As obesity rates skyrocket worldwide, along with associated comorbidities, including type 2 diabetes and cardiovascular disease, there is an increasingly urgent need for new drugs that impact satiety and food intake. The regulation of body weight in mammals involves complex and redundant endocrine and neuronal pathways (1), and this has made the quest for nonsurgical, antiobesity therapeutics a challenge. Peptides have distinct advantages as therapeutic agents given their potential for great efficacy and safety (2), and a number of gut and adipose tissue peptide hormones thought to be involved in appetite regulation—notably glucagon-like peptide 1 (GLP-1), leptin, islet amyloid polypeptide (amylin), cholecystokinin, peptide YY, and pancreatic polypeptide (PP)—have been explored with varying success as antiobesity therapeutic agents (3). A significant limitation of native peptide hormones as therapeutics is their rapid degradation and short circulating half-life. Standing out among this group of peptides in recent years have been GLP-1 and its analogs, which have been shown in multiple clinical trials to have significant effects on food intake and body weight, in addition to its glucose-lowering effects (4).

Although the satiety-inducing effects of PP were first recognized 40 years ago (5), its therapeutic potential has been less well explored, in part due to its short half-life in plasma of about 6 to 7 minutes. GLP-1 has an even shorter half-life, but its therapeutic effectiveness has been enhanced by recognition that the major pathway for its degradation and inactivation is via dipeptidyl peptidase 4 (DPP4), as well as the subsequent development of analogs resistant to the action of this enzyme. In this issue of Endocrinology, Cuenca et al. (6) provide new insight into the mechanisms of PP degradation, identifying key peptidases involved and testing nondegradable analogs of PP that have enhanced anorectic properties in mice.

PP, a 36–amino acid member of the NPY family of peptides, is produced by PP cells of the pancreatic islets. PP secretion is stimulated by food intake and is regulated by autonomic neural inputs to the islet as well as other gut hormones. The mechanism of action of PP to reduce food intake involves its interaction with Y4 receptors in the hypothalamus (7). To determine potential cleavage points in PP, Cuenca et al. (6) incubated synthetic PP with enzyme-rich fractions of rat liver microsomes and renal brush border membranes, and they identified the truncated peptides by mass spectrometry. The peptides generated were consistent with cleavage of PP by DPP4 or neprilysin, a possibility confirmed by incubation of PP with recombinant forms of these enzymes. Importantly, coinjection of PP with inhibitors of either DPP4 (sitagliptin) or neprilysin (phosphoramidon) resulted in prolonged suppression of food intake compared with PP alone, suggesting that both DPP4 and neprilysin partake in the proteolytic breakdown of PP into less biologically active forms. The authors then exploited this finding to generate PP analogs resistant to DPP4- and neprilysin-mediated proteolysis. A PP peptide with amino acid modifications conferring resistance to DPP4 and neprilysin action had a longer plasma half-life and induced more prolonged suppression of food intake in mice. Taken together, these findings raise the intriguing possibility that degradation-resistant PP analogs may have therapeutic potential in the treatment of obesity.

Interestingly, the impact of DPP4-mediated degradation of PP on food intake was significant but not profound, as the truncated product PP3–36 clearly acts on Y4 receptors.
receptors and attenuates food intake, albeit somewhat less so than intact PP. The data suggest that neprilysin-mediated proteolysis of PP is more impactful in terms of loss of biological activity. Given that DPP4 degradation products such as GLP-1(9–36)-NH₂ have been found to have unique bioactivities (8), it may be of value to learn more of the biology of this (and perhaps other) PP breakdown products. Also of note, neither sitagliptin (which is weight neutral in humans) nor phosphoramidon treatment alone had a significant effect on food intake in mice, speaking against a critical role of endogenous PP in regulation of satiety, or perhaps simply a reflection of the tremendous redundancy of neurohormonal pathways regulating food intake. Thus the value of this study seems to lie more in its advancement of PP analogs as potential therapeutics rather than its insight into PP biology.

Because exenatide administration in humans can be associated with nausea (which has not been reported with PP), long-acting PP analogs may offer some advantages over GLP-1–based therapies. Further study is clearly needed. Most important is the demonstration that long-term administration of PP analogs indeed induces weight loss, and that this occurs in the absence of adverse effects. In support of this, a phase I study of a DPP4- and neprilysin-resistant PP analog (PP 1420) reported few adverse events and no tolerability issues (9). Also, it is quite possible that other enzymes participate in proteolytic loss of bioactive PP in circulation, and that longer acting and more efficacious PP analogs can be developed. Hopefully this study may spur increased research into the biology of PP, which has remained an interesting but understudied enigma for many years, and its potential as a therapeutic for the treatment of obesity.

Acknowledgments

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Disclosure Summary: The authors have nothing to disclose.

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