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The effect of stress on menstrual function

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Historically difficult to define, stress is, in one sense, the factor that stressors have in common in their impact on the body. Menstrual function is disrupted by stressors that activate the hypothalamic–pituitary–adrenal (HPA) axis; this activation is part of a catabolic response of the whole body that mobilizes metabolic fuels to meet energy demand. Functional menstrual disorders are associated with an increase in cortisol and with a broad spectrum of other symptoms of energy deficiency. Recent experiments suggest that exercise and other stressors have no disruptive effect on reproductive function beyond the impact of their energy cost on energy availability. These studies suggest that treatments for functional menstrual disorders should aim at dietary reform and that stress is simply low energy availability. Future experiments should carefully test this hypothesis.

Recent reviews have summarized the extensive literature on the mechanisms by which the HPA axis affects reproductive function [1–3]. To continue a wider discussion begun in another recent review [4], here we draw attention to recent experiments that have investigated the independent effects of stress and energy availability on reproductive function. In finding no disruptive effect of stress on reproduction beyond the impact of its energy cost on energy availability, these experiments challenge the classic interpretation of earlier experiments and observational studies, in which energy availability was not controlled or confirmed.

Stress

Early in his career, Selye [5] acknowledged that "stress is an abstraction… a purely hypothetical thing, which possesses no real independent existence", but he maintained that in this regard the concept of stress is like the concepts of life and weight, which are also general characteristics that do not exist independently of tangible bodies. He therefore argued that stress should not be rejected as a worthless concept in biology. Nevertheless, 20 years later [5], he recalled that the term 'stress' in his sense had come into common usage, not by the logic of his argument but rather by habit: in other words, the more that people used it, the more people that used it.

A further 40 years later, Goldstein [6] observed that "despite the fact that thousands of research articles have been written about stress and stress-related diseases, until now no scientifically accepted definition of stress exists". Attempting to overcome this problem, he proposed a new definition 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".

Still, as Pacak and Palkovits [7] wrote recently, "many current views concerning what stress means and how to define it and approach it exist, but none has been widely accepted". New definitions continue to appear [8]; alternatively, the absence of a definition is simply ignored [4]. Thus, this fundamental empirical problem continues to confound stress investigators and, although others might be less troubled, we find that it is awkward to reason, to draw conclusions and to write scientifically about the effect on menstrual function of an abstraction that lacks a generally accepted definition, has no physical units of measure and resists quantification.

Stressors

Selye [5] was clear that he used the word stress to refer to a condition that is reflected in a nonspecific syndrome of responses to specific stressors, a key component of which is activation of the HPA axis. Thus, in a way that is difficult to define, stress is the factor that stressors have in common in their stimulation of the body. Occasionally we are reminded that stress encompasses the sympathoadrenal activation of the whole body – a catabolic state in which metabolic compounds are broken down to produce energy and which contrasts with the parasympathetic anabolic state of energy store replenishment, tissue repair and growth [9]. Typically, however, investigations of stress focus on the HPA axis and ignore the broader metabolic status and response of the body; in other words, they do not control or measure (i) access to and consumption of food, (ii) the mobilization and usage of metabolic fuels, or (iii) the broad spectrum of hormones that regulate these processes.

The under-appreciated metabolic impact of the purportedly psychological stress of social subordination is a case in point. In several mammalian species, including primates, socially dominant premenopausal females have lower frequencies of anovulation, luteal phase defects and hypoestrogenism [10]. Investigators in this field define

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social dominance as winning fights [10]. Not surprisingly, but rarely recorded, those who consistently win fights are bigger: 17% bigger in one such 24-month study [10]. This corresponds to the difference between women weighing 116 pounds and those weighing 140 pounds. Among other things, dominant animals monopolize access to food [11], whereas subordinate animals have lower glucose and insulin levels and progressively lose weight or fail to grow [12].

Episodes of physical restraint are another potent activator of the HPA axis and inhibitor of luteinizing hormone (LH) pulsatility [13], and they markedly suppress dietary intake and concentrations of insulin-like growth factor-I (IGF-I), leading to a reduction in body weight [14]. Footshock and the observation of footshock applied to other animals also reduce food intake [15]. Immune and inflammatory challenges activate the HPA axis and suppress gonadotropin secretion [16,17], while markedly suppressing food intake, increasing energy expenditure and profoundly altering energy metabolism in the whole body. During the initial acute phase of an immune response, glucose usage increases, hepatic glycogen stores are depleted, protein catabolism is induced, and hepatic gluconeogenesis is stimulated [18]. Glucose usage increases markedly in stressor-specific immune system tissues such as the spleen, but most of the increase occurs in muscle, skin and intestine [18]. Subsequently, as plasma glucose levels fall, insulin declines and tissues become resistant to insulin, thereby reducing glucose usage and increasing the mobilization and utilization of lipids [19–21]. Hemorrhagic shock also depletes hepatic glycogen stores [22].

Conversely, an increase in glucose availability ameliorates stress-induced clinical consequences as diverse as death rates from endotoxic shock [23], the size of gastric ulcers induced by activity stress [24] and hippocampal damage caused by chemically induced seizures [25]. Thus, animal research shows that experimental stressors physiologically activate the HPA axis as part of a catabolic process involving the whole organism.

Energy availability

It is therefore not surprising that, whereas one school of thought proposes that menstrual function is disrupted by stress (whatever that might be) and regards energy deficiency as one particular stressor, another school considers that menstrual function is disrupted by low energy availability and regards low energy availability as nothing less than the factor that all stressors have in common – in short, they consider that stress is low energy availability.

Dietary energy is partitioned among several fundamental physiological processes (cellular maintenance, thermoregulation, immune function, locomotion, growth and reproduction). Of course, energy expended in one of these processes is unavailable for others. Proponents of the energy availability hypothesis hold that the function of the gonadotropin-releasing hormone (GnRH) pulse generator depends either on neuroendocrine signals of the availability of metabolic fuels or on the availability to the brain of those fuels themselves [26]. The latter view resembles that of Sapolsky and Steinberg [27], who have proposed that glucose availability is a key factor in the 'energy crisis' that remodels and damages dendrites in the hippocampus.

Experimentally, anestrus has been induced in Syrian hamsters by food restriction, pharmacological blockers of carbohydrate and fat metabolism, insulin administration (which shunts metabolic fuels into storage), and cold exposure (which consumes metabolic fuels in thermogenesis) [28]. Research also suggests that the activity of GnRH neurons and LH pulsatility are regulated by glucose availability to the brain via two separate mechanisms involving the area postrema in the caudal brain stem and the vagus nerve [26]. Glucose-sensing neurons in the area postrema seem to transmit information to the GnRH pulse generator via neurons expressing catecholamines, neuropeptide Y (NPY) and corticotropin-releasing hormone. These glucose-sensing neurons are activated by fasting [29], owing in part to a reduction in the inhibitory influences of insulin [30] and leptin [31], as well as by glucose. Secretion of GnRH is also stimulated by the recently discovered galanin-like peptide [32], which is produced by neurons in the arcuate nucleus that express receptors for leptin, NPY, serotonin and orexin [33].

None of these observations denies that the HPA axis has an influence on reproductive function, and proponents of the energy availability hypothesis take no exception to descriptions by stress researchers of central nervous system pathways that are activated by stressors that disrupt GnRH pulsatility [1–3]; however, we place less emphasis on the HPA axis, regarding it as part of a more complex mechanism that mobilizes stored metabolic fuels when they are available in sufficient amounts and suppresses physiological processes when they are not.

Energy stores

An aspect of the energy availability hypothesis warrants emphasis. The energy in question is the amount of metabolic fuel available for energy production immediately, not over a protracted period such as a hypothetical future pregnancy [34]. Contrary to the early 'body fat hypothesis' [35], amenorrheic and eumenorrheic athletes span a common range of body composition that is leaner than that of eumenorrheic sedentary women [36–38]. Animal research has shown that a particular proportion of body fat is neither necessary nor sufficient for normal ovulatory cycles [28].

In food-deprivation-induced anestrus, normal function is restored by increasing energy availability without increasing body fat content, and cycles are inhibited by blocking the oxidation of metabolic fuels while promoting fat gain. Leptin levels, which were originally thought to communicate information about fat stores because leptin is synthesized in adipose tissue, vary profoundly in response to fasting, dietary restriction, refeeding after dietary restriction, and overfeeding before changes in adiposity occur [39]. Research now indicates that leptin is regulated by a tiny flux of glucose through the hexosamine biosynthesis pathway in both muscle and adipose tissue [40].

Menstrual disorders in athletes

Athletes affected with functional hypothalamic amenorrhea (FHA) produce low levels of estrogen and progesterone every day, indicating a complete absence of follicular development, ovulation and luteal function; however, even the most eumenorrheic athletes show extended follicular phases and abbreviated luteal phases with blunted progesterone concentrations as compared with eumenorrheic sedentary women [36]. Such subclinical luteal phase defects have been seen in eumenorrheic women who recreationally run as little as 12 miles per week [41]. Among competitive young runners the incidence of amenorrhea is as high as 65% [42], and among eumenorrheic recreational runners the incidence of anovulation and luteal phase defects is as much as 78% [43].

Both amenorrheic and eumenorrheic athletes eat much less than would be expected for their level of physical activity [36], and they show numerous endocrine and metabolic signs of energy deficiency or stress. Amenorrheic athletes have low plasma glucose [37], low insulin [37], low IGF-I [44], low leptin [45], low tri-iodothyronine (T_3) [46] and low resting metabolic rates [46], as well as high growth hormone levels [37] and mildly increased cortisol [36,37]. As compared with eumenorrheic sedentary women, luteally suppressed eumenorrheic athletes also have low insulin [37], low leptin [45] and low T_3 [47], coupled with high growth hormone levels [37] and mildly increased cortisol [36,37].

Independent effects of energy availability and exercise stress

We and our co-workers [48] resolved to determine the independent effects of energy availability and exercise stress on LH pulsatility, and to do so we needed operational definitions of both terms. An operational definition of energy availability is straightforward: energy availability was defined, measured and controlled in units of kilocalories per kilogram of fat free mass per day (kcal $kgFFM^{-1}$ day^{-1}) as dietary energy intake minus exercise energy expenditure. Presuming that exercise stress is something other than energy availability, but not knowing exactly what other aspect of exercise constitutes stress, we defined exercise stress independently and operationally as everything associated with exercise except the energy cost.

Our randomized, prospective experimental design assigned habitually sedentary women of normal body composition to sedentary or exercising groups that were each administered balanced (45 kcal $kgFFM^{-1}$ day^{-1}) and deprived (10 kcal $kgFFM^{-1}$ day^{-1}) energy availability treatments in a random order under controlled conditions for 4 days in the early follicular phases of separate menstrual cycles. In the sedentary women, balanced energy availability was achieved by controlled dietary intake alone (45 kcal $kgFFM^{-1}$ day^{-1}) and deprived energy availability was achieved by controlled dietary restriction alone (10 kcal $kgFFM^{-1}$ day^{-1}). In the exercising women, the deprived energy availability treatment was achieved by administering a dietary intake of 40 kcal $kgFFM^{-1}$ day^{-1} and by having the women expend 30 kcal $kgFFM^{-1}$ day^{-1} of energy in supervised exercise at 70% of aerobic capacity in the laboratory. Their balanced energy availability treatment was achieved by increasing the women's dietary energy intake to 75 kcal $kgFFM^{-1}$ day^{-1} to compensate for their exercise energy expenditure.

Contrasting results in the sedentary and exercising groups indicated that exercise stress had no suppressive effect on LH pulse frequency; in addition, contrasting results after the balanced and deprived energy availability treatments indicated that low energy availability suppressed LH pulse frequency, regardless of whether the low energy availability was caused by dietary energy restriction alone or by exercise energy expenditure alone. Low energy availability also suppressed T_3, insulin, IGF-I and leptin levels, and increased growth hormone and cortisol levels in a pattern very reminiscent of that seen in amenorrheic and luteally suppressed eumenorrheic athletes.

Others have since determined the independent effects of energy availability and exercise stress on menstrual function. Amenorrhea was induced in rhesus monkeys by training them to run voluntarily on a motorized treadmill for longer and longer periods while their food intake remained constant [49]. The diet of half of the monkeys was then supplemented without any moderation of their exercise regimen, which led to restoration of their menstrual cycles after a period of time that was directly related to the number of calories consumed [50].

The results of these experiments seem open to two interpretations. One is that reproductive function is disrupted by low energy availability and not by exercise stress; this interpretation places the stress and energy availability hypotheses into conflict. The other interpretation is that our initial assumption that exercise stress and low energy availability are different things is incorrect; this interpretation places the two hypotheses on potentially converging paths. If future, similarly designed experiments that compensate for the metabolic impact of other stressors yield similar results, we might draw the general conclusion that the assumption that stress and low energy availability are different things is incorrect for all stressors. Such experiments are needed so that their results can guide physicians either to focus treatments for FHA and other subclinical menstrual disorders on dietary reform or to continue pursuing stressor-specific interventions.

US Army Rangers

One such experiment has been already carried out on young male soldiers participating in an 8-week combat leadership training course for admission to the elite US Army Rangers [51]. In this experiment, energy availability was orthogonally contrasted not only with exercise but also with several other stressors in a multistressor environment. This course was divided into four 2-week phases in forest, desert, mountain and swamp environments. During the course, trainees expended about 4200 kcal day^{-1} of energy as they underwent daily military skill training, patrols of 8–12 km carrying 32-kg rucksacks, and sleep deprivation (~3.6 h of sleep per night), while consuming controlled diets providing

roughly 5000 and 2000 kcal day^{-1} in alternate odd and even weeks, respectively. In addition to heat and cold, illness, infections and injuries were commonplace. These rigors were so severe that only 30% of the highly motivated trainees completed the course.

Metabolic hormones (including cortisol, IGF-I and T_3) and two reproductive hormones (LH and testosterone) were measured at the end of each week of semistarvation, after the controlled refeeding during the fifth week, and after *ad libitum* refeeding after the end of the course. The *ad libitum* refeeding after the course fully restored all hormones to their initial values, but so did the controlled refeeding during the fifth week despite the continued exposure of the participants to all other stressors.

Psychogenic infertility

Associations between psychological disturbances and amenorrhea or infertility have long been interpreted as a causal relationship, but prospective studies demonstrating that psychogenic factors contribute to reproductive dysfunction in women are almost completely lacking [4]. Early psychoanalytic conclusions that psychological conditions underlie involuntary infertility in women have been criticized recently on several grounds [52,53]: first, the same psychological conditions have been found in analyses of fertile women; second, other women with very serious psychic problems conceive with ease; and third, couples with an unfulfilled desire for a child do not show psychological disorders any more frequently than do couples without fertility disorders. Even the direction of causality is questionable, because there are grounds for believing that infertility and its medical treatment cause the depression and anxiety observed in some infertility patients. These findings have led to the recommendation that the term 'psychogenic infertility' should be withdrawn from use because it is simplistic and anachronistic [52].

Others acknowledge only that in all but a very few cases psychological stress is not the sole cause of infertility, and call for more prospective controlled studies to determine the effects of psychological stress on fertility [53]. Kaplan and Manuck [4] maintain that "because psychological stress and excessive exercise are frequently accompanied by disordered eating, it is nearly impossible to disentangle their independent contributions to the natural history of FHA". We believe that prospective controlled experiments, such as those described and recommended above [48,50,51], are the way to determine these independent effects.

Where such experiments are impractical, observational studies of the effect of stress on reproduction in women would be greatly strengthened by including measurements of eating attitudes, dietary intake, energy expenditure and/or endocrine and metabolic signs of energy deficiency. Mere observations that cortisol levels are increased in some young amenorrheic women near 'ideal body weight' (e.g. see Refs [54–56]) do not convincingly indicate that cortisol disrupts menstrual function in the absence of energy deficiency. Ideal body weight is not a reliable indicator of energy balance in all individuals. The actuarial entries in Metropolitan Life Insurance Company tables of ideal body weight are selected to minimize claims by policyholders for all causes of mortality, not menstrual disorders. Furthermore, even when used for their intended purpose of maximizing life insurance profits, these entries do not apply to anyone under the age of 25 [57].

As an example of this approach, the principal finding in what its authors have described as the most complete current observational assessment of behavioral and psychological correlates in women affected with FHA was that "symptoms of disordered eating discriminate women with FHA from those with organic amenorrhea and eumenorrhea" [58]. Although the degree of psychosocial distress was found to be marginally greater in women with FHA, psychological dysfunction was not specific to FHA. Women with FHA also show functional hypothyroidism with their hypercortisolism [59], and both conditions are corrected together during recovery from FHA [60]. Furthermore, cognitive behavior therapy focusing on nutritional counseling has been found to restore ovulatory cycles in 75% of FHA patients within 5 months without the pitfalls of pharmacological modalities [61].

Conclusions

In summary, recent experiments suggest an approach through which separate hypotheses about the etiology of functional menstrual disorders might converge. The conclusion that energy imbalance is the primary mediator of FHA, even when psychogenic stress or exercise are present [62–64], has been declared "unsatisfactory because it does not identify the underlying factors initiating the changes in diet and physical activity that result in negative energy balance" [4]. This is a valid clinical concern, because an individual with anorexia nervosa is not likely to increase her energy availability simply because her physician explains to her that doing so would restore her menstrual cycle. If, however, recommended experiments reduce the ambiguity about stress and energy availability to the level of this concern, then we will have reached a clinically useful agreement about proximate and ultimate causes. We will have recognized that many ultimate causes (stressors) result in low energy availability (stress) and that this is the proximate cause of functional menstrual disorders and perhaps other morbidities. A benefit of this convergence for the wider scientific community will be that the concept of stress will have finally acquired a simple, clear definition and quantifiable, physical units of measure.

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