New animal model opens opportunities for research on the female athlete triad

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Invited Editorial

DEMARCO, DART, AND SANBORN have reported (2) the development of an innovative and important “modified activity-stress paradigm in an animal model of the female athlete triad.” This new animal model opens the opportunity to conduct controlled experiments to investigate many important questions about the female athlete triad that cannot be studied in humans or in short-term protocols with animal models. These questions include dose-response effects on various physiological systems, neuroendocrinological mechanisms regulating these systems, differences between the responses of adult and peripubertal animals, dependencies of systems and mechanisms on specific macronutrient availabilities, and development of pharmaceutical interventions to improve clinical outcomes.

In the classic activity-stress paradigm, also known as “activity-based anorexia,” rats are placed in running wheels with an adjoining cage and fed for 1 h per day (6). Under these conditions, rats increase their activity levels, decrease their food consumption, lose body weight, and die within 3–12 days unless they are removed from the apparatus. This rapid mortality has greatly limited the utility of this paradigm as a model for the female athlete triad, because the experimental animals do not survive long enough for long-term effects on slow physiological processes such as bone and other organ modeling and remodeling to occur.

The innovative modification of the activity-stress paradigm made by DiMarco et al. was to offer experimental animals a measured, restricted amount of food for an unlimited amount of time instead of an unlimited amount of food for a restricted amount of time. The paradigm-shifting result was that the animals survived, which opened the opportunity for prolonged experimental protocols. DiMarco et al. demonstrate this by reporting how 3 mo of exercise and food restriction reduce ovarian weight and bone mineral content.

The intellectual pedigree of this new animal model of the female athlete triad can be traced back to Selye’s seminal article on “The effect of adaptation to various damaging agents on the female sex organs in the rat” (9). In that 1939 article, Selye inaugurated what became the huge field of stress research. He defined stress as “a non-specific response of the body to any demands made on it.” The paradigm-shifting result was that the animals survived, which opened the opportunity for prolonged experimental protocols. DiMarco et al. demonstrate this by reporting how 3 mo of exercise and food restriction reduce ovarian weight and bone mineral content.

As important a step forward in the study of the female athlete triad as the development of this animal model is, it still has limitations that should be clearly understood and investigated. In potentially important physiological ways, rats are different from humans. Their diurnal rhythms are reversed. Endocrine responses to energy deficiency are not all alike. For example, growth hormone declines in rats and rises in humans. Unlike humans, rats eat many small meals per day, and when fasted they can lose up to a third of their body weight within 3 days depending on ambient temperature. The energy requirements of rat and human brains, where reproductive function is regulated, are also very different. In humans, the brain consumes 20% of resting energy expenditure in adults and 50% in children. In rats, the brain consumes only 2%. Working muscle competes directly against the brain for glucose as a metabolic fuel, in humans consuming much more glucose in an hour than the brain consumes in a day. Therefore, the effects of exercise on brains with such different energy requirements may also differ.

Healthy adult humans are also thought to possess neuroendocrine, physiological, and behavioral mechanisms that closely regulate body weight, and the epidemic of obesity in modern societies is thought to reflect a failure of these mechanisms. By contrast, adult rats fed ad libitum continue growing. Adult rats fed ad libitum have, if anything, a stable growth rate rather than a stable body weight. Of course, it is possible that the current epidemic of obesity reflects not the failure but rather the absence of weight-regulating mechanisms in adult humans fed ad libitum. The habitual overnutrition of sedentary individuals eating ad libitum may mirror the habitual undernutrition of physically active individuals eating ad libitum. Part of the nutritional challenge facing athletes appears to be that “there is no strong biological imperative to match energy intake to activity-induced energy expenditure” (11). When an experimental protocol opposite to the activity-stress paradigm is imposed on humans, that is, when their activity level is controllably increased instead of their dietary intake being controllably restricted, their ad libitum dietary intake declines, and it declines most when their diet is high in carbohydrates (10), like the diets recommended for endurance athletes.

A further limitation of the model of DiMarco et al. is that energy intake and exercise energy expenditure are not controlled independently. The investigators control the rats’ energy intake, and the rats decide how much exercise to do. By a further refinement of the model, however, investigators may be able to gain indirect control over the rats’ activity level. While one school of thought hypothesizes that the increased activity of rats in the activity-stress paradigm reflects an instinctual increase in foraging activity as a behavioral component of body weight regulation, another school of thought hypothesizes that mammals “eat to keep warm and stop eating to prevent hyperthermia” (1). By the latter hypothesis, rats in the activity-stress paradigm exercise to increase their body
temperature (4, 6), which drops with food restriction because ambient temperature in animal laboratories is typically regulated for the comfort of the human investigators at ~21°C rather than for the comfort of the rats, whose thermoneutral zone is 29–31°C (3). Indeed, when given the choice, food-restricted rats in a 21°C laboratory like that of DiMarco et al. prefer lying on a warm plate to running on a wheel (5). This suggests that investigators may be able to control rather than just measure the exercise behavior of rats in a further refinement of the modified activity-stress paradigm by varying ambient temperature. Addition of a calorimeter will also enable investigators to measure rather than estimate the resulting energy expenditure.

In closing, it should be noted that the results of the initial application of the DiMarco et al. modification of the activity-stress paradigm support the hypothesis that the female athlete triad is caused by low energy availability and contradict the hypothesis that it is caused by the stress of exercise. Voluntary wheel running activity was indistinguishable between control rats and those whose dietary intake was restricted. Anestrus occurred, ovaries atrophied, and bone mineral content declined selectively in those animals whose energy intake and therefore energy availability had been reduced. Thus the study of DiMarco et al. adds further evidence supporting the new clinical recommendation that the primary aim of treatment for the female athlete triad is to increase energy availability, either by increasing energy intake or by reducing exercise energy expenditure, according to the preference of the athlete (7).

REFERENCES