PYY3–36 “monkeys around” with energy balance

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THE LAST DECADE has witnessed an historic amount of effort and resources expended on the basic science of body weight regulation, and with good reason. The prevalence of obesity is escalating at alarming rates around the globe and will likely surpass tobacco as the leading cause of preventable death in the United States. As a result, new discoveries capture the attention and raise the hopes not only of researchers in the field of obesity and energy balance but also of the popular press, the pharmaceutical industry, obese patients, and their doctors. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Moran and colleagues (11) describe important new findings concerning one of these recent prominently reported discoveries, the gut hormone peptide YY(3–36) [PYY(3–36)].

Moran et al. (11) detail new studies that demonstrate PYY3–36 reduces food intake and markedly slows gastric emptying in rhesus monkeys. In 2002, Batterham et al. (3) reported that this peptide was an important physiological regulator of energy intake. In those experiments, peripheral administration of PYY3–36 decreased food intake in both rodents and humans. Additionally, long-term administration of the hormone to rats significantly reduced body weight gain. Furthermore, Batterham et al. (3) reported that injection of PYY3–36 reduced food intake in wild-type mice but not in mice deficient for the Y2 receptor subtype. These data were consistent with the hypothesis that PYY3–36 elicits satiety through neuropeptide Y (NPY)-Y2 receptors, which are believed to attenuate central NPY action via an autosensitizing mechanism. Finally, Batterham et al. (2) subsequently demonstrated that PYY3–36 reduced food intake in obese humans, a very exciting finding and one relatively rare in the field of obesity research. These results ignited hopes of generating an effective antiobesity agent based on PYY3–36 or a selective Y2-receptor agonist in the near future.

PYY1–36 is expressed at high concentrations in the distal small and large intestine and secreted into blood after the ingestion of nutrients. Importantly, PYY1–36 is not selective for the hypothalamic NPY-Y2 receptors and does, on the basis of its strong binding at NPY-Y1 and -Y5 receptors, potently increase food intake (e.g., Ref. 7). Although only a limited amount of published data is available, it appears that dipeptidyl-peptidase IV (DPP-IV) cleaves PYY1–36 into PYY3–36 (10). The precise regulation of this process remains largely unknown. On the basis of our current knowledge, DPP-IV gene-disrupted mice should also be “PYY3–36-deficient” mice. However, DPP-IV is a critical step for many peptides other than PYY, which makes simple conclusions from these animals more difficult. Nonetheless, the main phenotype of mice lacking DPP-IV suggests protection against diet-induced obesity, which is inconsistent with the absence of an important hypothesized satiety signal (5).

Several other key points about PYY3–36 are important to consider. First, both in vivo and in vitro experiments have demonstrated that PYY3–36 is not entirely selective for Y2 receptors but is also a less selective Y1- and Y5-receptor agonist (e.g., Ref. 9), the NPY receptors thought to be responsible for NPY-induced increases in food intake. Indeed, intracerebroventricular administration of PYY3–36 potently increased food intake and body weight in mice (14). Second, the relative abundance of these receptors varies widely between different regions of the brain. The arcuate nucleus, for example, has relatively more Y2 than Y1 receptor subtypes, which provides a logical explanation for the finding by Batterham et al. (3) that PYY3–36 decreases food intake. Additionally, the arcuate nucleus is thought to have a relaxed blood barrier, allowing PYY3–36 to easily cross and act on inhibitory Y2 receptors, and this was recently demonstrated in mice (12). Third, however, PYY3–36 inhibits food intake in mice lacking the genes for either proopiomelanocortin or the melanocortin-4 receptor (4, 8), the neuropeptide system hypothesized ultimately to mediate the anorexic effects of PYY3–36 in the brain (3). Thus the originally hypothesized central nervous system mediator of PYY3–36, the melanocortin receptor ligand α-melanocyte-stimulating hormone, does not appear necessary for its anorexic effects.

More controversy recently arose when a number of laboratories could not repeat a core observation that PYY3–36 suppressed food intake in rodents. Moran et al., other colleagues, and we (15) described a collection of 39 studies in which PYY3–36 neither consistently decreased food intake nor consistently decreased body weight gain in rats and mice. In fact, peripheral administration of PYY3–36 significantly increased food intake and body weight in several of those studies, which are described in detail elsewhere (see Ref. 15; www.pyyobesity.com).

The reason (or reasons) for these discrepancies is unknown, although the detailed comparison of methodologies and protocols has led to several hypotheses. High stress sensitivity of PYY-induced satiety, differences among rodent strains, and repeated vs. continuous PYY administration are just a few examples. More importantly, however, the publication of both positive and negative results on pharmacological effects and endogenous roles of PYY in energy balance has triggered new studies with increased attention to these details and experimental conditions.

Moran and colleagues (11) present an elegant example of such a study in this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology. In the new work, Moran et al. moved beyond rodents to primates because the physiology of primates is almost certainly a more relevant model to human obesity. On the first day of the study, Moran et al. observed that a single peripheral administration of PYY3–36 reduced 6-h food compared with vehicle-treated controls. More specifically, they found that PYY3–36 delayed...
the start of the monkeys’ first meal, without altering the first meal size. However, PYY3–36 reduced the size of subsequent meals without reducing the overall number of meals, resulting in a net decrease in energy intake. These data are consistent with an acute effect of PYY3–36 to delay meal initiation and, potentially, a role for PYY3–36 in meal size.

Interestingly, new complexities have also emerged from the recent work. Moran et al. (11) demonstrate here that PYY3–36 dose-dependently attenuated gastric emptying of the monkeys’ liquid meal. Because the size of the first meal was not reduced, the subsequent reduction in meal size may be secondary to effects of remaining gut contents. In fact, nonspecific vagal and brain stem-mediated signals may have modified meal patterns in response to delayed gastric emptying, rather than PYY3–36 acting directly on hypothalamic energy circuits. Additional work is required to delineate these possibilities and also assess whether PYY3–36 normally plays an important physiological role in gastric emptying.

Nonetheless, Moran et al. (11) conceptually replicate important findings of Batterham et al. (1–3), who found that PYY3–36 reduced acute feeding in rodents and 16-h food intake in humans. It is important to recall here that the controversies and interpretative challenges surrounding PYY3–36 (6, 13, 15) have focused exclusively on studies that used mouse and rat models. Therefore, one conclusion might be that anorexic effects of PYY3–36 in rodents are dependent on as-yet-unknown experimental factors, whereas the satiety effect may be more robust in monkeys and humans, at least acutely.

In another important respect, however, the new studies reported here did not find results similar to those originally reported by Batterham et al. (3). Although PYY3–36 inhibited 6-h food intake on the first day, this effect was not sustained across multiple days despite continued treatment with PYY3–36. In fact, Moran et al. (11) report that PYY3–36 had no effect on food intake from the second day of administration. That result bears more similarity to work (15) reporting negative effects of remaining gut contents. In fact, nonspecific vagal and brain stem-mediated signals may have modified meal patterns in response to delayed gastric emptying, rather than PYY3–36 acting directly on hypothalamic energy circuits. Additional work is required to delineate these possibilities and also assess whether PYY3–36 normally plays an important physiological role in gastric emptying.

In summary, this report again demonstrates that PYY regulates energy homeostasis. Hopefully, these and other preclinical data will provide important insights about experimental differences and also improve the design of future studies. Of course, only well-controlled experiments in humans, examining the chronic effects of PYY3–36 on body fat mass, will ultimately decide the fate of this peptide as a potential therapeutics.

REFERENCES


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