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Editorial

Guest editor's introduction: Energy homeostasis in context

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ABSTRACT

This article is part of a Special Issue "Energy Balance".

Energy homeostasis is achieved through neuroendocrine and metabolic control of energy intake, storage, and expenditure. Traditionally, these controls have been studied in an unrealistic and narrow context. The appetite for food, for example, is most often assumed to be independent of other motivations, such as sexual desire, fearfulness, and competition. Furthermore, our understanding of all aspects of energy homeostasis is based on studying males of only a few species. The baseline control subjects are most often housed in enclosed spaces, with continuous, unlimited access to food. In the last century, this approach has generated useful information, but all the while, the global prevalence of obesity has increased and remains at unprecedented levels (Ogden et al., 2013, 2014). It is likely, however, that the mechanisms that control ingestive behavior were molded by evolutionary forces, and that few, if any vertebrate species evolved in the presence of a limitless food supply, in an enclosed 0.5×1 ft space, and exposed to a constant ambient temperature of 22 ± 2 °C. This special issue of *Hormones and Behavior* therefore contains 9 review articles and 7 data articles that consider energy homeostasis within the context of other motivations and physiological processes, such as early development, sexual differentiation, sexual motivation, reproduction, seasonality, hibernation, and migration. Each article is focused on a different species or on a set of species, and most vertebrate classes are represented. Energy homeostasis is viewed in the context of the selection pressures that simultaneously molded multiple aspects of energy intake, storage, and expenditure. This approach yields surprising conclusions regarding the function of those traits and their underlying neuroendocrine mechanisms.

Introduction

> "…rats and mice used in biomedical research are sedentary, obese, glucose intolerant, and on a trajectory to premature death"
> [Martin et al., 2010]

For many years, energy homeostasis has been studied using methods that have afforded a great deal of experimental control but may have warped or limited our understanding. Most biomedical research is conducted in a small number of laboratory species housed under constant, standardized conditions, including static ambient temperature and day length, and widely-used commercial diets. The control groups are typically provided with an unlimited supply of food, and all subjects are housed in isolation from opposite-sex conspecifics or predators in relatively small, enclosed spaces. The underlying assumption seems to be that animals make decisions about when, what, and how much to eat in the absence of potential mating partners, competitors, predators, and family members. Among the many studies of ingestive behavior published in biomedical journals, an overwhelming majority of those experiments used mice or rats housed under these conditions (Ebling, 2014; Martin et al., 2010). Furthermore, the subjects are most often male, with no consideration given to females (Beery and Zucker, 2011). The obvious advantages of these well-worn practices include 1) a high degree of experimental control over relatively inexpensive experimental subjects with short lifespans and generation times; 2) standardized conditions that minimize error variance and facilitate collaboration, cross-laboratory comparisons, and meta-analyses; and 3) the ability to identify many different hormones and neuropeptides that influence energy intake, storage, and expenditure. The benefits, however, can turn into liabilities if standardized, artificial conditions obscure the reality of hormone–behavior relations as they exist in nature. Furthermore, mice and rats housed in standard laboratory conditions with *ad libitum* access to laboratory chow are overweight, insulin resistant, hypertensive, hyperglycemic, hyperinsulinemic, and hyperleptinemic (reviewed by (Martin et al., 2010)).

The question then is not "Why should we study other species in a more relevant context?" but rather, "Why are we still studying male

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mice and rats living 24-7 at the all-you-can-eat buffet and calling them 'the control group?'".

Regular readers of *Hormones and Behavior* are likely familiar with the limitations of studying animals confined to small enclosures. We need only remember the erroneous assumptions that were reinforced when female sex behavior was studied in rats or monkeys in small testing arenas with a single male conspecific, and the way that the dogma was shattered when females were housed in larger arenas with multiple conspecifics, and when female motivation was examined separately from that of the male (reviewed by Erskine, 1989; Wallen, 1990, 2001). A similar situation exists in the field of energy homeostasis, but we have not broken out of the traditional mode, and we are suffering the consequences. Despite enormous progress in identifying new neuropeptides and peripheral hormones that influence energy homeostasis (reviewed by (Schneider et al., 2013; Sohn et al., 2013), the global prevalence of obesity is still at its highest level in recent history (Ogden et al., 2013, 2014). It has been almost two decades since the watershed discovery of leptin, the adipocyte protein encoded by the *ob* gene (Zhang et al., 1994), and yet we still lack successful therapeutic treatments that ameliorate or prevent obesity.

One obstacle to progress might be the erroneous picture that is painted by studying homeostatic variables in isolation from the selection pressures that molded them. The mechanisms and function of the traits involved in energy homeostasis appear in a new light when animals of both sexes are considered within the context of development, opposite-sex conspecifics, fluctuations in food availability, ambient temperature, and day length.

Readers of this special issue are in for an upgrade if not a total transformation of their understanding of energy homeostasis. In these articles, energy intake, storage, and expenditure are viewed within the context of reproduction, seasonality, migration, and development, and in some cases the articles consider the interactions among these factors. Within these articles, there are representative species of mammals, birds, reptiles, amphibians, and fish. Mice and rats are not excluded, but where they are included, they are studied in relation to reproduction or sexual differentiation. The penultimate review article is concerned with sex differences in energy homeostasis, primarily white adipose tissue (WAT) distribution, in our own species. Each of these articles contains surprising conclusions about the mechanisms that underlie energy homeostasis. When viewed as a group, these articles compel us to face the true meaning of energy "homeostasis" and to more closely define the words "regulate" and "control."

The word homeostasis stems from the Latin words for staying "similar to," not "the same as," and thus it implies some degree of fluctuation as well as maintenance within a range of values (reviewed by (Friedman, 2008). These central points of equilibrium might change somewhat over the lifespan, during periods of growth, during different reproductive stages, and in response to changes in the environment. Examples of variables that must be maintained in relatively tight homeostasis include body temperature (in homeotherms), blood pH, and the intracellular availability of oxidizable metabolic fuels. Thermotaxis is controlled (not regulated) in service of regulating body temperature, i.e., maintaining body temperature homeostasis. If your body temperature were to rise above 107 °C (or your blood pH rises above 8.0) you would be in trouble. For you, the only alternative to tight regulation of these variables is death.

By contrast, excess levels of food intake or a high percentage of WAT can be tolerated for months or years prior to any major effect. In fact, survival often depends on the ability to increase food intake and accumulate WAT stores. This is because all cellular processes require a continuous supply of metabolic fuels, but energy is not continuously available in the environment. Most animals evolved in habitats where energy was not continuously available (Bronson, 1989), and survival in such environments often required anticipatory overeating and WAT accumulation as a buffer against future energy shortages. Periods of food scarcity coupled with high-energy demands are accompanied by hydrolysis and mobilization of fuels from lipids stored in WAT and loss of body weight and overall levels of body fat.

To defend a particular level of body fat content in the face of low food availability and high energetic demand would be a fatal mistake. Survival requires that we allow the level of body fat to fall as we use the fatty acids derived from those fat stores to fuel essential cellular processes. Another fatal mistake would be to defend a particular level of body fat content instead of accumulating body fat in preparation for future food shortages or impending periods of high energy demand when feeding is not continuously possible; e.g., migration. This concern for future food scarcity might be hard for first-world academics to imagine, but it would not be an unusual scenario for most wild animals or for the early hominids from which we evolved (Brown and Konner, 1987; Pennington, 2001). This explains why this special issue concerns *energy* homeostasis, not body weight homeostasis. A common feature in vertebrates is that body fat content and food intake are controlled (not regulated) in service of the regulated homeostatic variable: the availability of oxidizable fuels (Friedman, 2008). In response to such realities, it has been suggested that we replace the term "homeostasis" with "rheostasis" or "allostasis" (McEwen and Wingfield, 2003; Mrosovsky, 1990). Perhaps the best example is the control of energy intake, storage, and expenditure in service of reproductive success.

Review articles

Energy homeostasis in the reproductive context

In the first group of articles, we learn that energy intake, storage, and expenditure are controlled so the high energetic cost of female reproduction can be paid from the females' bank account or insurance policy. The bank account is often filled in advance of the metabolic challenge by increased food intake and the accumulation of body fat and/or external food caches. Instead of defending a low-medium body weight, females of many species will overeat or hoard food weeks or months in advance of mating. Furthermore, instead of maintaining some sort of homeostasis in food intake, females of many species increase their food intake, sometime three or more fold, during lactation (reviewed by (Schneider et al., 2013)) or posthatching (e.g., Koch et al., 2002, 2004; Ramakrishnan et al., 2007; Strader and Buntin, 2003). In times of food shortage or high energy demand, energy can be conserved for those processes necessary for survival, and thus, metabolic challenges can inhibit every aspect of the hypothalamic-pituitary-gonadal (HPG) system. The primary effect, however, is on the gonadotropin-releasing hormone (GnRH) pulse generator (reviewed by Wade and Schneider (1992)). In this way, the systems controlling energy homeostasis and reproduction are reciprocally linked. Virtually every hormone or neuropeptide that controls ingestive behavior also controls reproduction, and it is difficult to understand energy homeostasis except in the context of reproduction (reviewed by Schneider et al. (2013)).

1. *Nicole Bellefontaine and Carol Elias* review an excellent example of this link between energy homeostasis and female reproduction. Mice with mutations in the gene that encodes the adipocyte protein, leptin are both obese and infertile, and the obesity and infertility are ameliorated by treatment with leptin. In strains of mice that lack the functional leptin receptor, obesity and infertility are ameliorated with genetic restoration of leptin receptors restricted to neurons (reviewed by Donato et al. (2011)). This leads to an interesting question. Is the infertility secondary to the obesity? Members of the *Elias* laboratory answered this question using viral vector delivery and the Cre/loxP system. Whereas large body of data using traditional neuroanatomical methodologies has implicated kisspeptin cells in the arcuate as targets of leptin-induced effects on GnRH cells, the *Elias* laboratory refutes this idea. Rather, they demonstrate that leptin can reverse the effects of fasting on the HPG system via action in the ventral premammillary

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