EDITORIAL FOCUS:

Peptide YY: Obesity’s Cause and Cure?

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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 mainly resulted from concerns based on study results 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 anti-obesity 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 have to become a perfect anti-obesity agent? Such a perfect anti-obesity molecule should not only lead to sustained loss of body fat, but also induce the necessary negative energy balance without causing undesired side effects. What’s more, a perfect anti-obesity agent would preferably be a naturally occurring, endogenous, molecule and it should target a known specific mechanism. Finally, it should remove the cause for obesity rather than treating 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).

Based on published data, peptide YY may be the only currently known molecule which matches these criteria without exception: PYY has been reported to induce a negative energy balance by potently decreasing food intake in rodents (1) and humans (2) without causing any undesired side effects (1,2). This gut peptide is a naturally occurring hormone which is secreted by endocrine L-cells of the colon (3). The reported mechanism of action of its predominantly circulating form, PYY3-36, is based on the
specific activation of hypothalamic NPY-Y2 auto-receptors leading to increased firing of satiety-inducing POMC neurons (1). Based on the morbidly obese phenotype of PYY-deficient mice (4), PYY has also been considered as the most potent satiety factor of the gastrointestinal system. Finally, PYY uniquely also represents the possible cause for obesity as well as its ultimate cure, since obese individuals have been found to be PYY deficient (4,5), but do not seem to be resistant to PYY replacement therapy (2). In other words, the gut hormone PYY seems to be the perfect anti-obesity drug.

So why has the extensive search for efficient and safe anti-obesity 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 (6,7,8), but causes visceral illness and conditioned taste aversion (9). In follow up studies, PYY’s effects were not found to be mediated by satiety promoting POMC neurons (10), since PYY3-36 actually decreases their activity (11) and three other reports on PYY-deficient mouse models (12,13,14) failed to detect a substantial role in energy balance regulation. Finally, recent studies have demonstrated that obese individuals are not PYY deficient (15,16,17,18) and the first clinical trial reported that PYY infusion in humans was not side effect free but did induce nausea and vomiting (19). 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 anti-obesity 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 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, likely also 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 anti-obesity potential of PYY, but should also provide important advancement for efficient and meaningful use
of pre-clinical metabolic disease models in general. Independent from 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) (20,21,22). Sloth and colleagues 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 minutes in 12 lean and 12 obese male subjects in a blinded, randomized, crossover study (20). The study design and the concentration of PYY3-36 were chosen to repeat the originally reported design leading to substantial reductions in food intake (1,2). The main observations in this new study were that food intake was reduced, but due to severe nausea only 4 participants completed the infusion of PYY3-36 (20). Increases in insulin, postprandial glucose, energy expenditure and heart rate were interpreted as signs of increased sympatho-adrenergic drive. After reducing the dose of PYY3-36 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 and colleagues refined their study design based on the previously observed results (21) 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 (21). 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 flushes after injection of 75 and 150 pmol/kg FFM PYY. Encouragingly, in both studies, there were signs of increased lipolysis. Also, while food intake did not decrease independent from discomforting side effects, standard questionnaires seemed to suggest that there may be doses and administration patterns at which PYY3-36 may 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 and colleagues reported a randomized, 2-wk, single-blind placebo run-in study which was followed by a 3 months double-blind, placebo-controlled trial to test the tolerability, safety and efficacy of PYY in 133 obese patients (22). 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 which also underwent a parallel combination of a hypocaloric diet and a defined exercise regimen, completed the trial. No effects on body weight, the primary endpoint of the study, were observed compared to the control group. However, it was noted that no meaningful conclusions could be drawn based on the results in the higher dosed group due to the extremely high drop out rate related to nausea and vomiting (22).

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 sub-optimal and the right time and dose of administration, as well as the optimal patient population, could be of paramount importance. While 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 for 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® does not only seem to have a slightly more forgiving therapeutic window, but also represents a leading anti-diabetic agent, but as a “side effect” also leads to impressive lowering of body weight in humans (23,24). 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 unequaled, benefits of bariatric surgery (25). Moreover, recent findings from rodent studies suggest that there may be promising PYY-like Y2 receptor–specific antagonist drugs (26), that those Y2 receptors may actually represent an interesting peripheral target (27), and that combinations of PYY with other anti-obesity agents may generate additive or even synergistic benefits for energy metabolism (28). The current struggle of cannabinoid receptor 1 antagonists suggests that even a less controversial pre-clinical 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 if 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.
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