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Neuroendocrine alterations in the exercising human: Implications for energy homeostasis

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ABSTRACT

Complex mechanisms exist in the human to defend against adverse effects of negative energy balance. These include alterations of hormone secretion affecting the growth hormone/insulin-like growth factor system, the adrenal axis, and the reproductive system, particularly in females. Energy deficits are least partially offset by neuroendocrine mechanisms regulating appetite and satiety. The complex feedback mechanisms reporting peripheral fat and energy stores to the central nervous system involve secretion of the peptide hormones leptin and ghrelin, which act centrally on neurons in the arcuate nucleus and anteroventral periventricular area. In addition to appetite regulation, these hormones exert influences on spatially and functionally-related mechanisms regulating reproductive function, such as the kisspeptin-gonadotropin releasing hormone system. Negative energy balance often occurs partially as a result of strenuous and repetitive physical exercise. Exercise stress leads to increased cortisol secretion, but this action is mediated through the induced negative energy balance. In healthy adults with energy deficits, this exercise-induced stress appears to be more important than pure psychological stress in impairing reproductive function. Estrogen deficiency resulting from negative energy balance has important adverse effects on bone density as well as bone microarchitecture, and it may also adversely affect markers of cardiovascular disease.

1. Introduction

One of the fundamental precepts concerning energy is that it cannot be destroyed – only transformed. The homeostatic state in any biological system is maintained by energy balance. Indeed, that balance obeys the First Law of Thermodynamics which states the change in the internal heat (energy) of a system is equivalent to the heat added minus the work done by the system. In this sense we shall be discussing the energy expenditure primarily of the voluntary

Abbreviations: αMSH, α-melanocyte stimulating hormone; ACTH, adrenocorticotrophic hormone; AgRP, agouti-related peptide; ARC, arcuate nucleus; AVPV, anteroventral periventricular area; BMI, body mass index; BMR, basal metabolic rate; CART, cocaine amphetamine related transcript; CRH, corticotrophin releasing hormone; E_{basal}, basal energy expenditure; EEE, energy expenditure of exercise; E_{exp}, total energy expenditure; FFM, fat-free mass; FSH, follicle stimulating hormone; GH, growth hormone; GHRH, growth hormone releasing hormone; GnRH, gonadotropin releasing hormone; hCG, human chorionic gonadotropin; HPA, hypothalamic-pituitary adrenal axis; HPG, hypothalamic-pituitary-gonadal axis; IGFBP-3, insulin-like growth factor binding protein-3; IGF-I, insulin-like growth factor-1; KNDy, kisspeptin, neurokinin B, dynorphin; LH, luteinizing hormone; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, peptide YY; RMR, resting metabolic rate; T_3, triiodothyronine.

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muscles in which the total energy of the system may be considered as:

$$E_{exp} = E_{basal} + E_{tef} + EEE$$

Where E_{exp}=total energy expenditure; E_{basal}=basal energy expenditure (for most purposes, this is the resting metabolic rate or RMR), E_{tef} is the energy used to digest food (also called "dietary") and EEE, the most variable component, is the energy expenditure of exercise.

Clausius in 1850 stated this concept of energy homeostasis in a slightly different way: In a thermodynamic process the increment in internal energy of a system is equal to the difference between the increment of heat accumulated by the system and the increment of work accomplished by it.

In humans, if energy expenditure exceeds energy intake, homeostatic neuroendocrine mechanisms take over to conserve energy. In this context, relevant neuroendocrine axes include the hypothalamic-pituitary-gonadal (HPG), the hypothalamic-pituitary adrenal (HPA), the hypothalamic-pituitary-thyroid, and the hypothalamic-pituitary-end organ axis for GH and IGF-I. We shall emphasize alterations within the HPG and HPA axes.

Maintenance energy costs include the resting metabolic rate, (or, for the purists, the basal metabolic rate, BMR) and energy expended for activity. However, we who evaluate children and adolescents have an additional factor, the production costs of growth/maturation and the reproductive system. There are a number of causes of negative energy balance including myriad disease states which may impact the RMR, but for the purposes of this review, we shall focus on the increased energy expenditure and/or insufficient energy intake in a subset of exercising individuals.

2. Overview of appetite and satiety regulation

In the complex balancing mechanism that controls body weight, energy expenditure is offset by energy intake. Energy intake is controlled by a feedback system wherein energy stores manifested by body fat provide signals to the central nervous system to alter food intake. The core feedback signals in this homeostatic mechanism for energy intake are leptin and ghrelin.

Leptin is a 167 amino acid protein product of adipose tissue first discovered in 1994 [1]. It is produced and secreted in a constitutive fashion, and circulating leptin concentrations are directly proportional to body fat stores. In the ob/ob mouse, mutation of the leptin gene results in a bioinactive leptin molecule. These mice demonstrate increased appetite and obesity. In humans, mutations of the leptin gene or its receptor lead to a similar phenotype [2]. In addition to its effects on body weight, leptin plays a critical role in pubertal development and reproductive function. Children carrying mutations in the gene for leptin or its receptor fail to enter puberty [3], and systemic administration of exogenous leptin allows puberty to proceed in those with leptin gene mutations [4]. Although those with leptin deficiency are obese, obese individuals in the general population have high serum leptin concentrations, indicating a degree of incompletely understood leptin resistance.

Ghrelin is a 28 amino acid acylated peptide discovered in 1999 [5] and produced in the X/A-like cells of the gastric fundus [6]. Ghrelin is the endogenous ligand of the growth hormone secretogogue receptor, but its role in body weight regulation is more prominent than its role in growth hormone secretion. Ghrelin stimulates appetite and food intake [7]. Levels of ghrelin increase during fasting and decrease during feeding, but ghrelin functions in the long-term regulation of body weight as well [8]. Serum concentrations of ghrelin are inversely proportional to body mass index (BMI) and increase with weight loss. Cummings, et al. [8] studied 13 obese adults with mean BMI 35.6 kg/m^2. Subjects underwent a six-month supervised weight loss program, after which their mean BMI decreased to 29.4 kg/m^2, a 17.4% weight loss. Subjects were admitted to the clinical research center before and after the weight loss, ate standardized meals, and 24-hour serum ghrelin profiles were obtained. As expected, fasting plasma leptin decreased from 26.8±4.4 to 16.7±3.5 ng/mL ($p<0.003$). Plasma ghrelin profiles consistently increased at all time points following weight loss, and the area under the curve of ghrelin concentrations increased by 24% after weight loss. The percent decrease in body weight correlated with the percent increase in the ghrelin area under the curve ($r=0.67$, $p=0.01$). As with leptin, ghrelin has effects on reproductive function, although most of the data are from rodent models. In animals, ghrelin decreases GnRH secretion and gonadotropin production, thus acting inversely to leptin. In addition to its central action to inhibit the reproductive system, ghrelin appears to have direct suppressive effects on the testis and ovary [9]. Non-acylated forms of ghrelin do not bind to the growth hormone secretogogue receptor, but may have important physiologic roles in other systems nonetheless.

Leptin and ghrelin appear to exert their effects on appetite primarily via the arcuate nucleus (ARC) of the hypothalamus, acting on two critical populations of neurons. (Fig. 1) One population produces neuropeptide Y (NPY) and agouti-related peptide (AgRP), orexigenic neurotransmitters co-localized to ARC neurons [10]. These neurons are directly stimulated by ghrelin, leading to increased food intake and body weight [11]. Leptin suppresses activity of NPY/AgRP neurons. A second population of neurons produces pro-opiomelanocortin (POMC), the precursor to several hormones, including α-melanocyte stimulating hormone (αMSH). αMSH binds to the melanocortin-3 and -4 receptors (MC3R and MC4R) which inhibits food intake and in mice alters energy expenditure [12]. Leptin stimulates these POMC-producing neurons, thus suppressing appetite. Overlap in the actions of the POMC and NPY/AgRP neurons occurs via the action of AgRP, which antagonizes the action of αMSH at the MC3R and MC4R [13].

Additional inputs to the appetite/satiety regulatory mechanism include peptide YY (PYY), a 36 amino acid protein produced in the L cells of the distal GI tract. PYY secretion is induced by meals, particularly those high in calories and protein. PYY acts centrally to induce satiety, and its secretion is decreased in obese humans [14].

Glucagon-like peptide (GLP-1) is a product of the L cells of the distal small intestine and colon. GLP-1 is secreted in response to oral ingestion of glucose and potentiates glucose-stimulated insulin secretion by the pancreas. Thus, it is one of the incretin hormones. Additionally, it inhibits glucagon