Metabolic status has long been thought to determine reproductive status, with abnormal metabolic phenotypes altering reproductive cascades, such as the onset of puberty. In this issue of the JCI, Tolson and colleagues provide evidence that kisspeptin, a hormone that promotes sexual maturation, regulates metabolism. Female mice lacking the kisspeptin receptor (KISS1R) gained more weight than control animals, and this weight gain was caused not by increased food consumption, but by an overall decrease in energy and metabolism. While this study provides a direct link between the kisspeptin pathway and metabolic output, more work will need to be done to determine whether alterations in this pathway contribute to human obesity.
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 energetics and reproductive function. Soon after the discovery of kisspeptin’s role in regulating reproduction, investigators began to explore the possibility of a link between energy status and the kisspeptin system. States of negative energy balance, such as food deprivation, were found to induce suppression of the hypothalamic kisspeptin system, while administration of kisspeptin ameliorated the leptin-dependent effects on reproduction (3). Female, but not male, mice lacking KISS1R weighed significantly more than control animals. Furthermore, KISS1R−/− females exhibited decreased fat mass, hyperleptinemia, higher fasting glucose, and impaired glucose tolerance in the setting of reduced metabolism and energy expenditure (4).

Enthusiasm for the hypothesis that leptin and kisspeptin coordinate the onset of sexual maturation dampened in 2011 following a report that selective deletion of leptin receptors from kisspeptin-expressing neurons did not affect sexual maturation and fertility (5). This surprising finding suggested that direct leptin action on kisspeptin neurons is not required for puberty onset in mice; however, this study did not eliminate that possibility that leptin-dependent effects on reproduction are indirectly transmitted through kisspeptin-expressing neurons, potentially adding layers of complexity to the regulation of these hypothalamic networks.

Metabolic status determines 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 (6). 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, ovariecotomized KISS1R−/− females weighed significantly more than ovariecotomized 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 (7). Unfortunately, there are
almost no previously published data on the body weight of mice lacking kisspeptin or Kiss1r mice would yield insights into these different consequences of perturbations in the kisspeptin 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 reproductive 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.

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