Peptide YY(3-36) and food intake: a peptide waiting for a paradigm?

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PEPTIDE YY (PYY) is a 36-amino acid peptide belonging to the pancreatic polypeptide (PP)-fold family of peptides that also includes PP and neuropeptide Y. PYY is colocalized with GLP-1 in L-type endocrine cells of the distal intestinal mucosa and is released in response to intraluminal nutrient stimulation with peak levels occurring 1 to 2 h postigestion (1, 2). After its release, PYY is cleaved by depeptidyl peptidase IV to yield PYY(3-36), which comprises over half of all postprandial circulating PYY in humans (8).

Administration of PYY elicits a variety of gastrointestinal effects, including the inhibition of gastric emptying and a reduction in stimulated pancreatic exocrine secretion and intestinal transit time (9, 13). Although PYY(3-36) has also been demonstrated to inhibit gastric emptying (5, 10), its most prominent and indeed, most controversial action, is the ability to reduce food intake (3, 4).

In 2002, Batterham et al. (4) reported that PYY(3-36) injected peripherally twice daily for 7 days reduced cumulative food intake and prevented body weight gain in rats. In addition, intravenous administration of PYY(3-36) in human subjects decreased appetite and food intake in the 12-h period after the infusion. These results sparked a great deal of interest in the physiological significance of PYY(3-36) in ingestive control and the potential for PYY(3-36) as a therapeutic tool for appetite reduction.

However, the significance of these findings was soon challenged in a follow-up paper reporting on a number of studies from independent laboratories that were unable to replicate these results in rats and mice using several different experimental paradigms encompassing both acute injections delivered centrally and peripherally and multiple peripheral injections (14). In most cases, there was either no effect or a transient decrease in food intake and body weight, and in some studies, an increase in both measures. Despite these negative reports, there emerged several studies demonstrating that chronic infusion of PYY(3-36) by osmotic minipump delivery reduced food intake and body weight in rodents, but this effect did not persist beyond several days (11, 15, 16).

Subsequently, Chelikani et al. (6) published an interesting paper describing positive effects on food intake and body weight in rats using an experimental paradigm in which PYY(3-36) was delivered intermittently using two different dosing schedules. In the first, 30 pmol·kg⁻¹·min⁻¹ PYY(3-36) was infused during two 3-h sessions during the dark period over 8 days. This infusion schedule elicited a robust reduction in food intake after both infusion sessions that lasted for the duration of the experiment. However, the rats compensated for this decrease by increasing their food intake during the noninfusion periods. In the second dosing paradigm, rats were infused with 30 pmol·kg⁻¹·min⁻¹ PYY(3-36) every other hour beginning at 1200 and ending at 0900 the following day. Using this schedule of administration, they demonstrated that PYY(3-36) produced a sustained decrease in food intake accompanied by significant reductions in body weight gain and adiposity. The key component of this experimental paradigm was that infusions were timed such that animals did not engage in a compensatory hyperphagia that would negate the decrease in intake produced by the peptide.

In the present issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Chelikani and colleagues (4a) extend their previous study to investigate the effects of daily intermittent PYY(3-36) infusions on food intake and body weight in dietary-induced obese rats. Rats were maintained for 6–8 mo on high-fat pelleted chow in combination with a palatable liquid diet to promote obesity and were then evaluated for their response to intermittent delivery (two 3-h ip infusions during the dark) of varying doses of PYY(3-36) for a period of 21 days. Obese rats exhibited a sustained reduction in daily caloric intake for the entire treatment period, and daily PYY(3-36) infusions prevented body weight gain that was attributed to reduced fat deposition. Interestingly, the previous study showed that the same paradigm in lean rats produced a compensatory increase in intake during the interval between infusions that was not observed in obese rats. The failure of obese rats to compensate during noninfusion periods may be due to dysregulation in neuropeptide systems that maintain energy balance or could imply that obese rats may be more sensitive to the anorectic effects of PYY(3-36). The latter possibility is supported by studies showing that dietary-induced obese rats have increased binding of radiolabeled PYY to Y2 receptors in the arcuate nucleus (17), the receptor subtype and brain region implicated in the feeding effects of PYY(3-36) (4). Receptor upregulation may result from decreased levels of circulating PYY and decreased PYY release, a profile reported in obese human subjects (3, 12). This is in contrast with the feeding effects of other exogenously administered gastrointestinal peptides, such as cholecystokinin and bombesin, that are less effective in animals fed a high-fat diet, presumably due to increased endogenous release and subsequent insensitivity (7).

Chronic administration of PYY(3-36) has previously been reported to reduce body weight and improve insulin sensitivity in obese animal models without sustained alterations in food intake (11, 16), suggesting that these effects of PYY(3-36) are dissociated from changes in food intake. However, the studies by Chelikani et al. (6) are the first to demonstrate that decreased caloric intake induced by PYY(3-36) can be maintained over an extended period of time and that this effect can be generalized to obese animals. It is possible that a paradigm that results in decreased food intake would elicit additional reductions in adiposity and improve insulin sensitivity beyond those that only produce weight loss.

While the reason for inconsistent results on food intake with acute bolus PYY(3-36) injections is unresolved, the positive results reported by Chelikani et al. (6) highlight the necessity...
for the close scrutiny of potential factors that contribute to variability in experimental results. Whether the infusion schedule used by this experimental paradigm was effective because it more closely mimics a physiological response or whether the design circumvents two potential problems (i.e., compensatory hyperphagia and receptor tachyphylaxis) frequently encountered with repeated peptide administration is not known. It is possible that this experimental paradigm is conducive to the long-term activity of PYY(3-36), because the time course of nutrient-stimulated PYY release and the mechanisms leading to reduced feeding are different from that of several other gastrointestinal peptides (e.g., cholecystokinin and bombesin) involved in controlling food intake. Thus, it remains to be determined whether a similar strategy could be tailored to other peptide systems involved in food intake to produce sustainable effects on appetite and body weight.

**REFERENCES**