Glucoregulatory Endocrine Responses to Intermittent Exercise of Different Intensities: Plasma Changes in a Pancreatic β-Cell Peptide, Amylin

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Amylin, a peptide hormone released from the β cells of the pancreas and cosecreted with insulin, is reported to inhibit the release of postprandial glucagon and insulin and to modulate gastric emptying. Changes in insulin and glucagon are important for controlling blood glucose levels under conditions in which metabolic rate is elevated, such as during and following exercise. Amylin may participate in the regulation of blood glucose levels in response to exercise, although the role of amylin has not been investigated. The purpose of the study was to determine the effects of a progressive, intermittent exercise protocol on amylin concentrations and to compare its response to circulating levels of insulin, glucagon, cortisol, and glucose. Seven well-trained males completed an intermittent exercise trial on a treadmill at four progressive exercise intensities: 60%, 75%, 90%, and 100% of maximum oxygen consumption ($\dot{V}O_2$max). Blood samples were collected before exercise, after each exercise intensity, and for 1 hour following the exercise protocol. Subjects also completed a control trial with no exercise. Amylin and insulin rose from baseline (5.79 ± .78 pmol/L and 4.76 ± .88 μIU/mL) to peak after 100% $\dot{V}O_2$max (9.16 ± 1.35 pmol/L and 14.37 ± μIU/ml), respectively and remained elevated during much of recovery. Thus, a progressive intermittent exercise protocol of moderate to maximum exercise intensities stimulates increases in amylin levels in well-trained individuals in a similar fashion to that of insulin, whereas glucagon concentrations only increase after the greatest exercise intensity, then quickly decline. Future studies should examine the effects of higher amylin concentrations in exercise recovery on glucoregulation.

AMYLIN IS A 37-AMINO ACID peptide hormone discovered in 1987, and cosecreted from the β cells of the pancreas along with insulin.[1] The secretion of insulin from the β cells of the pancreas is mainly regulated by blood glucose concentrations; however, the hormones glucagon and amylin, as well as other hormones and neural factors, affect insulin release in healthy subjects.[2-4] Amylin inhibits the release of both glucagon and insulin and modulates gastric emptying.[5-7] Amylin appears to work in combination with insulin to regulate blood glucose levels by controlling the influx of glucose into the bloodstream and preventing hyperglycemia.[8] An important mechanism may be the inhibition of glucagon. When nondiabetic rodents are administered a selective amylin antagonist or neutralizing anti-amylin antibodies, there is a rise in glucagon.[9] Moreover, type II diabetes patients (with deficient β-cell function) treated with insulin alone will exhibit impaired suppression of postprandial glucagon and hepatic glucose release.[10,11] However, recent evidence demonstrates mealtime administration of pramlintide, an analog of amylin, along with insulin, will dramatically reduce the postprandial hyperglucagonemia in these patients.[12] These data demonstrate effects of amylin in vivo, independent of the actions of insulin.

Glucoregulatory hormones are important in meeting the demands of moderate intensity exercise and the endocrine/metabolic status[13] during exercise and exercise recovery, especially in people with diabetes. Whereas mainly muscle contraction and, to a lesser degree, insulin, facilitate glucose uptake during exercise, glucagon and cortisol increase circulating glucose levels. Glucagon and cortisol promote hepatic glucose release and inhibit glucose transport into peripheral tissues, respectively,[14] producing an elevation in blood glucose. The form of exercise employed may affect the time-course of glucoregulatory hormonal response during and after exercise.

Continuous cycling protocols (≤60% maximum oxygen consumption [$\dot{V}O_2$max]) suppress insulin concentrations during exercise[15-17] and there is tight glucoregulation in normal subjects with an increase in hepatic glucose production that is matched with increased utilization in exercising muscle.[18] During short-duration, intense exercise, greater than 85% $\dot{V}O_2$max glucose levels increase and plasma insulin levels remain unchanged or slightly decline.[6,19-21] Almost immediately following a brief bout of exercise ≥85% $\dot{V}O_2$max, hyperglycemia and concomitant hyperinsulinemia occur[6,21,22]; glucagon and cortisol concentrations increase and peak during recovery as well.[6,13] Moreover, physical training status has been shown to affect the insulin, glucagon, and cortisol responses to exercise and recovery.[6,13,23]

There are no reports of amylin responses to exercise. This study was designed to examine amylin's responses with respect to glucose and the glucoregulatory hormones: insulin, glucagon, and cortisol. In humans, amylin is secreted in response to elevated glucose and works primarily to reduce glucose production through a slowing of gastric emptying and a suppression of glucagon secretion without inhibiting the glucagon response to hypoglycemia.[1,5-8] Since insulin increases in the recovery phase following high-intensity exercise,[6,21,22] we hy-

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Submitted August 20, 2001; accepted November 19, 2001.

Supported by a Faculty Development Grant and an Orr Grant from Southeastern Louisiana University.

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0026-0495/02/5105-0019$35.00/0

doi:10.1053/meta.2002.32023

pothesized that amylin would follow a similar secretion pattern. Given the potent effects of amylin or an amylin analog on glucagon release in vivo,[7,12] such increases may play a role along with insulin to suppress glucagon secretion once elevated glucose concentrations are reached. We utilized a strenuous intermittent treadmill protocol designed to be a provocative stimulus for glucose and glucoregulatory hormone responses. Well-trained subjects were employed to enhance the effect of exercise on glucose responses[6] and to improve the likelihood that subjects could complete a rigorous exercise protocol.

MATERIALS AND METHODS

Subjects

Seven male subjects were recruited from the university community and provided written consent for participation in the study. Mean (±SEM) age, weight, height, percent fat, and $\dot{V}O_2$max were 28.71 ± 2.91 years, 73.39 ± 4.14 kg, 179.80 ± 2.53 cm, 11.08% ± 1.01%, and 61.01 ± 2.37 mL/kg/min, respectively. The subjects that participated had no history of metabolic or cardiovascular diseases, were between the ages of 18 and 39 years of age, were not taking any medications, and were following a normal dietary regimen. They all had previous running experience and a well-trained aerobic fitness level ($\dot{V}O_2$max > 52.0 mL/kg/min). These medical/descriptive data were determined through medical history screening, a 3-day dietary record, and a graded exercise test with a 12-lead electrocardiogram and measurement of respiratory gases. The study was approved by the Southeastern Louisiana University Institutional Review Board.

Preliminary Trial

Subjects completed a preliminary trial to determine standard fitness measures that included body composition and cardiorespiratory fitness ($\dot{V}O_2$max). Body composition was determined by measuring skinfold thickness at 4 sites: (1) triceps, (2) suprailiac, (3) abdomen, and (4) thigh.[24] $\dot{V}O_2$max was assessed on a treadmill by measuring respiratory gases with an automated system. Every 30 seconds, inspiratory air volume was measured using a pneumotach (series 3813;Hans Rudolph, Kansas City, MO) and pressure transducer (VRCD/HC-1; Consentius Technologies, Sandy, UT); expired O_2 and CO_2 were analyzed (S-3A/1 and CD-4 analyzers, Ametek, Pittsburgh, PA). Equipment was interfaced (OUS/MC; Consentius Technologies) to a personal computer and values were recorded. Before each $\dot{V}O_2$max determination, the O_2 and CO_2 gas analyzers were calibrated with gases of known composition.

Subjects completed a graded exercise test to exhaustion that began with a workload of 5 miles per hour and 4% grade. The workload increased 1 mile per hour every 2 minutes; treadmill grade remained at 4% throughout the test. All subjects reached $\dot{V}O_2$max when either the primary criterion of a plateau in $\dot{V}O_2$ with an increase in workload was met or 2 of 3 secondary criteria: (1) reaching predicted maximal heart rate, (2) respiratory exchange ratio greater than 1.1, or (3) a rating of perceived exertion (15-point Borg Scale) of 19 or 20. The treadmill speeds (at a 4% treadmill grade) that corresponded with 60%, 75%, 90%, and 100% $\dot{V}O_2$max were calculated from a regression equation generated from the relationship between $\dot{V}O_2$ and treadmill speed in the preliminary trial.

Exercise and Control Trials

Subjects refrained from exercise and alcohol consumption 24 hours before testing. Subjects reported for the exercise trial at 7:45 AM following an overnight fast. An intravenous catheter (Travenol, 22 g, 32 mm, Travenol Laboratories, Deerfield, IL) was inserted into an antecubital vein and a normal saline lock was attached. At 8:30 AM, 40 minutes prior to exercise (-40) and at 9 AM, 10 minutes prior to exercise (-10), resting blood samples were collected from the catheter. Subjects then completed an intermittent treadmill exercise protocol at 4 speeds predicted to elicit a specific $\dot{V}O_2$: 60% $\dot{V}O_2$max for 10 minutes, 75% $\dot{V}O_2$max for 10 minutes, 90% $\dot{V}O_2$max for 5 minutes, and 100% $\dot{V}O_2$max for 2 minutes. After each workload was completed at the prescribed intensity and duration, treadmill speed was reduced to a walking speed (for 3.5 to 4 minutes) to allow a blood sample to be collected. Gas samples were collected continuously and confirmed that the actual $\dot{V}O_2$ corresponded with the predicted $\dot{V}O_2$ for each workload.

In addition to blood samples collected from the intravenous catheter after each workload (60%, 75%, 90%, 100% $\dot{V}O_2$max), samples were also collected every 15 minutes during a 1-hour recovery (R15, R30, R45, and R60). Samples for glucagon analysis were collected in chilled EDTA tubes with protease inhibitor and centrifuged at 4°C. Samples for amylin analysis were collected in an identical fashion, but without protease inhibitor (in accordance with recommendations for sample collection by Linco Research, Inc, St Louis, MO). Samples for plasma glucose and lactate analysis were collected into tubes with sodium fluoride and potassium oxalate.

A control trial was conducted 1 month after the experimental trial under identical conditions with the exception of exercise.

Analyses

Serum samples were assayed for insulin and cortisol using a sensitive chemiluminescent assay (Immulite, Diagnostic Products Corp, Los Angeles, CA). Interassay coefficients of variation for a high serum pool were 10.6% and 5.6% for insulin and cortisol, respectively. Plasma samples were assayed for glucagon with a double-antibody radioimmunoassay (Diagnostic Products Corp) with an interassay coefficient of variation of 9.5%. For insulin, cortisol, and glucagon, intra-assay coefficients of variation averaged lass than 5.0%. Total amylin was determined by immunoenzymatic assay (IEMA; Linco Research Inc) with an interassay coefficient of variation less than 15% and intra-assay coefficient of variation less than 10%. Glucose and lactate were determined spectrophotometrically (Sigma Chemical, St Louis, MO). Hematocrit was determined using the microhematocrit method; colorimetric analysis was used to determine hemoglobin (Sigma Chemical). Hematocrit and hemoglobin were then used to determine the degree of hemoconcentration.[25]

Statistics

Three different statistical approaches were used. First, to examine the total response of the hormones and glucose to exercise, integrated area-under-the-curves (AUC) for the exercise and control trials were computed using a trapezoidal method after subtracting averaged baseline hormone concentration for each subject. Dependent *t* tests were used to determine differences between exercise and control trials. Second, a 2 × 10 (trial × time point) repeated-measures analysis of variance (ANOVA) was used to examine hormone changes over time and hormone concentrations between trials. Significance levels reported reflect Geisser-Greenhouse degrees of freedom adjustments. Third, to examine the relationship between insulin and amylin concentrations to exercise, we used Pearson correlation coefficients.

RESULTS

During the exercise trial mean percent changes in plasma volume were not reduced more than 9.9% between any 2 time points (workloads) during exercise and 2.2% between any time points during recovery. Since hormone and substrate increases were much greater than the extent of plasma volume loss (≤9.9%), factors other than hemoconcentration were presumed to produce most of the changes in hormone levels that were observed.[26-28] Lactate concentrations were analyzed to demon-

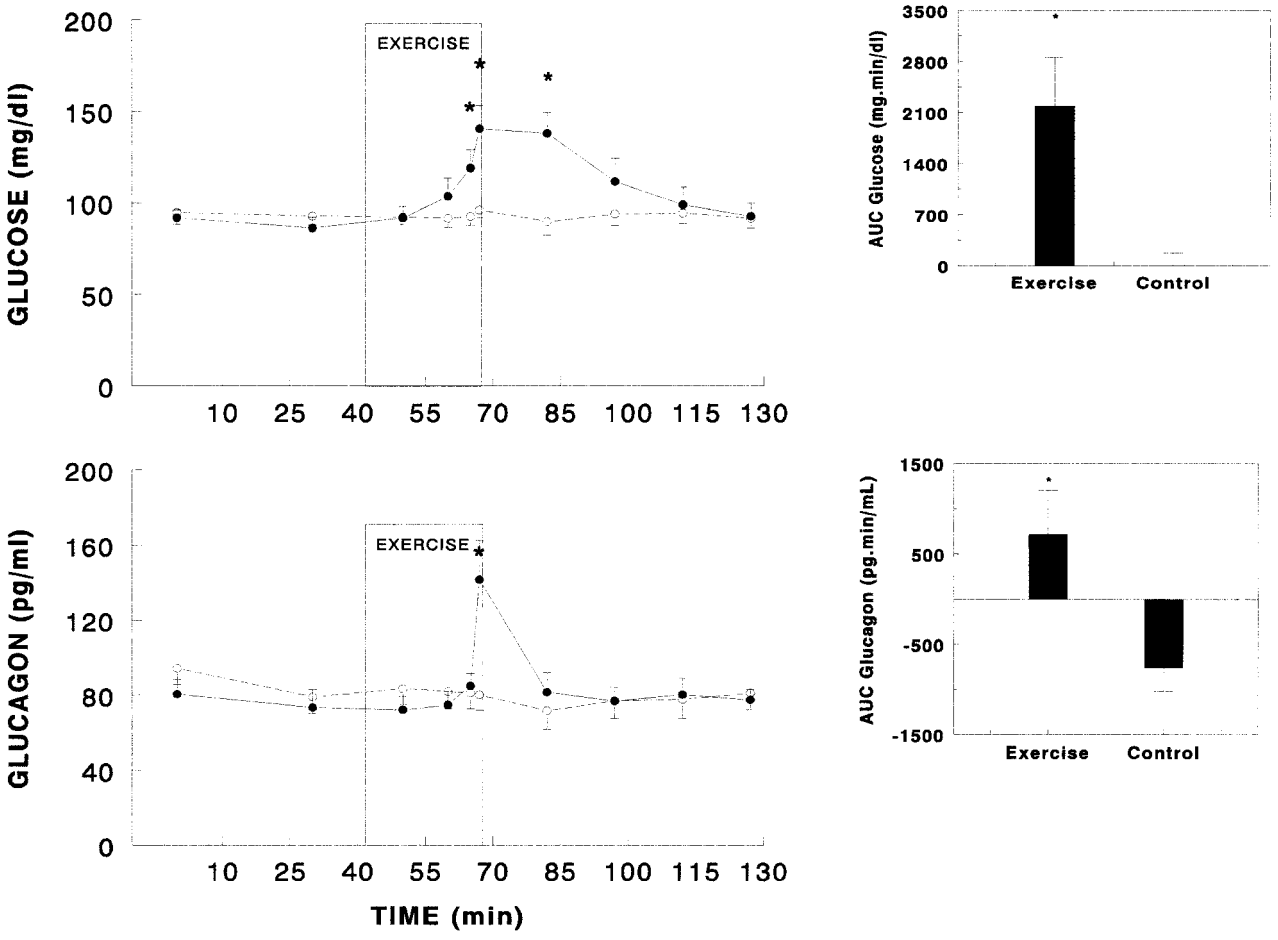

Fig 1. (Left) Means ± SE for exercise (●) and control (○) trials for glucose (top) and glucagon (bottom) before exercise, after each exercise intensity, and for 1 hour of recovery. (Right) AUC concentrations for glucose and glucagon. *Significantly different values for exercise compared with control.

strate the degree of metabolic stress on skeletal muscles. Lactate concentrations rose with progressive increases in workload from pre-exercise values of .96 ± .18 mmol/L at -10 to peak after 100% $\dot{V}O_2$max at 10.19 ± 1.2 mmol/L. Exercise lactate levels were significantly higher than baseline levels, as expected.

Glucose and Glucagon

There was a significant main effect for time [$F(9,108) = 11.84$, $P < .01$, $F(9,108) = 8.73$, $P < .01$] and trial × time point [$F(9,108) = 11.79$, $P < .01$, $F(9,108) = 9.13$, $P < .01$] for glucose and glucagon, respectively. Glucose and glucagon rose from baseline (86.13 ± 5.8 mg/dL and 73.42 ± 9.53 pg/mL) to peak after 100% $\dot{V}O_2$max (140.42 ± 12.56 mg/dL and 141.55 ± 20.91 pg/mL), respectively (Fig 1). Glucose remained elevated during the first 30 minutes of recovery whereas glucagon returned to resting concentrations 15 minutes into recovery. Student *t* tests revealed that concentrations were significantly higher during the exercise than the control trial for glucose after 90% $\dot{V}O_2$max, 100% $\dot{V}O_2$max, and R15 and for glucagon after 100% $\dot{V}O_2$max. Glucose and glucagon AUCs for the exercise trials were significantly higher than for the control trials (Fig 1).

Cortisol

There was a significant main effect for time [$F(9,108) = 3.34$, $P < .01$] and trial × time point [$F(9,108) = 7.95$, $P < .01$] for cortisol. Baseline cortisol levels (17.99 ± 2.23 μg/dL) increased in response to exercise after 90% $\dot{V}O_2$max to peak after R15 (24.64 ± 3.15 μg/dL) and remained elevated during the rest of recovery (Fig 2). Student *t* tests revealed that cortisol levels were significantly higher during the exercise than the control trial after 100% $\dot{V}O_2$max, R15, R30, R45, and R60. Cortisol AUC for the exercise trial was significantly higher than the control trial (Fig 2).

Insulin and Amylin

There was a significant main effect for time [$F(9,108) = 4.94$, $P < .01$, $F(9,108) = 3.85$, $P < .01$] and trial × time point [$F(9,108) = 5.66$, $P < .01$, $F(9,108) = 4.62$, $P < .01$] for insulin and amylin, respectively. Amylin and insulin concen-

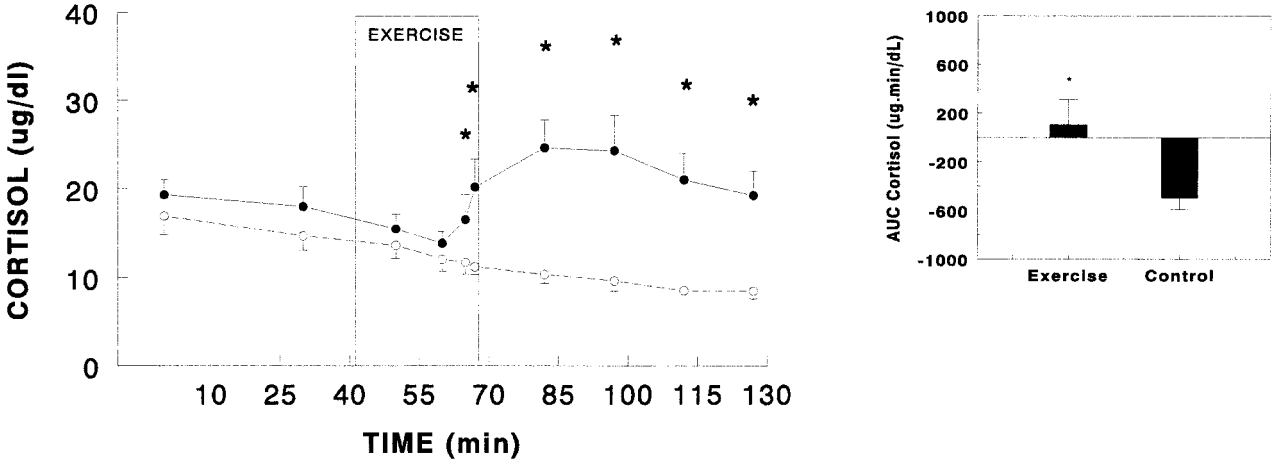

Fig 2. (Left) Means ± SE for exercise (●) and control (○) trials for cortisol before exercise, after each exercise intensity, and for 1 hour of recovery. (Right) AUC concentrations for cortisol. *Significantly different values for exercise compared with control.

trations changed in a similar fashion after each exercise workload, whereas glucagon increased only after the highest exercise workload. Baseline amylin and insulin concentrations (5.79 ± .78 pmol/L and 4.76 ± .88 μIU/mL) increased and peaked after 100% $\dot{V}O_2$max (9.16 ± 1.35 pmol/L and 14.37 ± μIU/mL, respectively) and were elevated during much of the recovery period (Fig 3). Student *t* tests revealed that hormone concentrations were significantly higher during the exercise than the control trial for amylin after 100% $\dot{V}O_2$max and R15 and insulin after 100% $\dot{V}O_2$max, R15, and R30. Insulin and amylin AUCs for the exercise trials were significantly higher than for the control trials (Fig 3).

There were strong and significant positive correlations between amylin and insulin for all time points except 90% $\dot{V}O_2$max and R15, at which moderate relationships were found (Table 1).

DISCUSSION

In the present study we used an intermittent running protocol to examine glucoregulatory responses following short bouts of different exercise intensities with brief active recovery (walking) after each bout. We observed no change in insulin or amylin levels following the 60% and 75% $\dot{V}O_2$max bouts, but the insulin/amylin response increased after 90% $\dot{V}O_2$max to peak after 100% $\dot{V}O_2$max and remained elevated during most of the 1-hour recovery. We demonstrated that the protocol stimulated increases in amylin in well-trained individuals in a similar fashion to that of insulin, whereas glucagon only increased after the greatest exercise intensity, then quickly declined. Cortisol also rose after higher exercise intensities, peaking and remaining elevated during recovery. This is the first study to document amylin responses to exercise.

Several previous investigations have documented the effects of exercise on circulating glucose and glucoregulatory hormones. Continuous and continuous graded cycling protocols result in suppressed insulin concentrations during exercise.[6,17,22] During moderate continuous exercise (60% $\dot{V}O_2$max) there is tight glucoregulation in normal subjects with an increase in hepatic glucose production (≈250% increase) matched with increased utilization in exercising muscle.[21] However, intermittent cycling at moderate exercise intensities does not change serum insulin levels or glucose levels.[17] It has been shown that sustained exercise at 80% $\dot{V}O_2$max for approximately 7 minutes will produce little or no change in plasma glucose or insulin during exercise in lean subjects, with a sharp rise during recovery.[29] Moreover, short-duration, high-intensity exercise at greater than 85% $\dot{V}O_2$max elicits a different response. For example, it has been reported that during exercise at 100% $\dot{V}O_2$max there is a 700% to 800% increase in production and approximately a 400% increase in utilization, resulting in increased circulating glucose levels, whereas plasma insulin levels remained unchanged[6,20,21] or slightly declined.[16,21,22] Almost immediately following a brief bout of exercise at greater than 85% $\dot{V}O_2$max, hyperglycemia and concomitant hyperinsulinemia occur.[6,21,22,30] Sigal et al[21] demonstrated increases in insulin after exercising to 89% to 98% of $\dot{V}O_2$max for approximately 12 minutes with peak insulin values being reached at 4 minutes of recovery. It has been suggested that postexercise hyperinsulinemia following intense exercise is necessary for the metabolic clearance rate response and to revert blood glucose levels to pre-exercise concentrations.[30] Collectively, data from these previous studies are in line with insulin and glucose responses following the intermittent exercise in the present study in which we collected blood samples following each exercise intensity, and the present data suggest that amylin increases in recovery from exercise.

The increase in blood glucose levels following exercise is even greater in well-trained subjects, who likely have greater glycogen stores.[6,31] In a postprandial state these responses are attenuated to some extent.[13] The sharp exercise-induced increase in glucose concentrations after a 12-hour fast in the present study may be explained by the high intensity of the exercise protocol,[22] as well as the well-trained status[6] of the subjects. In humans, high-intensity exercise produces a quick release of large amounts of catecholamines[6,16,32] that are ample enough to stimulate hepatic glycogenolysis and elevate blood

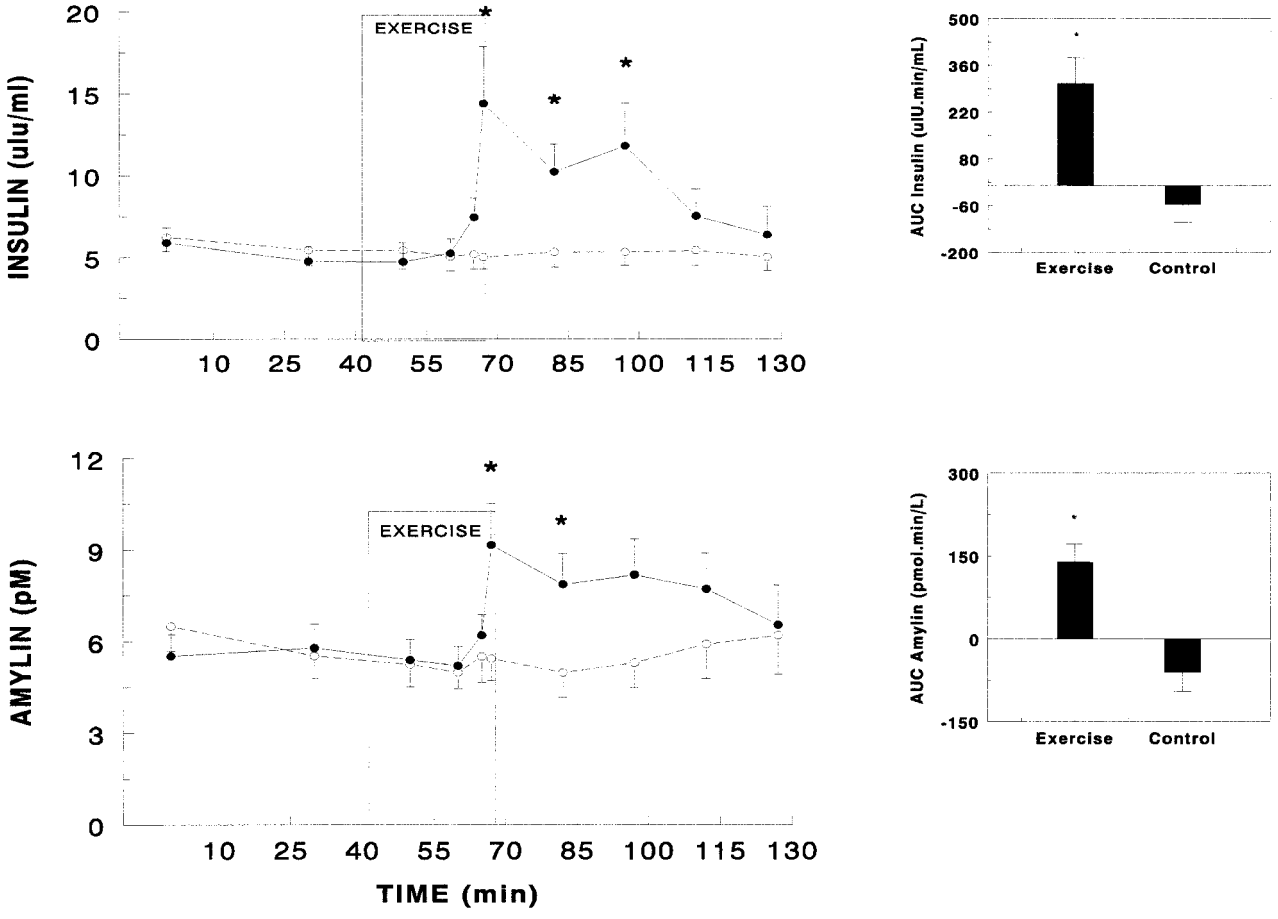

Fig 3. (Left) Means ± SE for exercise (●) and control (○) trials for insulin (top) and amylin (bottom) before exercise, after each exercise intensity, and for 1 hour of recovery. (Right) AUC concentrations for insulin and amylin. *Significantly different values for exercise compared with control.

glucose levels, which likely contributed to the elevated blood glucose levels in the present study.

Glucagon responses to exercise only occurred after the greatest exercise intensity and then quickly declined in recovery, which is consistent with previous exercise findings.[6] Compared with experiments examining postprandial hormone responses, this rise in glucagon, followed by a rapid drop, is indicative of normal pancreatic islet-cell function and glycemic control.[12] Baseline cortisol levels declined during lower exercise intensities, which is a likely result of well-known diurnal effects, also observed in the control trial. Cortisol then increased in response to exercise above the 75% $\dot{V}O_2$ peak intensity, which has been shown with exercise intensity ≥ 80% of $\dot{V}O_2$max,[4,7,13,19] and these elevated levels were maintained throughout recovery. Cortisol is known to block glucose uptake by tissues, which would result in the increase of circulating glucose levels.[14]

Table 1. Correlation Coefficients Between Amylin and Insulin During the Exercise Trial

Time of Sample	Pearson Correlation	Significance
−40	.784	.037
−10	.901	.006
+10	.931	.002
+20	.979	.0001
+25	.726	.065
+27	.956	.001
R15	.729	.063
R30	.906	.005
R45	.953.	.001
R60	.991	.0001

Amylin and insulin are cosecreted in response to nutrient stimuli[1,33] and other secretagogues such as sulfonylureas[34]; amylin also shows a similar 24-hour plasma concentration profile to that of insulin.[5] Although amylin is cosecreted with insulin, in vivo studies indicate that amylin plays an important role in glucose regulation independent of insulin. There is strong evidence that amylin is a potent suppressor of glucagon, both in rats[35,36] and in humans with type I and type II diabetes.[7,12,37] When plasma glucose and insulin levels of rodents are carefully controlled in hyperinsulinemic-euglycemic clamp studies, amylin has been shown to be a strong suppressor of glucagon.[36] Patients with type I diabetes had lower glucagon responses and better glycemic control following breakfast with

administration of an amylin analog, pramlintide, than with placebo.[7] Additionally, patients with type II diabetes exhibit an impaired β-cell secretory response to meals, leading to reduced insulin and amylin release.[37] When these patients are treated with insulin alone, suppression of postprandial glucagon and hepatic glucose output is impaired.[10,11] However, mealtime administration of pramlintide and insulin reduced postprandial glucose excursions and suppressed glucagon release.[12,38] Since high-intensity exercise in normal subjects elicits a sharp post-exercise rise in glucose and insulin, we hypothesized that amylin (known to be released in response to feeding) would increase during recovery, similar to insulin, and that this response could potentially be important in maintaining postexercise glycemic control. Not only were the patterns of change in amylin and insulin concentrations similar during exercise and recovery (with insulin and amylin concentrations elevated in recovery), but Pearson correlation coefficients were strong and significant for 8 of 10 time points. Future studies will be required to determine whether elevated amylin levels are important in preventing excessive glucose oxidation and depletion of carbohydrate stores necessary for maintaining exercise performance.

In summary, this is the first study to demonstrate the effects of exercise on amylin together with other glucoregulatory hormones. The data show that amylin and insulin are increased in a similar fashion in response to a treadmill protocol that included moderate and maximal exercise. The data suggest the need for future studies to examine the effects of high amylin levels in exercise recovery, and to clarify the role of amylin in the regulation of substrate supply.

ACKNOWLEDGMENT

The authors wish to thank the subjects who participated in the study. We also are grateful to Ginger R. Kraemer for her help with data collection.

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