RECENTLY, the United States Food and Drug Administration (FDA) decided for the present against approving the cannabinoid receptor antagonist Rimonabant for the treatment of obesity in the United States. This decision resulted mainly from concerns based on studies showing that the drug’s benefits would not outweigh its risks for side effects. This decision further diminished already limited hopes that a potent and safe antiobesity drug would soon emerge and remove one of the most serious health threats to industrialized and developing societies of today and tomorrow.

What would a new drug candidate need to have to become a perfect antiobesity agent? Such a perfect antiobesity molecule should not only lead to sustained loss of body fat but also induce the necessary negative energy balance without causing undesired side effects. Moreover, a perfect antiobesity agent would preferably be a naturally occurring, endogenous molecule, and it should target a known specific mechanism. Finally, it should remove the cause of obesity rather than treat symptoms of the disease. Looking at these requirements, it seems that such a silver bullet may already be available: the gastrointestinal hormone peptide YY (PYY).

On the basis of published data, PYY may be the only currently known molecule that matches these criteria without exception: PYY has been reported to induce a negative energy balance by potently decreasing food intake in rodents (16) and humans (17) without causing any undesired side effects (16, 17). This gut peptide is a naturally occurring hormone that is secreted by endocrine L cells of the colon (28). The reported mechanism of action of its predominantly circulating form, PYY3-36, is based on the specific activation of hypothalamic NPY-Y2 autoreceptors leading to increased firing of satiety-inducing proopiomelanocortin (POMC) neurons (16). Based on the morbidity obese phenotype of PYY-deficient mice (15), PYY has also been considered the most potent satiety factor of the gastrointestinal system. Finally, PYY also uniquely represents the possible cause of obesity as well as its ultimate cure, since obese individuals have been found to be PYY deficient (9, 15) but do not seem to be resistant to PYY replacement therapy (17). In other words, the gut hormone PYY seems to be the perfect antiobesity drug.

So why has the extensive search for efficient and safe antiobesity agents not been called off yet? One reason may have been that a series of follow-up studies painted an unusually contradictory picture. According to various reports, PYY3-36 did not induce a negative energy balance or decrease body weight in rodents (1, 2, 10), but causes visceral illness and conditioned taste aversion (27). In follow-up studies, PYY’s effects were not found to be mediated by satiety-promoting POMC neurons (26), since PYY3-36 actually decreases their activity (25), and three other reports on PYY-deficient mouse models (5, 11, 13) failed to detect a substantial role in energy balance regulation. Finally, recent studies have demonstrated that obese individuals are not PYY deficient (19, 20, 21, 24), and the first clinical trial reported that PYY infusion in humans was not side-effect free but did induce nausea and vomiting (18). In other words, depending on the selection of published studies, the gut hormone PYY may fulfill all—or none—of the criteria for an attractive antiobesity drug candidate.

Inconsistent, or even contradictory, results are not a rarity in the fast-paced search for novel metabolic drug treatments, although the number of controversially discussed issues surrounding PYY seems to be at above average. There are numerous potential causes for the observed inconsistencies between datasets, most of which have to do with a combination of small but important differences in the respective experimental designs. Varying validity and reliability of the specific tools and assays used in these different studies also likely contributed to the variability of the outcome. A better understanding of these details will not only be important for a more reliable analysis of the antiobesity potential of PYY but should also provide important advancement for efficient and meaningful use of preclinical metabolic disease models in general. Independent of that, however, independent and large-size human studies represent the most definite way to examine the value of PYY as a drug candidate.

Recently, three clinical trials testing PYY were reported, two of them in this journal (American Journal of Physiology Endocrinology and Metabolism) (3, 6, 7). Sloth et al. started by administering the two main circulating forms of PYY (PYY1-36 and PYY3-36; PYY3-36 at 0.8 pmol·kg−1·min−1) intravenously over 90 min in 12 lean and 12 obese male subjects in a blinded, randomized crossover study (6). The study design and the concentration of PYY3-36 were chosen to repeat the originally reported design leading to substantial reductions in food intake (16, 17). The main observations in this new study were that food intake was reduced, but, due to severe nausea, only four participants completed the infusion of PYY3-36 (6). Increases in insulin, postprandial glucose, energy expenditure, and heart rate were interpreted as signs of increased sympathoadrenergic drive. After the dose of PYY3-36 was reduced by 75%, effects on food intake disappeared, and side effects, including nausea, were reduced. PYY1-36 was better tolerated but failed to reduce food intake, even after doubling the dose.

In a follow-up study, Sloth et al. refined their study design on the basis of the previously observed results (7) by looking at the effect of escalating injections of subcutaneous doses of PYY on food intake in healthy human volunteers. In this blinded, placebo-controlled crossover study, they were unable to find a decrease in food intake following injection of PYY, but they did observe significant levels of nausea and vomiting.
(7). Briefly, the authors treated groups of 12 healthy male volunteers with four different doses of either the native peptide PYY1-36, or its naturally occurring and presumably more potent cleaved variant PYY3-36. The subcutaneous PYY injections did successfully generate dose-dependent increases in plasma PYY levels similar to previously published studies. No effect on food intake during ad libitum buffet meals was observed following the administrations of PYY1-36 or PYY3-36. Four individuals reported transient nausea following PYY injections between 75 and 200 pmol/kg of fat-free mass (FFM), and one individual dropped out of the study after experiencing sleep disorders and hot flashes after injection of 75 and 150 pmol/kg FFM PYY. Encouragingly, in both studies there were signs of increased lipolysis. Also, although food intake did not decrease independently of discomforting side effects, standard questionnaires seemed to suggest that there may be doses and administration patterns at which PYY3-36 might meaningfully enhance satiety.

Both of the studies summarized above were limited by their focus on the short-term effects of PYY and not on the more relevant chronic effects of PYY on body weight and adiposity. Earlier this year, Gantz et al. reported a randomized, 2-wk, single-blind, placebo run-in study, which was followed by a 3-mo double-blind, placebo-controlled trial to test the tolerability, safety, and efficacy of PYY in 133 obese patients (3). In this study, two doses of PYY3-36 were administered as an intranasal spray before breakfast, lunch, and dinner, which effectively generated PYY plasma levels similar to those reported to successfully reduce in food intake. Only 26% of the higher-dose group and 70% of the lower-dose group of patients, all of whom also underwent a parallel combination of a hypocaloric diet and a defined exercise regimen, completed the trial. No effects on body weight, the primary end point of the study, were observed compared with the control group. However, it was noted that no meaningful conclusions could be drawn on the basis of the results in the higher-dose group due to the extremely high dropout rate related to nausea and vomiting (3).

Again, there are a number of potential explanations for these overall discouraging results. The dose escalation may have moved or narrowed the therapeutic window where patients would be responsive to PYY without experiencing side effects. The likely differing pharmacodynamics and pharmacokinetics associated with intranasal or subcutaneous administrations may be suboptimal, and the right time and dose of administration, as well as the optimal patient population, could be of paramount importance. Although these clinical studies failed to put an end to the controversy surrounding PYY as a drug candidate for obesity, some confidence may be gained from the fact that at least based on this example the currently used preclinical rodent models may not be far off as a predictor of human efficacy and toxicity of metabolic drugs: the balance between PYY’s beneficial and adverse effects appears to be just as fragile in humans as it was found to be in rodents.

Additional confidence, as well as competitive pressure, arises from the fact that another gut hormone-based drug, Byetta (Exenatide, a glucagon-like-peptide-1 receptor agonist), is already available for the treatment of patients with type 2 diabetes and seems to cause substantial weight loss and improvement of different facets of the metabolic syndrome. Byetta not only seems to have a slightly more forgiving therapeutic window but also represents a leading antidiabetic agent, but as a “side effect” also leads to impressive lowering of body weight in humans (4, 22). Exenatide LAR, a once-a-week formulation, is now been tested in a Phase 2 multiple-dose study, and results will likely be available soon. The potential benefits of combinations of peptides and proteins such as PYY3-36, Pramlintide, Exenatide LAR, and leptin are currently being investigated.

There is still a lot we do not know about PYY, and from ongoing and future studies, a useful drug for human obesity might still emerge. For example, long-term effects on body fat mass may be more impressive than the impact on body weight. Intriguingly, PYY appears to be one of the more important endocrine factors involved in the poorly understood, but unequalled, benefits of bariatric surgery (14). Moreover, recent findings from rodent studies suggest that there may be promising PYY-like Y2 receptor-specific antagonist drugs (23), that those Y2 receptors may actually represent an interesting peripheral target (12), and that combinations of PYY with other antiobesity agents may generate additive or even synergistic benefits for energy metabolism (8). The current struggle of cannabinoid receptor-1 antagonists suggests that even a less controversial preclinical and early clinical body of data is no guarantee for a successful and safe drug treatment. It also means that we are still in urgent need of other candidate drugs for the treatment of obesity. Clarifying whether PYY does potently and safely reduced fat mass in obese humans will now require more, larger, and further-refined clinical trials. Those will be time consuming and very costly; but if PYY finally turns out to be the perfect cure it once promised to be, it will be worth it.

REFERENCES


