Fatness and fertility: which direction?

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Commentary

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Fatness and fertility: which direction?
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Leptin and kisspeptin: linking metabolism and reproduction?
The concept that a minimum weight-to-height ratio is necessary for the onset and maintenance of menstrual cycles was first introduced in the 1970s; however, uncovering the physiologic pathways that connect reproduction and metabolism has been challenging (1, 2). In the 1990s, the discovery that patients deficient for leptin (a cell-signaling hormone critical for weight regulation) or leptin signaling have abnormal pubertal development led many to hail leptin as the long-sought link between energy metabolism and reproduction — or does it? As work on the relationship between metabolism and kisspeptin progressed, it appeared that the directional arrow in this association begins with the metabolic status of the organism (i.e., undernutrition, overnutrition, or lactation), which then leads to abnormal phenotypes in the reproductive cascade (delayed puberty or infertility). In this issue of the JCI, Tolson et al. have turned this paradigm on its head and present data suggesting that perturbations in kisspeptin signaling affect metabolism (10). Female, but not male, mice lacking KISS1R weighed significantly more than control animals. Furthermore, Kiss1r−/− females had increased fat mass, hyperleptinemia, higher fasting glucose, and impaired glucose tolerance in the setting of reduced metabolism and energy expenditure. Moreover, ovariectomized KISS1R-deficient females weighed more than ovariectomized controls, which suggests that the obesity phenotype is independent of differences in gonadal steroids due to loss of kisspeptin signaling. Notably, weight differences between Kiss1r−/− females and control animals began to emerge at eight to ten weeks of age and continued to increase out to 18 weeks (10). Unfortunately, there are...
almost no previously published data on the body weight of mice lacking kisspeptin or KISS1R well into adulthood. A previous study reported that female mice lacking kisspeptin-expressing cells had weights at eight weeks that were comparable to the weights reported by Tolson and colleagues; however, this group did not extend their measurements beyond the eight-week timepoint (11). In another study, female kisspeptin-knockout mice were reported to be significantly smaller than their female littermates at two months of age (12), while a third group observed a decrease in weight of Kiss1r−/− males compared with WT and heterozygous littermates at nine weeks, but no decrease or noticeable difference in Kiss1r+/− females (13). During our laboratory’s initial characterization of Kiss1−/− and Kiss1r−/− mice that we generated by introducing ES cells from 129/S embryonic stem cells into C57BL/6 blastocysts, crossing chimeras with 129/S1/SvImJ females, and interbreeding the heterozygotes to generate knockout mice, we did not extend weight measurements past nine to 12 weeks (14). There was no overt difference in the weight of these female mice. The mice used by Tolson et al. were created on a mixed C57BL/6 and 129/S1/SvImJ background (10); therefore, continued exploration of metabolic consequences of perturbations in the kisspeptin signaling pathway will require studies using multiple strains of both male and female Kiss1−/− and Kiss1r−/− mice to further dissect the contributions of strain, gender, method of creation, and dependency on kisspeptin signaling (ligand vs. receptor) in this relationship.

Conclusions and future directions

While the revelation by Tolson and colleagues that disrupted kisspeptin signaling promotes murine metabolic dysfunction is exciting, it is unclear whether this weight phenotype is relevant to humans. Unfortunately, very few patients with terminating mutations of the genes encoding either kisspeptin or its receptor have been identified and described in the literature. Although these few individuals were evaluated at various ages, metabolic phenotypes were not reported; it is assumed that overt obesity would have been noted, but this phenotype was not commented upon (5, 15). Certainly, the need to phenotype animal models over time is an increasingly important theme in kisspeptin–neurokinin B–dynorphin biology. An important lesson emerging from these studies is that the reproductive phenotypes of both humans and mice bearing mutations and/or deletions in the kisspeptin pathway are not always static. For example, Kiss1−/− and Kiss1r−/− mutant mice have a dynamic phenotype characterized by persistent GnRH activity, which becomes more apparent over time (16). Reproductive maturation can occur in the absence of kisspeptin signaling prior to certain windows in development, presumably due to the emergence of compensatory pathways (11). In line with these observations, humans with mutations in the neurokinin B signaling pathway present with hypogonadotropism at a young age, but have shown a reversal of this phenotype as adults (17, 18). Thus, the greater the phenotypic armamentarium used to study sexual maturation and fertility, the greater the phenotypic complexity that may emerge.

On a final point, interactions between metabolic cues and kisspeptin signaling, regardless of directionality, have largely been envisioned as taking place within hypothalamic networks. Little attention to the role of kisspeptin in the periphery has been paid until recently, when a hormonal circuit linking hyperglucagonemia, hepatic kisspeptin secretion, and impaired insulin secretion was uncovered (19). Interestingly, in that circuit, kisspeptin production, specifically in the liver, inhibited glucose-dependent insulin secretion, which suggests that impaired kisspeptin signaling might actually stimulate insulin secretion—a finding not observed by Tolson et al. (10). Thus, kisspeptin’s role in metabolic circuitry may be unique and differentially influential in different tissues.

The interrelationship between reproduction and metabolism continues to intrigue investigators and clinicians alike. Studies able to dissect its directionality, compensatory pathophysiology, underlying genetic signatures, and central versus peripheral inputs will be required to solve its complexity.

Acknowledgments

S.B. Seminara is supported by grants K24 HD067388, R01 HD043341, and U54 HD028138 from the Eunice K. Shriver National Institute for Child Health and Human Development (NICHD).

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