td>
</tr>
<tr>
<td></td>
<td>ConGLU</td>
<td>0.8±0.1 0.8±0.1 0.7±0.0 0.7±0.0 1.1±0.4</td>
<td>1.1±0.3 1.2±0.3 1.1±0.3 1.1±0.2 1.1±0.1 1.2±0.1</td>
</tr>
<tr>
<td>β-Hydroxybutyrate, µmol/l</td>
<td>ExGLU</td>
<td>35±16 43±24 51±28 73±37 98±45</td>
<td>173±65 240±94 238±72 233±85 122±50 61±30</td>
</tr>
<tr>
<td></td>
<td>ExPL</td>
<td>10±1.0 18±7 24±11 38±17 61±28</td>
<td>94±39 141±57 178±63 167±41 158±32* 136±27</td>
</tr>
<tr>
<td></td>
<td>ConGLU</td>
<td>22±8 33±15 44±21 52±22 92±33</td>
<td>88±30 88±30 73±23 66±25 35±20 16±9.0</td>
</tr>
</tbody>
</table>

Values are means ± SE. ExGLU, glucose ingestion after exercise; ExPL, placebo ingestion after exercise; ConGLU, glucose ingestion after rest. *ExPL significantly higher response than with ConGLU, P < 0.05.
trials \((P < 0.01)\). During recovery from exercise, GIP levels increased after glucose ingestion. A similar response was observed during the ConGLU trial. GIP levels did not show any such trend during recovery from the ExPL trial; instead, concentrations were lower during the later 30-min period of recovery than they were with the ExGLU and ConGLU trials.

Before the start of each trial, resting plasma gastrin concentrations were similar (Table 3). During exercise, gastrin levels increased, and in both exercise trials the highest levels were reached at 120 min \((P < 0.05)\). During recovery from exercise, gastrin concentrations were at least twofold higher for each of the running trials, and for the ExGLU trial gastrin levels were higher \((P < 0.05)\) than they were with the ConGLU trial. Glucose ingestion did not change gastrin levels during the ConGLU trial.

Resting GLP-1 concentrations were similar for each of the three trials (Table 3). There was an increase in plasma GLP-1 during both exercise trials and also during the resting control trial \((P < 0.001)\); the increase was such that GLP-1 levels were similar at the 120-min time point for all three trials. During recovery from exercise, GLP-1 increased after both exercise trials, with a moderately higher response during the ExGLU trial \((P = 0.09)\). Glucose ingestion after rest also increased GLP-1, but there were no clear differences between the ConGLU and the ExGLU trials.

Correlation analysis revealed that, when glucose was ingested during recovery from exercise, the plasma VIP response curve was negatively associated with the plasma glucose \((r = -0.35, P < 0.03)\) and insulin responses \((r = -0.37, P < 0.03)\). In addition, the plasma GIP response was positively associated with both glucose \((r = 0.59, P < 0.001)\) and insulin \((r = 0.48, P < 0.002)\).

**DISCUSSION**

Endurance exercise has been described as being similar to starvation in that both show a negative energy balance, reduced insulin levels in response to carbohydrate feeding, and carbohydrate intolerance (5). Feeding after exercise has been reported to cause hyperglycemia and a delayed insulin response, which is similar to “starvation-induced diabetes.” The findings of this study are consistent with these observations and demonstrate that glucose ingestion after endurance running elicits a more sustained elevation of plasma glucose that is accompanied by a decrease and delayed insulin response. Of the four gut peptides evaluated in this study, VIP was the only one to show a marked and significantly greater exercise-related response that was greater when glucose was ingested after exercise than it was with the exercise placebo and ConGLU trials. Furthermore, VIP was negatively correlated with both glucose and insulin during the ExGLU trial. The physiological significance of this response will require further study but suggests that VIP may play a regulatory role in glucose metabolism during postexercise recovery.

Our data show a greater increase in the plasma glucose response when glucose is ingested postexercise, and this is in concert with previously reported data in humans and dogs (20, 30). Maehlum et al. (30) were among the first to show that this increase in plasma glucose is partially explained by an increase in the amount of glucose escaping from the splanchnic bed after exercise. These data were elegantly confirmed in dogs by Hamilton et al. (20). More recently, Rose et al. (39) used an isotope tracer approach to demonstrate a 30% increase in the appearance of oral glucose ingested by endurance-trained athletes 30 min after exercise. Muscle biopsy studies in humans by Maehlum et al. (30) and muscle samples taken from dogs (20) support the idea that the increased glucose appearance in the circulation is used to facilitate restoration of glycogen levels in the previously working muscle.

In addition to an increased glucose response, we also observed a lower insulin response to glucose ingestion after exercise. This reduced or delayed insulin response has also been reported by other investigators (21, 25, 27, 32, 33, 37, 38).

**Fig. 2.** Plasma insulin concentrations during exercise or rest (0 to 120 min) and during recovery from exercise or rest (120 to 180 min) with (ExGLU and ConGLU) or without (ExPL) glucose ingestion after exercise. Values represent means \(\pm SE\) for 6 subjects. *ExGLU trial significantly higher than the ConGLU trial, \(P < 0.05\); ‡ExPL trial significantly lower than the ConGLU trial, \(P < 0.05\).

**Fig. 3.** Plasma VIP concentrations during exercise or rest (0 to 120 min) and during recovery from exercise or rest (120 to 180 min) with (ExGLU and ConGLU) or without (ExPL) glucose ingestion after exercise. Values represent means \(\pm SE\) for 6 subjects. *ExGLU trial significantly higher than the ConGLU trial, \(P < 0.05\); ‡ExGLU trial significantly higher than the ExPL trial, \(P < 0.05\).
Table 3. Effects of carbohydrate ingestion after exercise on circulating GIP, gastrin and GLP-1

<table>
<thead>
<tr>
<th>Exercise (min)</th>
<th>Recovery (min)</th>
<th>Rest</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>45</th>
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<td>20:00</td>
<td>25:00</td>
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<td>GIP, ng/l</td>
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<tr>
<td>Rest</td>
<td>60.9±10.1</td>
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<tr>
<td>Trial</td>
<td>65.4±8.0</td>
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<td>GLP-1, ng/l</td>
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<tr>
<td>Rest</td>
<td>283±17.6</td>
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<tr>
<td>Trial</td>
<td>286±17.4</td>
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</tbody>
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Values are means ± SE. **p<0.05** | *p<0.01** | †p<0.005** | ‡p<0.001**

43). The mechanisms responsible for this response may include diminished insulin secretion, possibly as a result of a persistently high α-adrenergic tone, or reduced insulin action (37). Alternatively, the decrease in insulin may be due to increased clearance from the circulation (43). The exaggerated glucose response, accompanied by a reduced insulin response, is consistent with the idea that insulin resistance is present immediately after exercise. Although insulin resistance in the hours immediately after exercise has been observed by several laboratories, the etiology remains unclear (10, 25, 37). The effect may be due to insulin resistance in nonexercised muscle, the presence of elevated free fatty acids, or an altered hormonal response (10, 25, 37). Although the mechanism has not been fully delineated, it is clear that a lower insulin response is metabolically advantageous because it can allow lipolysis to support the metabolic demands of the body during recovery while sparing the need to use glucose as an energy source.

The contribution of gastrointestinal hormones to glucoregulation postexercise is not well understood. Thus data from the present study can shed some light on the possible role that the selected peptides may play during exercise and in recovery postexercise. Although the emphasis of this paper is on postexercise responses, we also measured gut peptide changes during exercise. The increased plasma VIP levels found while running are in accordance with previous reports that VIP increases during endurance exercise (18, 22, 34, 35). The increase in plasma VIP levels during exercise, as for the other substrate-mobilizing hormones, may be explained by VIP’s proposed role as a polypeptide of substrate need and is supported by its ability to stimulate lipolysis (16), glycogenolysis, and gluconeogenesis (31). Studies by Galbo et al. (18), Oktedalen and colleagues (34, 35), and Opstad (36) have reported that the VIP response to exercise is almost abrogated by glucose ingestion or infusion during exercise, suggesting that VIP has an energy-mobilizing function during exercise. In the present study, glucose ingestion without prior exercise failed to affect plasma VIP, and this is also in concert with the metabolic hypothesis that VIP increases only in time of need. One of the most interesting observations in the present study was the marked increase in VIP when glucose was ingested after exercise and the negative associations with the insulin and glucose responses during recovery. Because VIP has vasodilatory properties and can increase intestinal secretion, it is plausible that it contributes to the elevated glucose response seen in this study, possibly by facilitating an increase in splanchnic glucose. Support for this effect may be found from a study involving healthy young subjects that showed increased arterial glucose levels during VIP infusion (14). On the other hand, the negative association between VIP and glucose suggests that those subjects with the lowest glucose response had the highest VIP response. This is consistent with a feedback loop in which low glucose leads to stimulation of VIP secretion, which would in turn facilitate increased splanchnic glucose release after an oral glucose load; the increase in glucose would subsequently allow VIP levels to drop. A similar case could be made for an insulin-stimulated feedback loop with VIP. However, the transitory nature of the VIP increase and the fact that the direction of the glucose and insulin responses were not altered after this increase in VIP suggests that the operation of a feedback loop may be less relevant during the immediate postexercise period and that perhaps VIP’s potential contribu-

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<table>
<thead>
<tr>
<th>Exercise (min)</th>
<th>Recovery (min)</th>
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<td>GIP, ng/l</td>
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<td>Rest</td>
<td>60.9±10.1</td>
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<tr>
<td>Trial</td>
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<td>GLP-1, ng/l</td>
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<tr>
<td>Rest</td>
<td>283±17.6</td>
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<tr>
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<td>286±17.4</td>
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Values are means ± SE. **p<0.05** | *p<0.01** | †p<0.005** | ‡p<0.001**

43). The mechanisms responsible for this response may include diminished insulin secretion, possibly as a result of a persistently high α-adrenergic tone, or reduced insulin action (37). Alternatively, the decrease in insulin may be due to increased clearance from the circulation (43). The exaggerated glucose response, accompanied by a reduced insulin response, is consistent with the idea that insulin resistance is present immediately after exercise. Although insulin resistance in the hours immediately after exercise has been observed by several laboratories, the etiology remains unclear (10, 25, 37). The effect may be due to insulin resistance in nonexercised muscle, the presence of elevated free fatty acids, or an altered hormonal response (10, 25, 37). Although the mechanism has not been fully delineated, it is clear that a lower insulin response is metabolically advantageous because it can allow lipolysis to support the metabolic demands of the body during recovery while sparing the need to use glucose as an energy source.

The contribution of gastrointestinal hormones to glucoregulation postexercise is not well understood. Thus data from the present study can shed some light on the possible role that the selected peptides may play during exercise and in recovery postexercise. Although the emphasis of this paper is on postexercise responses, we also measured gut peptide changes during exercise. The increased plasma VIP levels found while running are in accordance with previous reports that VIP increases during endurance exercise (18, 22, 34, 35). The increase in plasma VIP levels during exercise, as for the other substrate-mobilizing hormones, may be explained by VIP’s proposed role as a polypeptide of substrate need and is supported by its ability to stimulate lipolysis (16), glycogenolysis, and gluconeogenesis (31). Studies by Galbo et al. (18), Oktedalen and colleagues (34, 35), and Opstad (36) have reported that the VIP response to exercise is almost abrogated by glucose ingestion or infusion during exercise, suggesting that VIP has an energy-mobilizing function during exercise. In the present study, glucose ingestion without prior exercise failed to affect plasma VIP, and this is also in concert with the metabolic hypothesis that VIP increases only in time of need. One of the most interesting observations in the present study was the marked increase in VIP when glucose was ingested after exercise and the negative associations with the insulin and glucose responses during recovery. Because VIP has vasodilatory properties and can increase intestinal secretion, it is plausible that it contributes to the elevated glucose response seen in this study, possibly by facilitating an increase in splanchnic glucose. Support for this effect may be found from a study involving healthy young subjects that showed increased arterial glucose levels during VIP infusion (14). On the other hand, the negative association between VIP and glucose suggests that those subjects with the lowest glucose response had the highest VIP response. This is consistent with a feedback loop in which low glucose leads to stimulation of VIP secretion, which would in turn facilitate increased splanchnic glucose release after an oral glucose load; the increase in glucose would subsequently allow VIP levels to drop. A similar case could be made for an insulin-stimulated feedback loop with VIP. However, the transitory nature of the VIP increase and the fact that the direction of the glucose and insulin responses were not altered after this increase in VIP suggests that the operation of a feedback loop may be less relevant during the immediate postexercise period and that perhaps VIP’s potential contribu-
tion to increased splanchnic glucose output may be more important.

It is also noteworthy that VIP increased when the placebo was ingested after exercise, although the increase was markedly attenuated compared with glucose ingestion postexercise. Together, these data indicate a complex VIP response to multiple stimuli such as exercise and glucose. One possible explanation is that, when glucose is ingested under normal resting physiological conditions the insulin response is adequate and appropriate to accommodate glucose metabolism. However, when the insulin response to glucose ingestion is impaired, as it was during the ExGLU trial, there is then a physiological need to stimulate further insulin secretion. Recent animal studies have revealed that VIP overexpression in pancreatic β-cells enhances glucose-induced insulin secretion (24). Although it is speculative at this time, it is possible that the increase in VIP reflects the prevailing metabolic milieu of high glucose and lower insulin during the postexercise glucose trial and is an attempt to trigger increased insulin secretion. We did not measure the VIP response after exercise without fluid ingestion, so we cannot determine whether the increase postexercise is due to exercise alone or exercise and fluid ingestion. Further work is clearly needed to determine VIP’s physiological role and response during the postexercise recovery period.

Previous studies have reported that circulating plasma GIP levels do not change during 3 h of cycling exercise at 40% \( \text{VO}_2\text{max} \) (22), during cycling at 75% \( \text{VO}_2\text{max} \) until exhaustion (2), or during a 30-km run (41). The findings of the present study are in agreement. GIP has been identified as a mediator of insulin secretion (12, 13), and the secretion of GIP and its subsequent potentiation of insulin secretion in response to oral glucose (8) are well established. It has been suggested that exercise might modify the plasma GIP response to ingested carbohydrate, thereby partly explaining the exercise effect on plasma insulin and the glucose response to oral carbohydrate. Blom et al. (2) suggested that the GIP response after exercise might help to explain the delay in the insulin response. However, the findings of this study show an elevated GIP response to glucose ingestion after exercise similar to that observed in the resting glucose trial. This suggests that the altered insulin response elicited by oral glucose postexercise is not caused by an exercise-induced attenuation of the GIP response.

Plasma GLP-1 levels showed a mild response to running, with slight increases in the latter stages of the run. However, these increases were matched by increases during the resting control trial, so it does not appear that exercise alone has a very powerful effect on plasma GLP-1 release. GLP-1 secretion is largely stimulated by oral nutrients, and GLP-1 is a potent insulinotropic that is known to rise in humans after glucose ingestion (26). This effect was confirmed in the resting glucose trial in the present study. GLP-1 levels were also increased during recovery from exercise in the ExPL trial, suggesting that exercise alone is sufficient to independently stimulate GLP-1 release after exercise. However, because the increase in GLP-1 was not significantly greater during the ExGLU than it was during either of the other two trials, it does not appear that exercise can significantly potentiate GLP-1 release in these athletes. Furthermore, despite the known insulinotropic effects of GLP-1, the increase during recovery in the ExGLU trial was inadequate to counter the attenuated insulin response that was found during this trial. It is likely that GLP-1’s insulinotropic effects are masked postexercise due to an α-adrenergic effect on the pancreatic β-cells.

The findings of this study show that circulating plasma gastrin levels are increased in response to exercise. This observation is consistent with previously published data from our group, which also showed an increased gastrin response at the end of a controlled 90-min bout of exercise (29). This increase in gastrin may be due in part to elevated adrenergic and reduced cholinergic activity and to reduced perfusion of the splanchnic vascular bed during exercise (3, 17, 29). The net physiological effect of these responses might be to increase antrum pH, and an increase in gastrin could serve to counter this effect. We also observed a twofold increase in gastrin when glucose was ingested after exercise. This increase was greater than the response observed when glucose was ingested after rest. It is likely that some of the increase in gastrin postexercise was due to reperfusion of splanchnic tissue, and this effect appears to be potentiated by glucose. Indeed, a greater gastrin response to exercise that was preceded by a meal was previously reported by Feldman and Nixon (15). Despite the higher gastrin levels, gastric acid secretion was not altered, and it was suggested that the release of inhibitors of acid secretion, such as VIP, may have countered the effect of gastrin. Because we did not measure acid secretion in the present study, we can only speculate that the increase in gastrin and the increase in VIP were acting in concert to optimally regulate homeostasis.

In conclusion, the findings of this study suggest that a number of regulatory peptide responses are altered by exercise and glucose ingestion postexercise, further implying a metabolic role for these peptides during recovery from exercise. The exaggerated glucose response in the face of reduced insulin suggests mild insulin resistance postexercise, and the increased VIP response may have contributed to this increase in glucose. The physiological significance of this VIP response warrants further investigation. The reduced insulin response when glucose was ingested after exercise suggests that the insulinotropic effects of GIP and GLP-1 may be blunted during the immediate postexercise recovery period. These data demonstrate the complex interplay between gastric peptides and glucose metabolism that is necessary to promote peripheral glucose delivery and, in turn, optimal glycogen repletion in previously exercised muscle.

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REFERENCES


