Future Therapies in Obesity

Octavia Pickett-Blakely, MD, MHS[a,*], Carolyn Newberry, MD[b]

KEYWORDS

• Obesity • Pharmacotherapy • Endobariatrics • Genetics • Microbiome
• Complementary/alternative therapies

KEY POINTS

- Obesity involves multiple pathophysiologic processes that can be targets for treatment.
- Endobariatric procedures are effective weight loss therapies.
- Microbiome manipulation is a popular area of study that holds promise for the treatment of obesity.

INTRODUCTION

As outlined earlier in this issue, obesity has grown to epidemic proportions in the past 3 decades. However, there has been a major lag in the development of effective therapies for obesity. Although the obesity epidemic is largely explained by environmental factors, such as calorie-dense diets and sedentary lifestyles, the discovery of other contributing factors, such as altered intestinal microbiota and genetic derangement, has unlocked additional therapeutic pathways. Therefore, development of novel therapeutic interventions for obesity is in high demand and remains an active area of investigation. Although the mainstay of therapy is behavioral modifications via diet and exercise, innovative pharmaceutical, mechanical, hormonal, and device options are introduced in this article.

PHARMACOTHERAPY

There are numerous pharmacologic targets for the treatment of obesity. Pharmacotherapy for obesity is covered extensively (see Jeanette N. Keith's article, "Pharmacotherapy in Treatment of Obesity," in this issue), but this article discusses possible new therapies that may be used as a supplement to diet therapy and exercise.

[a] GI Nutrition, Obesity and Celiac Disease Program, Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, 3400 Convention Avenue, 4 South, Philadelphia, PA 19104, USA; [b] Division of Gastroenterology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104, USA
* Corresponding author.
E-mail address: octavia.pickett-blakely@uphs.upenn.edu

Gastroenterol Clin N Am ■ (2016) ■–■
http://dx.doi.org/10.1016/j.gtc.2016.07.008 gastro.theclinics.com

Therapeutic targets address 3 basic mechanisms: (1) decreasing caloric intake/absorption, (2) increasing energy expenditure, and (3) modulation of adipocytes. To date, most of the drugs approved for the treatment of obesity decrease oral intake by suppressing appetite via central nervous system neurotransmitters. However, other physiologic pathways hold promise as potential therapeutic targets.

Decrease Caloric Intake/Increase Energy Expenditure

Beloranib is a drug that inhibits methionine aminopeptidase 2, an enzyme involved in fat biosynthesis, oxidation, and breakdown. Caloric intake is also reportedly decreased in patients treated with beloranib and is associated with an increased level of serum adiponectin. Based on early data, beloranib seems to be an effective weight loss agent. In a 12-week, phase II trial, beloranib resulted in significantly greater weight loss compared with placebo (-10.9 ± 1.1 kg vs -0.4 ± 0.4 kg, respectively; $P < .0001$ vs placebo).[1] Compared with the currently available pharmacotherapies, beloranib may have a promising future in light of the robust weight loss observed in early studies.

Gut hormones have been heavily investigated as potential therapeutic interventions for obesity. As an endocrine organ, the gastrointestinal tract secretes numerous neurohormones that affect energy intake and satiety.[2,3] For example, amylin (synthetic analogue of Symlin) is a beta cell–derived peptide that slows gastric emptying and decreases food intake. Likewise, glucagonlike peptide 1(GLP-1) has similar physiologic effects and the synthetic GLP-1 agonist liraglutide (Saxenda) is US Food and Drug Administration (FDA) approved for weight loss.[2] Other neurohormones that also decrease food intake include pancreatic polypeptide, which is secreted from the pancreas; ghrelin, which is secreted from the stomach; oxyntomodulin and peptide YY, which are secreted from intestinal L cells; and cholecystokinin, which is secreted from the small bowel.[2,3] Given the many gut neurohormones involved in food intake, a combined pharmacologic approach targeting multiple physiologic pathways may offer optimal efficacy to treat obesity.

Adipocyte Modulation/Increase Energy Expenditure

Adipose tissue is metabolically active tissue and has been targeted as a potential therapeutic pathway for obesity. In particular, brown adipose tissue (BAT), which is less functional in obese versus lean individuals, is involved in fat burning and thermogenesis.[4] In contrast, white adipose tissue (WAT) is responsible for obesity. A recent animal study used nanoparticles that selectively delivered rosiglitazone (peroxisome proliferator-activated receptor gamma) and prostaglandin E2 to adipose tissue leading to (1) transformation of WAT to the thermogenic BAT, and (2) increased angiogenesis-induced expansion of BAT.[5] Increasing the conversion of WAT to thermogenic BAT is an attractive method to increase energy expenditure and ultimately weight loss. An recently proposed additional target for brown fat activation is mirabegron (Myrbetriq), which is a β3-adrenoceptor agonist currently used to treat overactive bladder. β3-Adrenoceptor agonism has been shown to increase resting the basal metabolic rate in humans,[6] but whether this increase leads to substantial weight loss remains to be seen.

ENDOBARIATRICS

Endoscopic bariatric therapies (EBTs) represent an evolving and exciting therapy for obesity. Discussed in detail elsewhere in this issue, EBTs offer an effective weight loss option for individuals who fail traditional therapies and/or are not eligible for (or do not wish to) undergo weight loss surgery. These procedures also may serve as