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Altered metabolic homeostasis is associated with appetite regulation during and following 48-h of severe energy deprivation in adults☆,☆☆

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ABSTRACT

Background. Military personnel frequently endure intermittent periods of severe energy deficit which can compromise health and performance. Physiologic factors contributing to underconsumption, and the subsequent drive to overeat, are not fully characterized. This study aimed to identify associations between appetite, metabolic homeostasis and endocrine responses during and following severe, short-term energy deprivation.

Methods. Twenty-three young adults (17 M/6 F, 21 ± 3 years, BMI 25 ± 3 kg/m^2) participated in a randomized, controlled, crossover trial. During separate 48-h periods, participants increased habitual energy expenditure by 1647 ± 345 kcal/d (mean ± SD) through prescribed exercise at 40–65% VO_{2peak}, and consumed provided isovolumetric diets designed to maintain energy balance at the elevated energy expenditure (EB; 36 ± 93 kcal/d energy deficit) or to produce a severe energy deficit (ED; 3681 ± 716 kcal/d energy deficit). Appetite, markers of metabolic homeostasis and endocrine mediators of appetite and substrate availability were periodically measured. Ad libitum energy intake was measured over 36 h following both experimental periods.

Results. Appetite increased during ED and was greater than during EB despite maintenance of diet volume (P = 0.004). Ad libitum energy intake was 907 kcal/36 h [95% CI: 321, 1493 kcal/36 h, P = 0.004] higher following ED compared to following EB. Serum beta-hydroxybutyrate, free fatty acids, branched-chain amino acids, dehydroepiandrosterone-sulfate (DHEA-S) and cortisol concentrations were higher (P < 0.001 for all), whereas whole-body protein balance was more negative (P < 0.001), and serum glucose, insulin, and leptin concentrations were lower (P < 0.001 for all) during ED relative to during EB. Cortisol concentrations, but not any other hormone or metabolic substrate, were inversely associated with satiety during EB (R^2 = 0.23, P = 0.04). In contrast, serum glucose and DHEA-S concentrations were inversely

Abbreviations: BCAA, branched-chain amino acids; BHB, beta-hydroxybutyrate; DHEA-S, dehydroepiandrosterone-sulfate; EB, energy balance condition; ED, energy deprivation condition; FFA, free fatty acids; RMR, resting metabolic rate; SLIM, Satiety Labeled Intensity Magnitude scale; TDEE, total daily energy expenditure; TG, triglycerides.

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☆☆ Clinical trials registration: clinicaltrials.gov #NCT01603550.

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associated with satiety during ED (R^2 = 0.68, P < 0.001). No associations between physiologic variables measured during EB and ad libitum energy intake following EB were observed. However, serum leptin and net protein balance measured during ED were inversely associated with ad libitum energy intake following ED (R^2 = 0.48, P = 0.01).

Conclusion. These findings suggest that changes in metabolic homeostasis during energy deprivation modulate appetite independent of reductions in diet volume. Following energy deprivation, physiologic signals of adipose and lean tissue loss may drive restoration of energy balance. Clinical trials registration: www.clinicaltrials.gov #NCT01603550.

1. Introduction

Military personnel, disaster-relief professionals, and some athletes frequently endure intermittent periods of substantial energy deficit [1,2] which can compromise immune health [3], impair physical performance and cognition [4,5], degrade lean body mass [6,7], and may promote excess accretion of fat mass during weight regain [8,9]. Some of the more severe energy deficits have been reported in military training environments where energy expenditure often averages >4000 kcal/d [10], and can reach up to 7000 kcal/d [6,11]. In these environments, energy intake is consistently insufficient to maintain energy balance, even when enough food is provided to meet energy demands [4,11]. Insufficient time, stress, desire to lose weight, hypohydration, various environmental factors, and an unwillingness or inability to carry enough food have all been cited as contributing factors [4,11]. Shifts in metabolic homeostasis, and altered secretion of endocrine mediators of appetite and substrate availability may also contribute to changes in appetite [12], but have received less consideration.

Multiple interrelated peripheral endocrine and metabolic signals reflecting energy availability are integrated by the central nervous system to regulate appetite [13]. Metabolic signals may include glucose, free fatty acids (FFA), and ketone bodies. Glucose and FFA are thought to stimulate appetite at low concentrations and suppress appetite at elevated concentrations [14,15]. Ketone bodies including beta-hydroxybutyrate (BHB) circulate at very low concentrations during energy balance, but rise during energy and carbohydrate restriction and are thought to suppress appetite [15,16]. Endocrine signals include insulin and leptin. Both hormones are secreted in proportion to fat mass, and reflect energy stores. Insulin and leptin concentrations fall during energy deficit, stimulating appetite by altering sensitivity to appetite-mediating gastrointestinal hormones within the central nervous system [17]. Insulin, cortisol and dehydroepiandrosterone-sulfate (DHEA-S) may also impact appetite indirectly by altering the availability and oxidation of metabolic substrates including glucose, FFA, ketones and branched-chain amino acids (BCAA) [18–20]. However, not all studies have substantiated associations between these metabolic and endocrine signals with appetite, and the relative contributions of these factors to appetite regulation remain controversial [12,21], underpinning a need for novel approaches to studying appetite physiology.

Our group recently developed a novel model for studying appetite regulation physiology during energy deprivation [22,23]. The model utilizes a supervised laboratory environment and custom-made isovolumetric diets differing in energy density (energy per unit mass) but otherwise similar in volume, taste, texture and appearance. This model enables investigations into the physiological effects of energy deprivation independent of reductions in diet volume, and free from potentially confounding environmental factors. Using this model, our group reported the possible dissociation of perceived appetite from cortisol, insulin and DHEA-S concentrations during short-term energy deprivation [23]. However, the magnitude of energy deficit imposed in the study (~2200 kcal/d) was less severe than that endured by soldiers during military training [4,11,24,25]. In this study, the energy deprivation model was utilized in combination with carefully prescribed exercise to create a more severe level of energy deprivation than was previously investigated in order to examine relationships between appetite, metabolic substrate availability, and related endocrine markers under metabolic conditions more closely representing those experienced during military combat and training.

2. Methods

2.1. Subjects

Healthy male and female soldiers, age 18 to 39 years, were recruited from the US Army Natick Research, Development and Engineering Center, Human Research Volunteer platoon between 2012 and 2013. Thirty one individuals who did not have any acute or chronic physical limitations that would prevent exercise provided written informed consent. Four withdrew prior to starting the study due to relocation (n = 2) or illness (n = 2). The remaining 27 volunteers (20 males/7 females, age 21 ± 3 years, BMI 24.9 ± 3.0 kg/m^2) were medically cleared for study participation. The study was approved by the institutional review board at the US Army Research Institute of Environmental Medicine, Natick, MA. Investigators adhered to the policies for protection of human subjects as prescribed in the US Department of Defense Instruction 3216.02, and the research was conducted in adherence with the provisions of 32 CFR Part 219.

2.2. Study Design

The primary study objective was to determine the effects of severe energy deprivation on cognitive function. This report details secondary study objectives of characterizing the metabolic response to severe energy deprivation and the subsequent impact on appetite regulation. Volunteers participated in two separate experimental sessions in random order: (1) an energy balance condition (EB), and (2) and energy deprivation condition (ED) (Fig. 1). Sessions were separated by