Metabolic effects of low cortisol during exercise in humans

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Del Corral, Pedro, Edward T. Howley, Mike Hartsell, Muhammad Ashraf, and Mary Sue Younger. Metabolic effects of low cortisol during exercise in humans. J. Appl. Physiol. 84(3): 939–947, 1998.—This study examined the physiological effect of reduced plasma cortisol (C) during prolonged exercise in humans. The effects of normal C (NC) were compared with metyrapone-induced low C (LC) on plasma substrate availability and the respiratory exchange ratio during 2 h of exercise at ~60% peak O2 consumption in nine subjects. The C responses were compared with preexercise (Pre) levels and with a rest day (Con). At rest, C was attenuated by ~70% for LC compared with NC. At rest, plasma glucose, lactate, glycerol, β-hydroxybutyrate, alanine, branched-chain amino acids, insulin, glucagon, growth hormone, epinephrine, and norepinephrine were similar under LC and NC (P > 0.05). During exercise under NC, plasma C increased compared with Pre, whereas it remained unchanged during LC. During NC, plasma C was elevated at 90 min (compared with Con) and at 120 min (compared with Con and Pre). During exercise, plasma glucose decreased to the same extent and lactate was similar under both conditions, whereas plasma glucocerol, β-hydroxybutyrate, alanine, and branched-chain amino acids were higher (P < 0.01) under NC. Plasma insulin declined (P = 0.01) to a greater extent under LC, whereas growth hormone, epinephrine, and norepinephrine tended to be higher (0.05 ≤ P ≤ 0.10). Plasma glucagon increased under both conditions (P < 0.01). The respiratory exchange ratio did not differ between conditions. We conclude that, during exercise, 1) C accelerates lipolysis, ketogenesis, and proteolysis; 2) under LC, glucoregulatory hormone adjustments maintain glucose homeostasis; and 3) LC does not alter whole body substrate utilization or the ability to complete 2 h of moderate exercise.

THE RATES OF HEPATIC glucose production, lipolysis, and proteolysis are normally regulated by the nervous and endocrine systems (i.e., insulin and the counterregulatory hormones). During intense exercise (~85% maximal O2 consumption [V̇O2max]), hepatic glucose production increases six- to eightfold, matching or slightly exceeding glucose uptake (24, 33). This accelerated hepatic glucose production is observed in the presence of little or no change in plasma glucagon and plasma insulin concentrations. On the other hand, plasma catecholamines are elevated 7- to 10-fold, suggesting that during intense exercise the major regulators of hepatic glucose production are the catecholamines (24, 33). At moderate exercise intensities and longer durations (e.g., 60 min at 60% V̇O2max), the primacy of the catecholamines in maintaining hepatic glucose production is questionable (26), whereas the primacy of insulin and glucagon in preventing hypoglycemia has been established (20, 38). However, this does not prove that other hormones or neurotransmitters are not involved in the prevention of hypoglycemia during exercise.

It has been >40 years since the effects of exercise on glucocorticoid levels were first described in humans (34). Since then, we have learned that the increase in cortisol is dependent on the intensity and duration of the exercise bout (9). We recently reported that the cortisol response is also observed in children (12). Additionally, it is known that, after the administration of a labeled glucocorticoid, glucocorticoid receptor activation steadily increases to a similar extent during rest and exercise (8). However, little is known about the physiological significance of cortisol during exercise in humans. At rest, some of the metabolic functions of cortisol related to fuel homeostasis include 1) modest increases in hepatic glucose production; 2) proteolysis, allowing amino acid oxidation and/or their entrance into gluconeogenesis; 3) lipolysis, allowing oxidation of nonesterified fatty acids, glycerol’s entrance into gluconeogenesis, and ketogenesis; 4) a reduction in insulin-dependent peripheral glucose uptake, thus ensuring blood glucose supply to the brain; and 5) an increase in the rate of synthesis of gluconeogenic enzymes in the liver (4, 10, 14–18, 30, 31). Furthermore, it is well known that cortisol plays an important role in the defense against prolonged insulin-induced hypoglycemia at rest (4, 10). Thus it is plausible that during prolonged exercise (>60 min) the role of cortisol in glucose homeostasis may become apparent.

The few studies that have examined the effect of adrenocortical insufficiency during exercise have suggested a reduced work capacity, which is improved by appropriate cortisol replacement. The decrease in work capacity is characterized by cardiovascular instability and skeletal muscle weakness (28, 40). Others have reported (2, 21) that hypopituitary and adrenalectomized subjects showed proper or even exaggerated metabolic responses during moderate to heavy exercise when glucocorticoid and mineralocorticoid replacement was adequate. Unfortunately, these studies did not provide information on substrates or hormonal responses when the cortisol replacement was discontinued.

There is a paucity of data on the effects of high and/or low cortisol on blood glucose and other substrates during exercise in humans. The effects of cortisol during exercise are by and large based on studies performed on animals (see Ref. 36 for review). Furthermore, very little is known concerning the physiological significance of the transient increase in cortisol levels during exercise. This lack of information is probably
because many of cortisol’s effects are delayed compared with the more fast-acting hormones. However, this does not negate its potential significance during exercise. Perhaps contrasting a prolonged bout of exercise under normal and low preexercise cortisol levels will provide insights about the metabolic effects of cortisol during exercise in humans. The objectives of this study were to evaluate the physiological effects of a low plasma cortisol concentration on 1) the concentration of plasma substrates, 2) whole body substrate utilization, 3) substrate-regulating hormones, and 4) selected cardiovascular responses during prolonged exercise. To address these issues, we administered metyrapone (a pharmaceutical agent that blocks cortisol synthesis) to maintain a low-cortisol (LC) condition and compared that treatment with a control condition [normal cortisol (NC)] in which the subjects received a placebo (allowing the morning cortisol peak to occur).

**METHODS**

Subjects. Nine healthy, nonsmoking college students (5 men and 4 women) were recruited from the University of Tennessee, Knoxville, to participate in the study. The subjects’ age, height, weight, and peak O2 consumption (VO2peak) were 26.6 ± 1.1 yr, 1.72 ± 0.02 m, 73.6 ± 4.3 kg, and 40.6 ± 1.3 ml kg−1 min−1, respectively. Each subject completed a health history questionnaire and was asked to read and sign an informed consent form, which was approved by the University of Tennessee’s Institutional Review Board. The subjects were not taking any medication (including oral contraceptives) or suffering from any metabolic disorder (i.e., diabetes, thyroid gland abnormalities). Additionally, the subjects were asked to refrain from exercise, alcohol, and caffeine for 24 h before reporting to the laboratory. The subjects were reminded to maintain consistent preexercise diets during the course of the experiment. The menstrual phase shows no consistent effect on cortisol levels (13, 23) during prolonged exercise and, therefore, was not controlled. Each subject reported to the laboratory on 3 separate days, completing baseline measurements and a graded exercise test on the first visit and a submaximal exercise test on the second and third visits.

Baseline measurements and graded exercise test. On the first visit each subject arrived at the laboratory at ~0730, and height and weight were measured and recorded. The subject was then taken to a quiet room and seated in recumbent position, and the right hand was heated with an electrically heated pad kept at 65–70°C. A 21-gauge Teflon catheter was placed in a retrograde fashion into a right hand dorsal vein to obtain arterialized venous blood (27). Each subject remained seated for the collection of a 2-ml blood sample at 30-min intervals from 0800 to 1000. The intravenous line was kept patent with a continuous drip of 154 mmol/l NaCl solution. The blood samples were used to monitor the cortisol circadian rhythm for statistical comparison between resting and exercise conditions (5, 35).

After the collection of the last resting blood sample the subject sat on a pendulum-style cycle ergometer (model 817E, Monarck, Varberg, Sweden). A graded exercise test was conducted to determine the subject’s 2.5 mmol/l lactate threshold and VO2peak. The expired gas was analyzed continuously by previously calibrated O2 (Ametek O2 analyzer) and CO2 (model S-3A/1 LB-2, Beckman) analyzers. An Apple II+ computer was interfaced with the gas analyzers and the dry gas meter by using Rayfield REP-200C software to calculate O2 uptake and CO2 production, ventilation, respiratory rate, and respiratory exchange ratio (RER). Each subject pedaled the cycle ergometer for successive 3-min stages starting at a work rate of 60–105 W depending on the subject’s fitness level (as assessed by the medical history questionnaire) with subsequent 15- to 17.5-W increments every 3 min. At the end of each stage, a 2-ml blood sample was collected from the previously inserted catheter for immediate lactate analysis. When two subsequent stages generated blood lactate levels >2.5 mmol/l, the power output was increased by 30–35 W per 1-min stage until volitional fatigue. The lactate threshold was defined as that power output at which the concentration of blood lactate was ~2.5 mmol/l.

Submaximal exercise test. Approximately 1 wk after the first visit, each subject performed one of two submaximal rides (metyrapone or placebo) using a single-blind design with test order balanced. Both exercise bouts required the subject to pedal at the power output associated with the 2.5 mmol/l lactate concentration. To examine the effects of low cortisol levels during exercise, metyrapone or placebo was self-administered (orally) by each subject at midnight. Each subject was given a dose equivalent to 30 mg/kg to the nearest 250 mg and advised to take it with a glass of milk or yoghurt at midnight immediately before sleep (22). Additionally, the subjects ingested two capsules (500 mg metyrapone or placebo) with water at the onset of the exercise. Metyrapone causes few side effects in healthy individuals and can be taken without hospitalization. If any clinical symptomatology indicated the presence of adrenal insufficiency (i.e., hypotension), hydrocortisone (100 mg) was to be infused, and the test would have been terminated. To allow sufficient time for washout of the drug, the submaximal exercise tests were separated by at least 4 days (4–10 days). Each subject arrived at ~0730, and weight was measured and recorded. A 21-gauge Teflon catheter was placed in a retrograde fashion into a right hand dorsal vein to obtain arterialized venous blood (27), and a constant drip (~1 ml/min) of 154 mmol/l NaCl solution was used to keep the catheter patent. At ~0800 each subject was transferred to the cycle ergometer to pedal at a power output equal to the previously determined 2.5 mmol/l lactate threshold for 120 min. The exercise intensity was set relative to the fixed 2.5 mmol/l lactate threshold to reduce intersubject variability in blood glucose kinetics that exists when exercise intensities are set relative to percent VO2max (6).

VO2 was measured from the onset of the exercise to the 8th min and for 5 min at 25, 55, 85, and 115 min of exercise. A 12-lead electrode placement was used with an electrocardiograph (model ECG-MAC II/ST, Marquette Electronics, Milwaukee, WI) to monitor heart rate and electrocardiogram every 15 min. The rating of perceived exertion (RPE) was recorded at 30, 60, 90, and 120 min of exercise. Systolic and diastolic blood pressures were measured and recorded at rest and every 15 min thereafter by an automated system (Colin STBP-780). The laboratory was maintained at 21–26°C, and subjects were cooled by fans blowing from the front and back throughout exercise. Additionally, subjects drank cold water ad libitum. At the end of the experiments, the catheter was removed and the subject was fed 80 g of carbohydrate in the form of fruit juice and fruit bar. Additionally, after both trials the subject was given a prophylactic oral dose of 20 mg of cortisone and monitored for 15 min before being discharged from the Applied Physiology Laboratory.

Sample collection and analysis. A 10-ml blood sample was collected at rest and at 30, 60, 90, and 120 min of exercise; an additional 2-ml blood sample was withdrawn and immediately analyzed for blood glucose and lactate at 15, 45, 75, and 105 min of exercise. The 10-ml blood samples were separated...
RESULTS

Metyrapone treatment. In general, the overnight metyrapone dose was well tolerated, and no serious side effects were reported by the subjects who completed the study. One of the nine subjects reported feeling dizziness and confusion after the overnight dose; another subject reported stomach discomfort and a burning sensation. However, the former subject later reported failing to ingest metyrapone as instructed (i.e., with milk/yogurt). These side effects started soon after metyrapone ingestion and lasted ~15 min. Additionally, we documented a hypotensive reaction in one subject. The subject arrived at the laboratory, was catheterized, and soon developed persistent hypotension, which was corrected with infusion of 100 mg IV hydrocortisone sodium succinate (Solu-Cortef). It is possible that LC (166 nmol/l compared with 552 nmol/l on a control day) and the emotional stress of inserting the catheter might have precipitated the hypotension, which was rapidly corrected by increasing the cortisol levels (1,932 nmol/l). This subject chose to withdraw from the study. The additional metyrapone dose that subjects ingested at the onset of exercise caused no serious side effects. Nevertheless, two subjects reported mild stomach discomfort that subsided within 15 min of metyrapone ingestion. Importantly, this discomfort could have been due to the use of water to ingest the drug at the onset of exercise (rather than milk). We conclude that, despite mild side effects, this drug can be used safely in exercise studies if appropriate precautions are followed.

Plasma cortisol levels. At rest (0800) cortisol concentrations averaged 512 ± 42 and 493 ± 44 nmol/l on NC and control days, respectively; metyrapone lowered the resting cortisol concentration by 70% to 145 ± 31 nmol/l (P < 0.01). Figure 1 shows that during the control day plasma cortisol fell rapidly (P < 0.01) from 0800 to 0930 and leveled off from 0930 to 1000. During exercise under NC, plasma cortisol increased 20% to 617 ± 64 nmol/l by the 120th min compared with preexercise values (P < 0.01). However, when the cortisol response was compared with the same time point during the control day, an 80% increase was detected at 90 min (P < 0.05) followed by another increase to 120% at 120

![Fig. 1. Plasma cortisol before and during 120 min of exercise and during 120 min of rest on a control day. NC, normal cortisol; LC, metyrapone-induced low cortisol. **Significantly different from preexercise (P < 0.01). **Significantly higher than same time points during control day (P < 0.05). **Significantly lower than same time points during NC (P < 0.01) and control day (P < 0.01).](http://jap.physiology.org/)


min (P < 0.01). During exercise under LC, cortisol remained unchanged and was significantly lower than on the control day (P < 0.01) and the NC trial (P < 0.01), providing an adequate model for the study.

Vo2peak, heart rate, RPE, and blood pressure. Table 1 shows that during both exercise trials the subjects exercised at a similar percent Vo2peak, heart rate, diastolic blood pressure, and RPE, whereas systolic blood pressure tended to be lower (P = 0.11).

Plasma glucose and blood lactate. Figure 2 shows that preexercise plasma glucose (4.96 ± 0.18 and 4.71 ± 0.15 mmol/l) and blood lactate (0.84 ± 0.05 and 0.92 ± 0.04 mmol/l) were similar under NC and LC, respectively. Exercise led to a small but significant decrease in plasma glucose during both trials (P < 0.05), whereas the blood lactate rose to ~2.5 mmol/l at 15 min under both conditions, but by the 120th min it had declined to nearly resting values. Lactate tended to be slightly elevated under LC compared with NC conditions (P = 0.13).

Plasma glycerol and β-hydroxybutyrate. Preexercise glycerol (0.078 ± 0.014 and 0.090 ± 0.012 mmol/l) and β-hydroxybutyrate (0.103 ± 0.012 and 0.095 ± 0.010 mmol/l) were similar under NC and LC, respectively. During exercise, glycerol and β-hydroxybutyrate (Fig. 3) increased in both trials but showed a different rate of change for the two conditions (P < 0.01 and P < 0.01, respectively). Under LC, glycerol and β-hydroxybutyrate increased more slowly over time.

Plasma alanine and BCAA. Figure 4 shows that preexercise plasma alanine was similar (P = 0.22) under both experimental conditions (0.217 ± 0.009 and 0.176 ± 0.012 mmol/l). Although this difference was not statistically significant, it appeared to be large enough to warrant an analysis of the data in terms of change from baseline. During the first 60 min of exercise, alanine increased in both trials (P < 0.01), but by 120 min it had declined to nearly resting levels. Furthermore, during LC an attenuation was observed at 30, 60, 90, and 120 min (P < 0.05) compared with NC.

Table 1. Cardiovascular and perceptual responses during 120 min of exercise

<table>
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<tr>
<th>Time, min</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
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<td>%Vo2peak</td>
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<tr>
<td>NC</td>
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<td>59.6±1.7</td>
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<tr>
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<td>59.0±2.2</td>
<td>59.1±2.0</td>
<td>60.6±2.2</td>
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<tr>
<td>RPE</td>
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<tr>
<td>NC</td>
<td>12.4±0.4</td>
<td>14.1±0.5</td>
<td>15.0±0.7</td>
<td>15.8±0.9</td>
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<tr>
<td>LC</td>
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<td>13.5±0.4</td>
<td>15.0±0.6</td>
<td>16.1±0.9</td>
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<tr>
<td>SBP</td>
<td>110±3</td>
<td>137±3.1</td>
<td>135±5.3</td>
<td>135±4.7</td>
<td>135±3.2</td>
</tr>
<tr>
<td>DBP</td>
<td>113±3</td>
<td>125±6.5</td>
<td>120±3.8</td>
<td>125±4.4</td>
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<td>HR</td>
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<td>60±4.0</td>
<td>63±5.3</td>
<td>63±3.7</td>
</tr>
<tr>
<td>NC</td>
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<td>61±2.3</td>
<td>68±5.0</td>
<td>60±5.3</td>
<td>63±3.0</td>
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<tr>
<td>LC</td>
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<td>136±3.6</td>
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</tr>
</tbody>
</table>

Values are means ± SE. Vo2peak, peak O2 uptake; NC, normal cortisol; LC, low cortisol; NM, not measured; RPE, rating of perceived exertion; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Fig. 2. Plasma glucose (A) and blood lactate (B) before and during 120 min of exercise. *Significantly different from preexercise (P < 0.05).

BCAA (Fig. 4) tended to be lower at rest (P = 0.073) under LC than under NC. Again, to distinguish the differences between the treatment and exercise effects, we analyzed the data in terms of change from baseline. The analysis indicated a treatment effect at 120 min of exercise (P < 0.01). Furthermore, during exercise under NC, plasma BCAA increased at 90 and 120 min (P < 0.05), whereas under LC a decrease in BCAA was detected by 120 min compared with preexercise (P < 0.05).

Plasma insulin, glucagon, and growth hormone. Preexercise plasma insulin (86.1 ± 10.6 and 78.6 ± 11.4 pmol/l) and glucagon (41.4 ± 5.5 and 43.3 ± 5.3 pmol/l) were not different between treatments (Fig. 5). Plasma insulin declined over time under both conditions; however, insulin was reduced to a greater extent under LC than under NC (P < 0.01). This effect was detected at 30 (P < 0.05), 60 (P < 0.05), 90 (P < 0.01), and 120 min (P < 0.01). Plasma glucagon rose over time to a similar extent under both conditions, peaking at 120 min (P < 0.01). However, the increase was observed earlier during NC (90 min) than during LC (120 min). Preexercise plasma growth hormone (3.04 ± 0.58 and 2.25 ± 0.61 µg/l) was similar during both trials. Growth hormone (Fig. 6) increased over time under both conditions (P <
cortisol replacement. Consistent with previous studies at rest (30, 31), metyrapone suppressed cortisol by \( \sim 70\% \) during exercise, ranging in intensity from \( \sim 50 \) to \( 70\% \) \( \dot{V}O_{2\text{peak}} \). During NC, cortisol levels increased by \( \sim 20\% \) at the 120th min of exercise compared with preexercise values. However, when the exercise responses were compared with those measured during the control day, the increase was detected earlier (i.e., 90 min of exercise) and was of greater magnitude (80%). Moreover, the difference at the 120th min reached 120%. These results confirm and extend the findings of others (5, 35) who have recommended that exercise-induced cortisol responses be compared with values measured at the same time points of a rest day rather than with a preexercise value.

In both trials the subjects exercised at a similar heart rate and percent \( \dot{V}O_{2\text{peak}} \) and reported similar RPE values. This is important in making appropriate comparisons between trials and suggests that an acute three- to fourfold reduction in the plasma cortisol level

**DISCUSSION**

Metyrapone has been found to have no intrinsic effects on substrates and counterregulatory hormones and has been extensively used in metabolic studies with (10, 14, 15, 30, 31) and without (30, 31) peripheral
has little bearing on tolerance to prolonged exercise of moderate intensity. On the other hand, it is known that chronic adrenocortical insufficiency limits work capacity and tolerance to prolonged exercise in animals (36) and in humans (28, 40). These studies have suggested that glucocorticoid deficiency limits exercise tolerance by inducing cardiovascular instability and muscle weakness and pain. To our knowledge, this is the first study to demonstrate that an acute cortisol deficit does not alter blood pressure, heart rate, RPE, and the ability to complete a prolonged exercise bout, at least in healthy young men and women.

Blood glucose is tightly regulated during exercise, and seldom does overt hypoglycemia develop. It is well known that when one or more of the glucoregulatory hormones is pharmacologically suppressed, there is a compensatory response by one or more of the others. This defense of the glucoregulatory control system is based on redundant mechanisms (7). In keeping with this concept, our results suggest that blood glucose is tightly regulated during exercise independent of cortisol levels. This is in contrast to previous studies in humans at rest (10, 14, 15, 18), which have consistently demonstrated an attenuating effect of LC on plasma glucose and hepatic glucose production/gluconeogenesis. The discrepancy may be explained, at least in part, by the fact that in those studies longer experimental protocols and more sophisticated designs were used (i.e., hormone clamps with fixed peripheral replacement and multiple tracers). In the present study, metyrapone suppressed cortisol but allowed the other glucoregulatory hormones to change. Insulin levels were consistently lower during the LC trial, whereas growth hormone, epinephrine, and norepinephrine tended to increase (P = 0.05–0.10), thus providing reasonable evidence of a compensatory response. For instance, a drop in insulin (a well-known regulator of hepatic glucose production during exercise) could account for the glucose counterregulation (38). Surprisingly, plasma glucagon did not differ between trials. The present study did not show a treatment effect on glucose and lactate concentrations or the RER. These are gross estimates of whole body carbohydrate metabolism during exercise. Thus we cannot automatically rule out quantitative and/or qualitative alterations in hepatic glucose production, tissue glucose uptake, and muscle glycogen utilization. Our findings indicate that when the glucoregulatory hormones are allowed to change, glucose homeostasis is preserved independent of three- to fourfold differences in plasma cortisol. To better isolate the effects of cortisol on glucose homeostasis, a more elaborate methodology is in order. For instance, the pituitary-adrenal-pancreatic clamp, in which the release of glucocorticoid hormones is blocked and peripherally replaced at a fixed rate (11), and the use of tracers would provide a more powerful model to examine the effects of cortisol on substrate kinetics during exercise.

The present study examined the effect of cortisol levels on lipid catabolism. Our findings indicate that cortisol alters lipid availability during exercise. We found that cortisol had no significant effect on baseline plasma glycerol and β-hydroxybutyrate concentrations,
whereas during exercise the rate at which glycerol and β-hydroxybutyrate increased over time was attenuated under LC compared with NC. The magnitude of the attenuating effects on lipid catabolism was modest (20–35% by 120 min) and did not affect fat oxidation (RER was the same). At rest, it is well known that lipid catabolism is affected by glucocorticoids. For instance, it has been reported that physiological hypercortisolinenia (−970 nmol/l) increases palmitate turnover within 2 h of hydrocortisone infusion when insulin is clamped (16). Schade and associates (31) showed that when cortisol secretion is blocked with metyrapone the plasma concentrations of ketone bodies and free fatty acids are suppressed by 60 and 25%, respectively. However, when cortisol is replaced to normal and high levels, plasma concentrations of ketone bodies and free fatty acids increase in a dose-response fashion. In agreement with these studies (16, 31), our findings suggest that during exercise there is a direct and positive relationship between lipid catabolism (suggested by glycerol and β-hydroxybutyrate levels) and plasma cortisol levels. Furthermore, a study using rodents reported that inhibition of the rise of glucocorticoids significantly depressed plasma free fatty acids at exhaustion (32). This study and ours suggest that glucocorticoids may exert their effects within the time frame of a prolonged exercise bout.

During exercise, LC caused alterations in plasma insulin, growth hormone, and epinephrine concentrations. Together, the lower insulin and higher catecholamine and growth hormone concentrations would have favored lipolysis. However, even in the presence of this hormonal milieu, LC led to a decrease in the rate of change of glycerol and β-hydroxybutyrate. The lower response of glycerol and β-hydroxybutyrate presumably reflects decreased lipolysis and ketogenesis. Recently, Samra and associates (30) studied the effects of cortisol on lipolysis in the subcutaneous adipose tissue of the anterior abdominal wall by arteriovenous differences. The researchers reported that, when the morning rise of cortisol was prevented by metyrapone, the venoarterialized differences for nonesterified fatty acid and glycerol were decreased. Moreover, the mechanism of action was attributable, at least in part, to a decrease in lipoprotein lipase and hormone-sensitive lipase action.

We found that the preexercise plasma alanine concentration was similar in both experimental conditions. However, during exercise the alanine levels were attenuated by ~25% under LC compared with NC. At rest, BCAA tended to be lower under LC than under NC (P = 0.07); the difference between both exercise trials became significant at 120 min. Interestingly, during the 2nd h of NC, plasma BCAA increased, whereas at the end of the 2nd h of LC the plasma concentration of these amino acids dropped slightly but significantly. Consistent with our findings, Garrel and associates (18), after infusing cortisol to increase cortisol levels to ~870 nmol/l, reported increases in the plasma leucine concentration and its rate of appearance and oxidation. These changes in leucine were prevented by a cortisol receptor antagonist (RU-486). Others have reported...
that when the morning rise of cortisol is prevented by administration of metyrapone and replacement of cortisol peripherally at a basal rate, the postprandial alanine concentration is attenuated (14). These studies (14, 18) demonstrate that cortisol is involved in amino acid metabolism at rest. With respect to exercise, Viru and associates (37) evaluated the interaction of exercise-induced increases in alanine and glucocorticoids in adrenalectomized and normal rats. In normal rats a 3-h swim induced increases in alanine levels in blood, quadriceps muscle, and liver, whereas adrenalectomy blunted these effects. Similarly, the increase in muscle alanine aminotransferase activity was prevented by adrenalectomy. However, when glucocorticoids were replaced, the exercise-induced increases in alanine levels and alanine aminotransferase activity were restored. These results coupled with our findings support the view that glucocorticoids promote alanine supply and utilization during exercise.

With regard to our measurements of proteolysis, a change in the alanine concentration could be due to a change in de novo alanine synthesis from pyruvate, a decrease in alanine utilization, and/or an increase in availability due to proteolysis. However, during exercise under LC, a slightly higher (P = 0.12) blood lactate concentration, a rough index of muscle glycolytic flux, argues against substantial differences in de novo synthesis from pyruvate. In addition, lower BCAA concentrations found under LC suggest an attenuation of proteolysis.

Importantly, despite modest differences in substrate concentrations, no differences were observed in calculated rates of substrate oxidation between the LC and NC trials. The present results suggest that, during exercise, carbohydrate and lipid oxidation (as measured by indirect calorimetry) are not affected by acute changes in cortisol levels. Indirect calorimetry is an overall whole body estimate of substrate oxidation, and we cannot rule out the potential for alterations in lipid metabolism that are not apparent at the level of whole body oxidation. There has been a paucity of data on the effects of cortisol on blood glucose and other substrates during exercise in humans. The effects of cortisol during exercise were by and large based on studies performed on animals (see Ref. 36 for a review). The present study suggests that, during exercise, 1) NC normally plays a demonstrable role by accelerating lipolysis, ketogenesis, and proteolysis; 2) LC drives glucone regulatory adjustments to maintain glucose homeostasis; 3) despite modest changes in substrate availability, LC does not alter whole body substrate utilization; and 4) in the short term, LC does not alter the ability to complete 2 h of moderate exercise.

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