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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

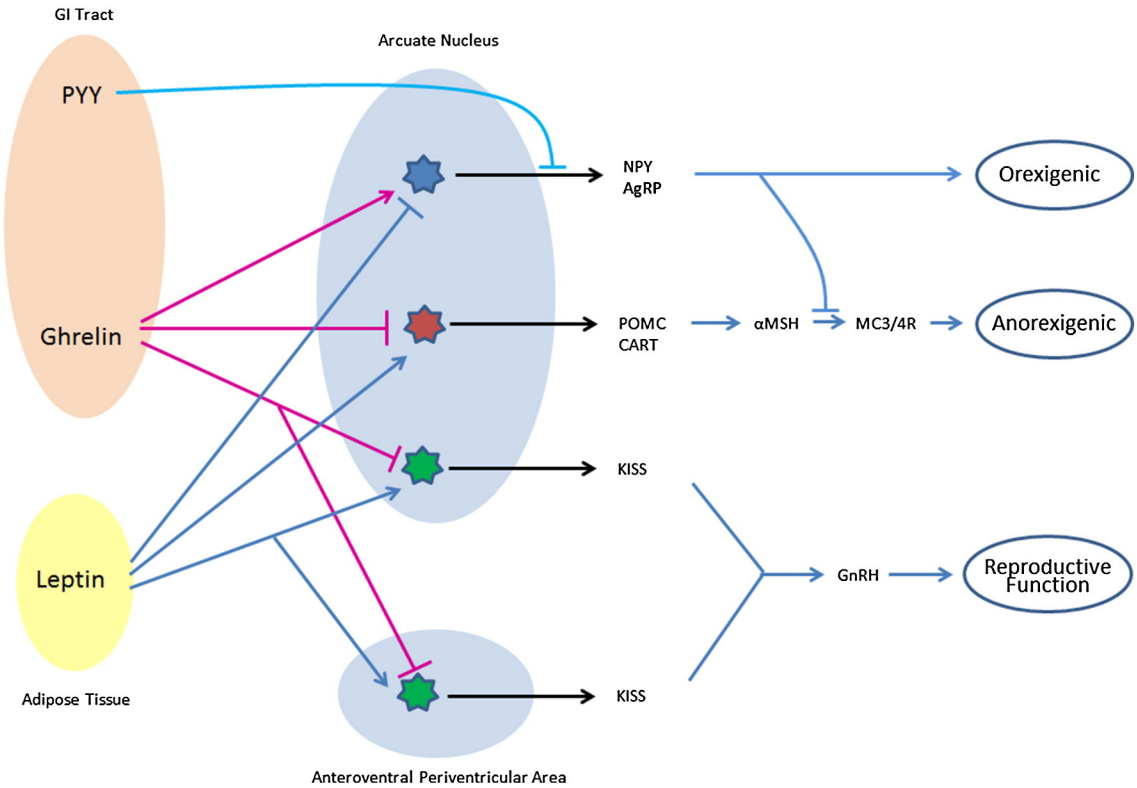

Fig. 1 – Schematic of the overlap between appetite regulation and control of reproductive function. Ghrelin and leptin are the two primary influences. Ghrelin has appetite stimulatory functions and suppresses kisspeptin production, thus inhibiting GnRH secretion. Leptin has appetite suppressive functions and stimulates kisspeptin production. Positive influences are shown as arrowheads and inhibitory influences are shown as bars.

secretion, delays gastric emptying, and increases satiety. GLP-1 is also produced in neurons of the nucleus tractus solitarius in the brainstem, and GLP-1 receptors are distributed in multiple locations throughout the brain. Stimulation of GLP-1 neurons also leads to appetite suppression, but the relative roles of peripheral and central GLP-1 on satiety remain under investigation [15].

Cocaine amphetamine related transcript (CART) is co-secreted with αMSH from POMC-expressing neurons in the ARC. Like αMSH, it has anorexigenic activity, although its mechanism of action is not well understood. In rodents, its secretion is suppressed by activation of the growth hormone secretogogue receptor [16].

In addition to the homeostatic mechanism of appetite and satiety control, there is significant input from higher centers of the brain on food intake. Factors influencing whether one eats or not include cognitive influences, reward mechanisms, and emotional inputs and are collectively referred to as hedonic stimuli. The neuronal interactions between the homeostatic and hedonic regulatory pathways are the subject of active investigation [17].

Another factor in the regulation of energy balance is the peripheral nervous system. It coordinates with the hormonal factors noted to adjust moment-to-moment energy intake, expenditure and storage. These hormonal factors were deduced from the phenotypes (extreme obesity or cachexia) of animals with surgical lesions in the hypothalamus or from humans with destruction of the cognate nuclei [18,19]. Although leptin action in the central nervous system is apparently sufficient to regulate body weight, feeding, energy expenditure and glucose metabolism [20], its effects are modulated by the sympathetic nervous system. For example, leptin's modulation of glucose homeostasis (increasing gluconeogenesis and decreasing glycogenolysis) may be modified by the alpha-adrenergic system [21,22]. Alpha adrenergic blockade can reverse the insulin lowering effects of central administration of leptin in mice [23]. It is likely that POMC neurons located in the arcuate nucleus are both leptin sensitive and project to pre-ganglionic sympathetic neurons [24]. These circuits apparently act over the short-term and are some of those that affect moment-to-moment energy balance at the whole animal level. Other systems that may be involved in short-term regulation include cholecystokinin, ghrelin and the vagus nerve [25–27].

Chronic leptin therapy in animals and perhaps "simple" obesity in humans have different effects on insulin sensitivity and glucose homeostasis, such that hypothalamic insulin sensitivity is reduced [28]. This is the rationale for treating both leptin deficient patients and those with generalized lipodystrophy with leptin [4,29,30]. The former show marked reduction in oral intake, rapid weight loss, normalization of glucose metabolism, and reversal of hypogonadotropic hypogonadism resulting in normally-timed pubertal development [4].

Thus, there is an intimate relationship between mechanisms controlling appetite and those regulating pubertal maturation and reproductive function. Body fat stores are an important regulatory point for these systems. Increases in energy expenditure tend to be offset by increases in appetite induced by loss of body fat, but in situations in which food intake is relatively restricted compared to exercise energy expenditure, reproductive function may be disrupted. Examples of this include athletes with hypothalamic amenorrhea and starvation.

3. Hypothalamic/pituitary axes

Interaction of energy balance with pubertal maturation and reproductive function occurs via classical endocrine feedback loops whereby trophic hormones produced in the anterior pituitary gland stimulate end organs to secrete a hormone product that subsequently inhibits secretion of the pituitary factor. Three hypothalamic/pituitary axes are critical in this regard.

3.1. *Growth hormone-IGF-1 axis*

Growth hormone (GH) is secreted by the somatotrophs of the anterior pituitary gland. Its production is under the control of hypothalamic growth hormone releasing hormone (GHRH) and somatostatin. GHRH promotes GH gene transcription and translation and increases GH release. Somatostatin has inhibitory influences on GH release. GH is secreted in a pulsatile fashion, occurring in irregular bursts. The largest GH secretory burst occurs at the time of the first cycle of stage 3/4 sleep, and several additional bursts occur throughout the night. The pulsatility is a result of varying production of GHRH and somatostatin in the hypothalamus. Food intake suppresses GH release, while fasting increases production and induces daytime secretory bursts [31].

Circulating GH binds to receptors on a wide variety of cell types. In the liver, GH stimulates production of insulin-like growth factor-1 (IGF-1), raising circulating levels of this hormone. In other GH-responsive tissues, IGF-1 is released and acts locally in a paracrine or autocrine fashion. Circulating IGF-1 is carried in the ternary complex consisting of IGF-1, IGF binding protein-3 (IGFBP-3), and acid labile substance, all of which are secreted in a GH-dependent manner. The ternary complex significantly increases the plasma half-life of IGF-1. Both circulating and locally-produced IGF-1 are anabolic, acting through the IGF-1 receptor on many different tissues to increase cell growth, inhibit cell death, and promote cellular differentiation. GH has independent effects as well, acting through its receptor to stimulate cartilage growth and differentiation, promote bone growth, increase lipolysis in adipose tissue, and stimulate amino acid uptake in muscle. GH is also in part the cause of the physiologic insulin resistance at puberty [32]. IGF-1 acts in a negative feedback fashion to decrease pituitary GH release, stimulating somatostatin and inhibiting GHRH in the hypothalamus [33].

Additional factors influence GH release, including sex hormones and nutritional status. The sex hormones testosterone and estradiol, produced during and after puberty, lead to large increases in GH secretion. In a cross-sectional study of 44 normal, non-obese males of ages 7–27 years, 24-hour profiles of serum GH concentrations were obtained [34]. Using deconvolution analysis, total GH secretion increased from a mean of 610±65 μg/24 hours in prepubertal subjects up to 1810±250 in late pubertal males and then declined to 910±150 in adults. When normalized to body surface area to account for increases in size, there was still a doubling of GH secretion between prepubertal and late pubertal boys (600±58 to 1160±160 $\mu g/m^2$/24 hours). The increased secretion was due to higher amplitudes of individual pulses rather than increases in pulse frequency or duration. GH secretion was positively correlated with serum testosterone concentrations. However, multiple lines of evidence indicate that most of the effects of testosterone on GH production require local aromatization of testosterone to estradiol. In humans, treatment of boys with delayed puberty using testosterone led to increases in the 24-hour integrated concentration of GH from 3.12±0.90 to 13.67±6.0 μg/L. However, in boys treated with the non-aromatizable androgen dihydrotestosterone, integrated GH levels decreased [4.32±0.61 vs. 2.39±0.42 ($P<0.025$)] [35]. Similar effects were noted for IGF-1. Administration of the estrogen receptor blocker tamoxifen decreases GH production and serum IGF-1 concentration in pubertal boys [36]. Thus, although androgen secretion at the time of puberty increases GH secretion, this process appears to be estrogen-mediated.

Short-term exercise induces GH secretion. Whereas obesity is associated with low GH levels, both short- and long-term starvation increase GH secretion but lower serum IGF-1 concentrations. Ghrelin stimulates the growth hormone secretagogue receptor in the ARC and on somatotrophs and promotes GHRH and growth hormone release. Leptin appears to be antagonistic to the effects of ghrelin on growth hormone production, acting at least in part by decreasing the expression of the growth hormone secretogogue receptor [37]. The effects of leptin on GH and IGF-1 secretion in both acute and long-term energy deprivation have been evaluated [38]. These investigators studied eight men and six women while receiving a net energy-neutral diet and then on two occasions while fasting for 72 hours. During one of the fasts, subjects received recombinant methionyl human leptin, and during the other fast, placebo. No changes in GH or total and free IGF-1 were noted in the energy-neutral phase. During the placebo fast, serum leptin concentrations decreased by 80% whereas indices of GH production were increased, including GH pulse amplitude and frequency and area under the curve. Abolition of acute hypoleptinemia by administration of exogenous leptin had no effect on GH production, while the decline in IGF-1 levels was partially reversed. Similar findings were noted in a small cohort of seven women with hypothalamic amenorrhea treated with leptin for two weeks. These results indicate that the negative energy-induced increases in GH secretion and decreases in IGF-1 are not related to hypoleptinemia. The reason for this dissociation is unclear but may be related to down-regulation of hepatic GH receptors, post-receptor changes, or alterations in other hormones such as insulin or thyroid hormone.

3.2. *Hypothalamic-pituitary-gonadal axis*

Perhaps more than any pituitary axis, the hypothalamic-pituitary-gonadal (HPG) axis changes function dramatically over the lifespan. By 12 weeks gestation, the fetal hypothalamus and pituitary gland have developed sufficiently to regulate ongoing secretion of testosterone by the fetal testis, which previously had been under the control of placental hCG. Second and third trimester testosterone production leads to phallic growth in utero. The fetal ovary seems to be relatively quiescent during intrauterine life. In both sexes, however, withdrawal of placentally-derived estrogen at delivery leads to increases in gonadotropin secretion after birth, a period known as the "minipuberty of infancy" (reviewed in References [39,40]). In the male, higher concentrations of LH and to a lesser degree FSH result in increased Leydig and Sertoli cell activity as indicated by increased concentrations of testosterone and inhibin b, respectively [39,40].Testosterone levels peak at about two months of age and are in the prepubertal range by 4–6 months. In boys the minipuberty appears to lead to a modest amount of additional phallic growth and may be important for promoting the earliest stages of spermatogenesis [41]. In the female, the gonadotropin surge is predominantly FSH and to a lesser extent LH, but the extent and duration are more variable. Serum FSH levels peak between 3–6 months, begin declining by 12 months, but may still be above the prepubertal norms at 24 months. This gonadotropin surge is associated with the rapid increase in follicular maturation in the first four months. Concentrations of estradiol and inhibin b also variably increase, with estradiol peaking at 2–4 months and inhibin b between 2–12 months. By six months of age in boys and 1–3 years of age in girls, the minipuberty subsides into the "juvenile pause," which lasts until the onset of true puberty. The juvenile pause is marked by increasing sensitivity to the negative feedback effects of sex steroids at the level of the hypothalamus and pituitary, decreasing the amplitude and frequency of GnRH pulses and reducing secretion of gonadotropins and sex steroids.

The onset of true puberty typically occurs between ages 9–14 years in boys and 8–13 years in girls, although there is strong evidence indicating that the age at the first signs of puberty in girls, typically breast development, may have decreased over the last 40–50 years. In the years leading up to the clinical appearance of pubertal signs, there is an increase in the pulse amplitude and, to a lesser extent, the pulse frequency of GnRH secretion. This reawakening of the HPG axis initially occurs during the nighttime hours and results in overnight and early morning secretion of testosterone and estradiol. As puberty progresses, GnRH pulsatility becomes more persistent and sex steroid concentrations remain high during the day. Clinically, this leads to typical progressive signs of pubertal maturation: pubic and axillary hair, genital growth in boys, and breast development in girls, as well as linear growth acceleration in both sexes. Further maturation of the HPG axis in girls results in the establishment of the menstrual cycle at an average age of 12–12.5 years, with cyclic variation in concentrations of gonadotropins, estradiol, and progesterone.

Control of the onset of puberty has been the goal of ongoing investigation. The discovery of kisspeptin as a hypothalamic trigger of gonadotropin secretion allowed for increased understanding of the developmental physiology [42]. Indeed, activating and inactivating mutations of the KISS1R gene encoding the kisspeptin receptor, have been identified in patients with precocious puberty and hypogonadotropic hypogonadism, respectively [43,44]. The regulatory inputs to kisspeptin-producing neurons that initiate the hormonal manifestations of normal puberty remain uncertain. Neurokinin B and dynorphin are peptides that are co-secreted by kisspeptin neurons, leading to the term KNDy neurons. The roles of these peptides in primates are not well established, but they appear to have autoregulatory effects, with neurokinin B promoting kisspeptin secretion and dynorphin inhibiting it [45]. This reciprocal mechanism allows for fine regulation of KNDy neuron activity. KNDy neurons project to the median eminence of the hypothalamus, where they synapse with GnRH-secreting neurons. In rodent models, it is clear that decreased energy availability leads to decreased kisspeptin mRNA production in the arcuate nucleus (ARC) and the anteroventral periventricular area (AVPV) and that decreases in leptin mediate this effect [46] (Fig. 1).

Because of the known relationship of body fat stores and timing of puberty, it was theorized that this might be the trigger for the initiation of puberty, although it is now thought to be permissive rather than the trigger. In both sexes, serum leptin levels are similar and gradually rise prior to the onset of puberty. The first identification of leptin changes with puberty was a small longitudinal study of eight boys followed from pre-puberty through Tanner stage 5. Serum concentrations of leptin were high at the initiation of puberty and subsequently declined with attainment of full maturation [47]. It was later identified that leptin levels increase during the pre-pubertal years in both sexes [48]. A sexually dimorphic pattern in leptin secretion with puberty has subsequently been identified, with girls having gradually increasing levels and concentrations in boys decreasing as puberty progresses. These differences are closely correlated with fat mass and appear to be caused by androgen-mediated suppression of leptin secretion and estrogen-mediated augmentation [49,50].

3.3. *Hypothalamic-pituitary-adrenal axis*

The hypothalamic-pituitary-adrenal (HPA) axis plays a critical role in the ability of the organism to respond to physiologic stress. Under the regulatory influence of hypothalamic parvicellular neurons in the paraventricular nucleus, corticotrophin releasing hormone (CRH) leads to pituitary secretion of adrenocorticotrophic hormone (ACTH), which stimulates cortisol release from the adrenal cortex. Cortisol in turn provides negative feedback to decrease release of CRH and ACTH. CRH is also produced in the placenta, with secretion increasing exponentially as delivery approaches. The role of placental CRH is not clear, but it appears to regulate placental blood flow and myometrial function, and it may influence fetal pituitary function. It is likely involved in a placental stress response, with increased secretion in conditions affecting fetal or maternal well-being, possibly serving as a trigger for labor in these situations [51]. Unlike the HPG axis, the HPA axis does not undergo dramatic shifts in activity with age once the normal diurnal variation in cortisol

concentrations is established early in life. Vasopressin, a small peptide hormone secreted by the posterior pituitary that increases water absorption in the renal collecting ducts, is also secreted by parvicellular neurons into the median eminence of the hypothalamus, where it increases ACTH secretion.

Cortisol has wide-ranging effects, including alterations of carbohydrate, protein, and lipid metabolism; catabolic effects on skin, muscle, connective tissue, and bone; immunomodulatory effects; blood pressure and circulatory system regulation; and effects on mood and central nervous system function. In the short term, activation of the HPA axis in response to stress is adaptive. However, long-term stress promoting chronic exposure of tissues to high cortisol concentrations becomes maladaptive.

Exercise, particularly sustained aerobic activity, is a potent stimulus of cortisol secretion. The circulating concentrations of cortisol are directly proportional to the intensity of exercise as measured by oxygen uptake. As is the case for the GH/IGF-1 and HPG axes, the HPA axis also receives many other inputs, including the light/dark cycle, feeding schedules, immune regulation, and many neurotransmitters that mediate the effects of exercise and physical and psychic stress [52].

4. Effects of stress on the adrenal and gonadal axes

For the present purposes one may define stress as "a condition where expectations, whether genetically programmed, established by prior learning, or deduced from circumstances, do not match the current or anticipated perceptions of the internal or external environment, and this discrepancy between what is observed or sensed and what is expected or programmed elicits patterned, compensatory responses" [53].

The HPA is activated by stress, whether physical (exercise) or psychological. Increased cortisol production, along with activation of the sympathetic nervous system, affects whole body metabolism. This is apparently part of the catabolic response of the entire organism, with the purpose of mobilizing metabolic fuels that are subsequently broken down to produce energy and to dampen the threat or perceived threat.

Physiological processes, in this case the ovarian cycle, may be suppressed as "non-essential" to conserve energy for core functioning. There is a basic anatomic-physiologic basis for the interactions between the corticotrophs and gonadotrophs. The cells of the anterior pituitary are not randomly distributed but arranged in an organized manner (clusters) denoted as homotypic networks. Cells of the corticotroph and gonadotroph lineage individually form monotypic cell networks during development [54]. The gonadotrophs are in close proximity to the microvasculature, although the corticotrophs are not [55]. Moreover, the differentiated corticotroph network acts as a scaffold for the gonadotroph network and additionally sends processes to the gonadotrophs (heterotypic interactions). It is likely that these anatomic connections subserve some of the physiologic interactions between these two hypothalamic-pituitary end organ axes, such as the inhibition of the HPG axis due to the stress of chronic energy deficits. These types of interactions are likely part of the ultrashort loop feedback regulation within many of the hypothalamic-pituitary end organ axes and may permit experience-dependent responses to physiologic changes ("plasticity") as the whole organism adapts to the longer-term stressor.

An example of this mechanism is functional hypothalamic amenorrhea induced by high energy expenditure of exercise in the setting of inadequate energy intake independent of the effects of energy availability (kcal.kg-FFM^{-1}.day^{-1}) and exercise stress. The fat-free mass (FFM) is the metabolically active tissue and is more related to energy balance than is total body mass. In an elegant series of experiments in exercising women, Loucks and colleagues [56] separated the effects of exercise stress from psychological stress. Their finding of no suppressive effect of "pure" psychological stress on LH pulsatility, the HPG output signal, is very important to energy homeostasis. In studies of animal models, in this case the rhesus monkey, low energy availability suppresses LH pulse frequency irrespective of how the low energy availability is accomplished – whether by dietary restriction or by keeping the caloric intake stable, but increasing the energy expenditure of exercise [57,58] (Fig. 2). Similar findings were noted by Loucks and Thuma [59] in a clinical protocol in which exercising women undergoing constant exercise energy expenditure (15 kcal.kg-FFM^{-1}.day^{-1}) had their dietary energy intake held constant at adequate (45 or 30 kcal.kg-FFM^{-1}.day^{-1}), or frankly inadequate (10 or 20 kcal.kg-FFM^{-1}.day^{-1}) levels. The output variable was the frequency of LH pulses in the general circulation. There was no alteration in that frequency as long as at least 30 kcal.kg-FFM^{-1}.day^{-1} was available. However when the energy intake fell to 10 or 20 kcal.kg-FFM^{-1}.day^{-1}, the frequency of LH pulses diminished and as is usual, the amplitude increased. Concomitant metabolic indices also followed the pattern of increasing derangement, including a graded decrease in the serum IGF-I concentration as GH levels increased, indicative of GH resistance and an increase in β-hydroxybutyrate and decrease in glucose levels as the body switched from predominantly carbohydrate metabolism to ketogenesis. In a similar manner there were graded increases in cortisol levels but decreased levels of insulin.

Thus, a negative net energy balance leads to activation of the HPA axis and the circulating concomitants of the catabolic state in an attempt to keep core processes functional, realizing that the stress of exercise has no effect on cortisol and circulating metabolic substrates beyond the impact of the exercise energy expenditure on energy availability [60]. Thuma et al. [61] had already made the important observation that the reported differences in cortisol levels pre- and post-exercise depended on whether this difference was measured from a single pre-test level or from the physiologic circadian baseline as determined in an independent session in the resting state. By this analytical technique, these investigators showed that increasing energy expenditure led to significant cortisol release. This release was apparent if they subtracted the physiologic circadian baseline from the post-exercise value. However, if they just subtracted the pre-test baseline cortisol value from the post-exercise value, they were unable to show an effect of exercise energy expenditure on cortisol production – an error of more than 90% in the morning and almost 40 % in the evening. A similar finding was noted using the circulating free cortisol level, the metabolically active form

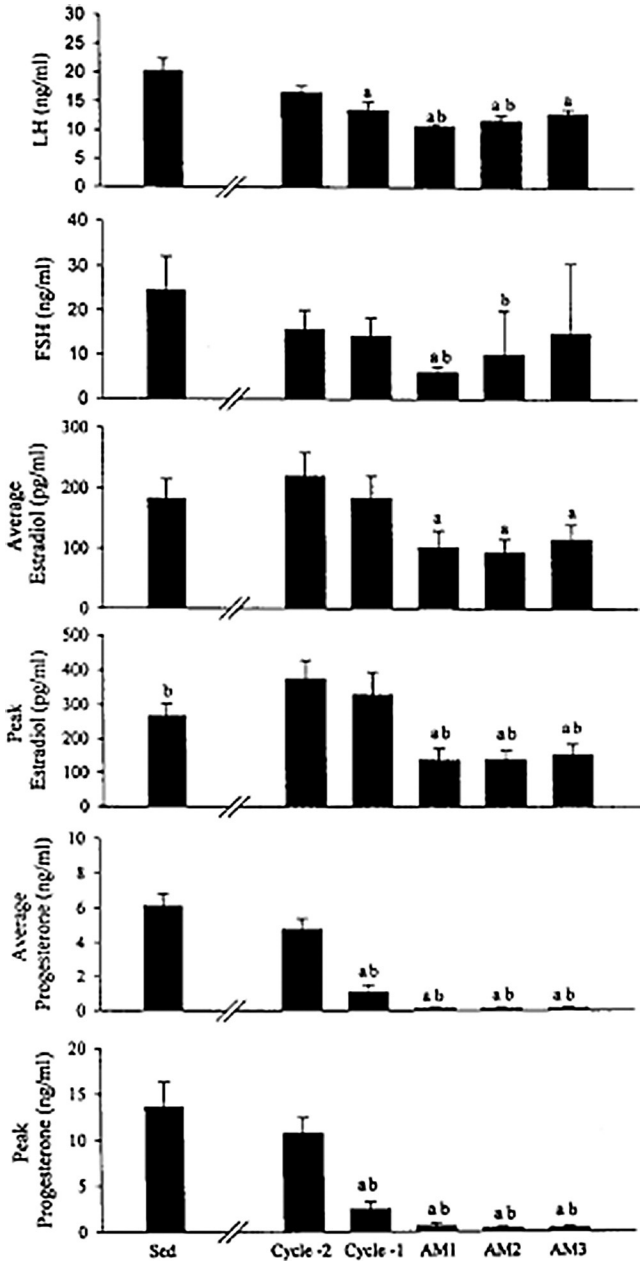

Fig. 2 – Reproductive hormone changes in exercising cynomolgus monkeys undergoing energy restriction. Monkeys were placed on a fixed caloric intake and then trained to run on a treadmill for increasing lengths of time. A control group remained sedentary. Cycle-2 and cycle-1 are the last menstrual cycles experienced by the exercising monkeys, while AM1-3 are the next three blocks of time when menses would be expected. The data show decreases in gonadotropins, estradiol, and progesterone as amenorrhea develops [57].

of the hormone. The responses were indistinguishable whether obtained in the morning (high basal cortisol) or in the evening (low basal cortisol). These findings may explain conflicting observations in the literature, especially those that ignored the physiological diurnal rhythm of the HPA axis.

Another human model used to decipher the independent effects of physical activity and psychological stress on the functioning HPA axis was carried out in soldiers undergoing the rigors of Ranger training [62]. In this group of men, there were major exercise and psychological stresses, and low energy availability occurred in alternate weeks. During the weeks of low energy availability, serum concentrations of cortisol were elevated, and those of IGF-1, T_3, LH, and testosterone were suppressed. However, in the re-fed state, these circulating metabolic hormones were restored to their homeostatic pattern. These investigators concluded that it was the energy deficit rather than the psychological stress that was proximate to the disruption of homeostasis.

Thus, there is compelling evidence in both animal models and in men and women that the stress that leads to dysfunction within the HPG axis only occurs when energy availability is inadequate with regard to exercise energy expenditure vs. energy intake.

5. Long-term effects of negative energy balance

In young women, there is a spectrum of health-related consequences of energy deficit-induced hypogonadism (Table 1). As gonadotropin secretion diminishes, the ovaries produce less estrogen. Apparently the first target is bone, for which estrogen is both anti-catabolic as well as weakly anabolic. This prevents the full achievement of whole body bone mineral content with the near-term consequence of stress fractures, especially in the lower limb, and earlier osteoporosis in the longer term. Increasing severity of the hypogonadism affects the health of the reproductive system tissues – uterus and breast – and in its more significant state leads to the Female Athlete Triad: hypogonadism (amenorrhea), osteoporosis, and an eating disorder significant enough to have a chronic energy deficit, where energy intake is significantly diminished compared to the resting energy rate and the energy expenditure of exercise. Serum leptin concentrations in subjects with the female athletic triad are low,

Table 1 – Effects of chronic negative energy balance.

Hormone concentrations		Bone-related effects	
Leptin	↓	Mineral density	↓
Ghrelin	↑	Trabecular area	↑
NPY	↑	Cortical perimeter	↑
PYY	↓	Cortical area	↓
		Trabecular number	↓
GH	↑	Trabecular thickness	↓
IGF-I	↓	Trabecular separation	↑
Gonadotropins	↓	Cardiovascular-related effects	
Testosterone	↓	Endothelial function	↓
Estradiol	↓	Low grade inflammation	↑
		Regional blood flow	↓
ADH	↑	Lipid profiles	↓
		Heart rate	↓
ACTH	↑		
Cortisol	↑		

commensurate with their decreases in fat mass. In a proof-of-concept study, Welt et al. [63] treated a small group of women with energy deficit-induced hypothalamic amenorrhea with replacement doses of recombinant methionyl human leptin and noted return of HPG axis function. This was followed by a randomized placebo-controlled trial of leptin in 20 women with hypothalamic amenorrhea over a 36 week time course [64]. There were no baseline differences in age, body composition, or endocrine and reproductive function. Of the ten women receiving leptin treatment, seven had recurrence of menses, while two of the nine receiving placebo had return of menses. Estradiol and progesterone levels increased in the treatment group compared to controls. These changes occurred despite a mean loss in fat mass of 2 kg. Although there was an increase in serum concentrations of osteocalcin, a marker of bone formation, bone mineral density did not change over the 36 weeks of the study. However, an analysis of the subjects receiving treatment in a 12 month extension demonstrated increases in bone mineral density at the lumbar spine [65]. These results indicate that decreased serum leptin concentration is a major contributor to the components of the female athletic triad. As discussed by Gordon in an accompanying editorial, administration of leptin may not be effective in all cases, particularly in leptin-resistant states [66]. These data are clearly preliminary, and larger scale clinical trials will help to elucidate long-term effects, both positive and negative. However, leptin administration seems to be a promising tool in the treatment of hypothalamic amenorrhea and its endocrine sequellae.

The circulating hormones that affect appetite, ghrelin, leptin, and PYY, are intimately involved in the flux of energy in the exercising athlete. The higher ghrelin levels suppress pulsatile LH secretion in adult males administered ghrelin [67] and in young amenorrheic athletes [68]. Lower leptin secretion was also found in the latter group, which had lowered intermittent secretion during an overnight sampling period. There may be cardiovascular consequences of the dampened HPG axis in addition to those on the reproductive system (see above) and on bone (see below). O'Donnell and co-workers [69] reviewed articles reporting cardiovascular changes in women with functional hypothalamic amenorrhea (all causes), but emphasized those with exercise-associated amenorrhea, that is, those with significant estrogen deficiency. A large series of "markers" for cardiovascular disease were catalogued: endothelial function, regional blood flow, lipid profiles, and autonomic control of blood pressure, heart rate, and baroreflex sensitivity. Despite the disparate sets of data from many small and a few larger studies, these investigators noted that in those athletes who were premenopausal, the markers considered cardioprotective in eugonadal women were indicative of cardiovascular dysfunction. However, it should be noted that no long term data indicating actual cardiovascular disease were described nor were the issues of "dose" or "duration" of exercise quantitated.

Bone physiology and pathophysiology have been more intensively studied in athletes. More recently the skeleton has been noted to have a relevant endocrine role in whole body energy homeostasis. The details are beyond the scope of this

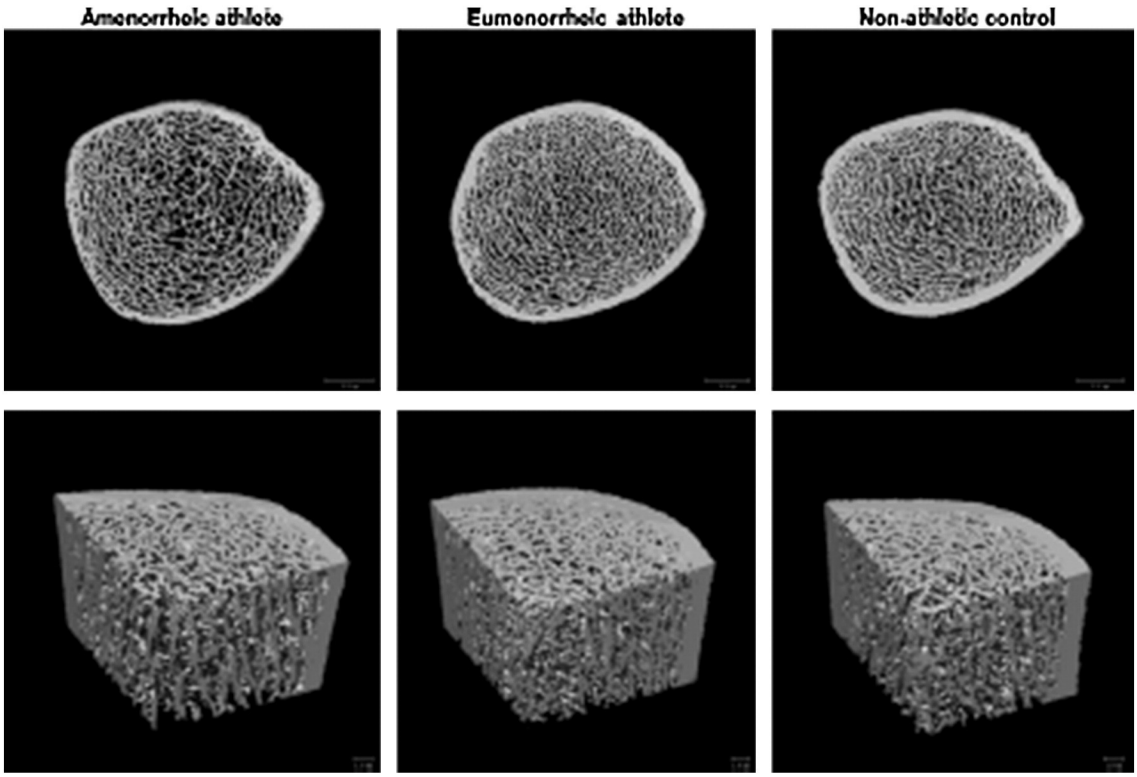

Fig. 3 – Representative bone microarchitecture images from an amenorrheic athlete, a normally menstruating athlete, and a non-athlete control. The images demonstrate decreases in trabecular number and increases in trabecular separation in the amenorrheic athlete. The images were acquired using high-resolution peripheral quantitative computed tomography [75].

review. However, they have been noted by reports from Karsenty's laboratory (predominantly in the mouse) [70,71] and in the human in a review by Schwetz and co-workers [72]. One of the critical molecules helping to orchestrate these physiological processes is osteocalcin, a known bone anabolic hormone [72,73].

Bone metabolism is adversely affected in amenorrheic athletes and likely to a greater degree in adolescent athletes (i.e., younger gynecological age) than in young women. Adolescent athletes with amenorrhea had lower bone mineral density scores at the spine and whole body than either eumenorrheic athletes or control subjects [74]. In addition they had levels of bone markers that indicated slower bone turnover. As this was a short-term study, one could not determine whether return of physiological menstrual function could reverse the alterations in bone and the endocrine system pathophysiology or their ultimate peak bone mass. This same group of investigators studied a similar group of adolescent athletes and noted impaired bone microarchitecture as well: specifically, in weight bearing bones (tibia). The athletes had greater total area, trabecular area and cortical perimeter that the non-athletes, but the cortical area and thickness were non-significantly diminished in the amenorrheic athletes. Likely of greater significance, however, the trabecular number was lower and the trabecular separation higher in those with amenorrhea [75] (Fig. 3). A similar finding, lower trabecular density, was also noted at the non-weight bearing radius. The data show that there are both local effects (weight bearing bones) and systemic effects of hypothalamic amenorrhea in endurance athletes. These are likely more severe if endurance training is begun pre- or peri-pubertally.

That the HPA axis is involved in this stress response has been noted above, but it appears at least for bone physiology, and likely many of the other homeostatic systems, that the signals include: cortisol [76], PYY and adiponectin [77], ghrelin [68], leptin [68], and now osteocalcin [71,72].

6. Conclusions

Complex endocrine changes accompany negative energy balance. These changes occur in dynamic systems, and if negative energy balance occurs in adolescents, the alterations are superimposed on systems already undergoing dramatic maturational changes, including the GH/IGF-1 and HPG axes. At the core of these adaptive and sometimes maladaptive effects is the hypothalamus, which receives inputs reporting energy stores from the periphery and with input from higher cognitive centers integrates them and outputs changes in food intake, metabolic rate, and energy expenditure. Long-term effects of negative energy balance include alterations in adrenal activity, menstrual function and bone loss.

Studies of these alterations are often pursued in animal models, which are of course different from humans in many respects. Although many of the human studies cited have recruited healthy volunteers, the numbers in any given study are usually small. Prospective studies of energy deprivation or nutritional stress with appropriate controls are difficult due to ethical considerations and are prone to biases. Nevertheless, studies over the last 10 years have added significantly to our understanding of the neuroendocrine alterations in the energy deprived human.

Additional research is needed. Further exploration of the therapeutic effects of recombinant human leptin in negative energy balance states may prove fruitful. Extension of this therapy to other hypoleptinemic states such as lipodystrophy or anorexia nervosa should be explored. Exploitation of ghrelin physiology by the development of ghrelin antagonists for weight loss may be another therapeutic avenue to combat obesity. Although investigation of energy homeostasis may seem daunting, there is great potential to acquire important insights.

Conflict of interest

The authors have no conflicts of interest to disclose.

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