The Ketogenic Diet Alters Endocrine Regulation of Energy Metabolism in Ultra-Endurance Athletes

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Introduction

Background Information

• The ketogenic diet profoundly increases reliance on fat oxidation as the primary energy source. For endurance athletes, this decreases dependence on glycogen and exogenous glucose and has therefore led to increased interest in the use of the diet to support performance. [1]

• In the present study, participants following the ketogenic diet oxidized fat at a higher rate during submaximal exercise and had more than a two-fold higher rate of peak fat oxidation during maximal exercise. [2]

Objective

• Glucagon, leptin, cortisol, and growth hormone are all involved in the regulation of fat metabolism. Therefore, the intent of this work was to determine the influence of the ketogenic diet on these hormones during exercise and rest, and to evaluate the contribution of these hormones to the increased fat oxidation associated with the diet.

Methods

Participants

• Twenty elite ultra-endurance athletes were matched for age, physical attributes, and competition times and distances.

• Participants were grouped based on at least 60 mo adherence to a LC (>20% carbohydrate) or high-carbohydrate diet (HC) (>55% carbohydrate).

Exercise Protocol

• Participants ran on a treadmill for 3 h at 64% VO2max. Blood samples used for this analysis were collected 2 h prior to exercise; 60 and 120 min into exercise; and immediately, 60 min, and 120 min after exercise.

Biochemical Analysis

• ELISA kits were used to measure serum cortisol (Calbiotech, Spring Valley, CA) and plasma glucagon, growth hormone, and leptin (R&D Systems, Minneapolis, MN).

Statistical Analysis

• Main effects of time and diet were determined by two-way repeated measures analysis using mixed-effects modeling.

• Assumptions of normality and constant variance were evaluated with the Shapiro-Wilk and Levene’s tests, respectively. Data was transformed prior to analysis if either test failed (p<0.1).

• Within group comparisons between baseline and each subsequent timepoint were determined with paired t-tests.

• Between group comparisons at each timepoint were determined with unpaired t-tests. The non-parametric rank-sum test was used for comparisons in which the assumptions of normality and constant variance could not be met with data transformation.

• Relationships between hormones and markers of fat metabolism were evaluated with Spearman’s rank correlations.

• The influence of hormones on fat oxidation during exercise was evaluated with stepwise linear regression.

• Leptin is reported relative to fat mass to decrease the large variance observed among HC athletes.

• All analyses were completed using R 3.2.3.[3]

Results

Exercise had an overall effect on glucagon, leptin, cortisol, and growth hormone (Fig. 1, p<0.001 for all).

Diet had an overall effect on glucagon and growth hormone (Fig. 1, p<0.05) and a tendency for an overall effect on leptin (Fig. 1B, p=0.10).

Glucagon was higher in HC athletes during exercise (Fig. 1D Run 60, 496.38 vs. 333.77 nM/mL).

Cortisol was higher in LC athletes during exercise (Fig. 1D Run 60, 496.38 vs. 333.77 nM/mL).

During exercise (Run 60), 51% of the variation in fat oxidation is explained by glucagon and leptin.

Across all timepoints, leptin correlated with body fat mass (0.79, p<0.001), glucagon correlated with total ketones (r=0.64, p<0.001), cortisol correlated with non-esterified fatty acids (r=0.57, p<0.001), and cortisol plus growth hormone correlated with glycerol (r=0.58, p<0.001).

Glucagon levels are correlated with total ketones across all timepoints (r=0.64, p<0.001).

Conclusions

Glucagon is strongly influenced by the ketogenic diet (Fig. 1A). In addition to maintaining glucose availability and increasing lipolysis, glucagon also promotes ketogenesis [4] by inducing transcription of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) synthase, [5] which is the rate limiting enzyme for ketogenesis. [8] This is consistent with the correlation observed between glucagon and total ketones (Fig. 2C).

The correlation between leptin and fat mass is consistent with previous findings. [7] Despite the lower leptin levels in LC athletes (Fig. 1B) and the lack of difference in fat mass across diets, [2] stepwise regression indicates that leptin is an important predictor of fat oxidation, which was much greater in LC athletes. This, combined with the much smaller variance in leptin among LC athletes (Fig. 1B) may suggest increased leptin sensitivity, greater cycling of fat stores, or a high sensitivity of leptin to small differences in fat mass.

Cortisol and growth hormone act together to synergistically enhance lipolysis. [8] Which is consistent with the higher levels observed in LC athletes and the correlations between cortisol and cortisol plus growth hormone markers of lipolysis.

References


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