STRATEGIES FOR TREATMENT OF OBESITY
by
XIAOXUE SHEN
(Under the Direction of Dexi Liu)

ABSTRACT
The prevalence of adult obesity has dramatically increased in recent decades. In 2015, more than 107 million children and 603 million adults were obese in the world. Since 1980, the obesity prevalence has doubled in more than 70 countries and the trend is seen in most other countries. Obesity has become a global epidemic. Many non-communicable diseases are correlated with obesity, including type 2 diabetes, certain kinds of cancer, heart diseases and musculoskeletal disorders. Significant effort has been made in the past few decades to develop strategies and various methods in dealing with obesity epidemics. This thesis aims to provide summary on methods and strategies that have been developed or those remain at development stage. The focus was centered around description about pathology of obesity, principles and procedure of bariatric surgeries. Chemical approaches employing drugs are also described. Future perspectives is provided to present the pros and cons of the currently available methods and future direction in development.

INDEX WORDS: Obesity, Obesity treatment
STRATEGIES FOR TREATMENT OF OBESITY

by

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STRATEGIES FOR TREATMENT OF OBESITY

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DEDICATION

I would like to dedicate this thesis to the people who have loved, supported, motivated, and believed in me: my parents, Youqiang Shen and Fengbi Ye. They give me endless love and support me economically and spiritually throughout my life.
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1. INTRODUCTION

Obesity is a condition with excessive fat accumulation in the body. It is commonly defined by body mass index (BMI), a ratio of body weight in kilograms and the square of height in meters. World Health Organization (WHO) defines obesity (Table 1) as an individual with a BMI value greater than 30 kg/m$^2$. Patients with BMI value higher than 40 are classified as very severe or class III obesity.

BMI is the most commonly used parameter for obesity due to its simplicity, convenience and practicability. Other methods are also used including body fat mass, waist circumference, waist-to-hip ratio, skinfold thickness. The most reliable measure for body fat is can be accomplished using computed tomography scans (CT), magnetic resonance imaging (MRI) or X-ray. Different standards may be used to define obesity based on gender, age and ethnicity. Without an exception, all parameters used to define obesity are indicators of potential weight problem and do not serve as evidence for disease.

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The prevalence of adult obesity has dramatically increased in the past few decades. Obesity prevalence in 1990 was below 15% in the US, and none of the 50 states had an average prevalence greater than 15% (Flegl et al., 2010). Worldwide obesity population was twice increased since 1980. In 2015, there were 603.7 million obese adults and 107.7 million obese children globally. Egypt leads the world with the highest obesity prevalence at 35.3% followed by the US, which had the most obese adults with 79.5 million (34.8%), followed by China. The US had the highest level of age standardized childhood obesity at 12.7% (Afshin et al., 2017). The forecast predicts that the obese population could be up to 1.12 billion with an unabated trend by 2030 (Kelly, Yang, Chen, Reynolds, & He, 2008).

Many non-communicable diseases are correlated to obesity, including type 2 diabetes, certain kinds of cancer, heart disease and musculoskeletal disorders (Eckel et al., 2002). Obese individuals had significantly lower scores of health related life quality compared to the normal weight individuals (Jia & Lubetkin, 2005). Different classes of obesity have different risk in development of other diseases. American Heart Association has identified obesity as a major risk factor for coronary heart disease (Eckel & Krauss, 1998). Obesity increased the economic burden for both private and public (Finkelstein et al., 2009), and individuals with obesity had around 30% greater than the normal weight on the medical costs between 1990 and 2009 worldwide (Withrow & Alter, 2011). Class II or III obese population has 9% higher diabetes prevalence than normal population (Gregg et al., 2007). Class III obesity has higher risk of mortality and life expectancy (Bray, 1992; Kitahara et al., 2014)
2. CAUSE OF OBESITY

There are many factors that may cause obesity, including environment, lifestyles, genetics, illness, drug use, and psychological factors. Obesity usually results from the combination of these contributing factors.

The association between the epidemic of obesity and environment can be partially explained by the changing trend in living environment. The opportunity to access physical activity is decreasing while the consumption of a diet high in calories is increasing. Unhealthy lifestyle, in which individuals are sedentary, consume high-fat or high-sugar diets and high quantities of alcohol, and have high amounts of stress, increases the risk of obesity. There is also a negative association between sleep hours and BMI. One meta-analysis that included 604,509 adults revealed that a −0.35 (−0.57 to −0.12) unit of change occurs in BMI per hour of sleep (Cappuccio et al., 2008). Genetic factors also play a role. Each individual has a unique genotype, which results in the diversity in capacity for cell function and development. The presence of several obese members within their family suggests that genetic factors might be involved in obesity (Kasper et al., 2015). Children with obese parents or several obese relatives within their family have a two- to three-fold risk of becoming moderately obese and up to an eight-fold risk for severe obesity (Bouchard, 2001). Furthermore, the mutations of the genes in the receptors that regulate food intake can cause obesity or increase the risk of obesity. The landmark discovery that a leptin receptor deficiency in the hypothalamic area is a major factor causing obesity in human and
rodents also points to genetic influence on this disease (Bouchard, 2001; Clement et al., 1998). Another study showed that there is a high frequency (4%) of mutations in the MC4-R receptor among a large population of morbidly obese patients, while this mutation is not present in non-obese individuals (Vaisse et al., 2000).

Even though many factors are involved in development of obesity, energy surplus is a direct cause. When the energy intake is greater than the energy expenditure for an extended time period, it will result in weight gain and eventually obesity if the situation continues.

Adipose tissue is a special organ for energy storage. Adipogenesis involves synthesis and accumulation of triglycerides in adipocytes, leading to an expansion of adipocytes’ size and increase of their total number (Faust et al., 1978). In an adult rodent, increase of cell size appears prior to cell amplification until adipocytes reached their maximum fat-storage capacity (Faust et al., 1978). However, in another diet-induced obesity experiment, adipocyte size was enlarged without significant change in total number of adipocytes in adult men with 15%-25% weight gain in three months (Salans et al., 1971; Sims et al., 1967). Additionally, when the normal adult individuals lost their weight by altering energy balance, the body dramatically changed only the size of the adipocytes (Knittle & Fellner, 1972). For an adult, the total number of adipocytes usually remains stable even in significant weight loss situations (Spalding et al., 2008). In other word, adult obesity is caused by energy surplus with the major process of adipocyte enlargement, indicating a possible difference between humans and rodents.
3. OBESITY PATHOLOGY

Not all obese individuals develop obesity-related metabolic syndromes. Obese individuals whose adipocytes and adipose tissue remain in normal architecture and function can still be healthy. The major function of adipocytes is storing free fatty acids (FFAs) as energy after food intake, it also can release FFAs during fasting (Singh et al., 2009). Adipocytes secrete a wide range of adipocytokines, which are co-regulators of appetite, inflammation, lipid and glucose metabolism, and activation of the complement cascade (Tilg & Moschen, 2006).

Figure 1. Obesity Pathology

Source: Modified based on the Figure 2 of Samaan (2011), Figure 4 of Cao (2010)

Organ diagrams, retrieved on June 30, 2017 from http://www.anatomylibrary.us
There is a significant association between obesity and chronic, low-grade inflammation (Lumeng & Saltiel, 2011). The positive correlation between BMI and the number of peripheral leukocytes in adipose tissue of obese individuals was first reported in 1985 (Nanji & Freeman, 1985). Both M1 and M2 type macrophages exist in adipose tissue (Gordon & Taylor, 2005). In the adipose tissue of obese individuals, M1 macrophages are more prevalent than M2 type (Otto & Lane, 2005). Macrophages and adipocytes interact with each other via paracrine function, and this interplay can induce adipocyte dysfunction. Figure 1 explains obesity pathology. Adipocytokines such as resistin, adiponectin, interleukin-6, and C1 reactive protein affect inflammation and macrophage accumulation (Engeli et al., 2005). The enlarged adipocytes release FFA, which can induce nuclear factor kappa B (NF-κB) activation and tumor necrosis factor-α (TNF-α) production by binding toll-like receptor-4 on the macrophages. FFA can attract monocytes and induce differentiation of macrophages into a pro-inflammatory state (Permana et al., 2006; Suganami et al., 2005). Inflammation is responsible for development of other metabolic diseases including type-2 diabetes. Moreover, the TNF-α released from macrophages can also activate adipocytes and induce lipolysis (Permana et al., 2006). Regarding glucose metabolism, adipokines, FFA and TNF-α could decrease the insulin signaling cascade by reducing the insulin receptor capacity (Boden & Shulman, 2002; Permana et al., 2006). There is a theory that obesity associated metabolic syndromes are direct results of the induced cellular stress from overload energy. The abnormal cellular stress induces the release of pathophysiological adipokines by adipocytes (Iyer et al., 2010), leading to inflammation, insulin resistance and leptin resistance. Furthermore, adipose tissue dysfunction might induce obesity because obese
individuals with leptin resistance experience difficulty losing weight and being hungry persistently.
4. CURRENT STRATEGIES FOR TREATMENT OF OBESITY

Obesity is commonly considered a condition resulting from an energy imbalance in which energy intake is greater than energy expenditure. Therefore, the strategies for obesity treatment have been centered on ways to reduce energy intake or/and increase energy expenditure. The following is a summary of the most commonly used methods for obesity treatment.

Contemporary Bariatric Surgeries

A direct and most commonly used strategy to manage obesity is to control energy intake. Among many approaches taken, bariatric surgery is a procedure to decrease the volume and surface areas of gastric-intestinal tract to reduce food adsorption. The total number of bariatric surgery procedures performed dramatically increased from 1997 to 2013: the number of bariatric surgeries in 2013 was over ten times that of the procedures performed in 1997 (Angrisani et al., 2015). The newest report shows that number of bariatric surgery each year continues to increase (Angrisani et al., 2015; Angrisani et al., 2017). Adjusted gastric banding, gastric sleeve, and gastric bypass are the three most common weight-loss surgeries currently performed. Weight loss stomach pump is the most recently bariatric procedure approved by FDA.

Adjusted gastric banding

Adjusted gastric banding is a procedure applying an adjustable band to the upper part of the stomach to create a small pouch. This procedure is routinely performed with the laparoscopic
method. The band is an inflatable silicone device, which can adjust the internal diameter of the small pouch by injecting cold saline or water to the lumens to straighten out the ring via a port under the skin (Axelsson, 2006; Robert, 2003). Gastric banding is the least invasive and completely reversible. The small pouch created by the adjusted gastric band procedure can limit the amount of food that can be consumed at one time and slow gastric emptying, thus giving the opportunity for the body to signal satiety.

Figure 2. Artistic illustration of adjusted gastric banding

Source: Figure 2 of Pories (2008)

*Gastric bypass*

Gastric bypass is a procedure that includes two main parts: partitioning or dividing the upper stomach into a small pouch and attaching it to the middle part of the intestine using the laparoscopic method. Currently, gastric bypass is performed with the dividing procedure rather than the partitioning because the partitioning procedure applies a double row of staples to create a small pouch, but this staple row is easily disrupted. Gastric bypass includes several types, such as Roux-en-Y gastric bypass (RYGB), gastric bypass loop and banded gastric bypass (combined gastric band and gastric bypass) (Johnson et al., 2007). RYGB is the major one and one of the most frequently conducted bariatric surgery procedures. There are three types of limbs involved in the RYGB: biliopancreatic limb, roux limb, and a common channel. The biliopancreatic limb is
the beginning part of the intestine that transmits bile and pancreatic secretions. The roux limb is the middle part of the intestine, which transmits the digested nutrients from the small pouch. In RYGB, the biliopancreatic limb distal part is re-attached to the roux limb, forming a “Y” shaped intersection and a common channel (Buchwald et al., 2004; Wittgrove & Clark, 2000).

![Figure 3. Artistic illustration of adjusted gastric bypass](image)

Source: Figure 2 of Pories (2008)

**Gastric sleeve**

Gastric sleeve (sleeve gastrectomy) removes about 80 percent of the stomach, permanently creating a long, banana-shaped pouch. The reduced size of the stomach limits the size of meals, but the stomach could be dilated later in life. The procedure is performed laparoscopically and is irreversible. The gastric sleeve can be a modification to the biliopancreatic diversion and combined with a duodenal switch, a combination that was first reported in 1998 (Gumbs et al., 2007).
Weight loss stomach pump

Weight loss stomach pump, also called the AspireAssist Aspiration Therapy system, is the newest device approved by FDA, in June 2016 (Voelker, 2016). This reversible therapy system drains the food from the stomach via a tube which is inserted into the stomach and inputs water instead via a disk-shaped port valve lying outside the body. The food draining procedure takes from 5 to 10 minutes. In a clinical study, the obesity patients with mean BMI 39.8 kg/m^2 turned into 32.1 kg/m^2 after one year, and further turned into 31.0 kg/m^2 after two years, both with life quality improvement and no serious adverse events or electrolyte disorders (Norén & Forssell, 2016). Compared to the previous bariatric surgery procedures, it is less invasive as the surgery does not directly harm the digestion system. The patients seem to have full control over how much food in the stomach he/she wants to remove at a time.
Overall, the principle of bariatric surgeries is to promote satiety by modulating the digestive system, such as reducing stomach size and resetting the digestive tract. Creating a small pouch on the upper side of the stomach can reduce the size of the stomach and arouse satiety signaling with less food. The digestive tract resection induces decrease in food absorption by accomplishing distal mixing of digestive enzymes.

Bariatric surgeries only target morbidly obese patients with a BMI value higher than 40 kg/m² without coexisting medical problems or patients with a BMI greater than 35 kg/m² and one or more severe obesity-related comorbidities (Mechanick et al., 2013). Meta-analysis of a dataset on bariatric surgery studies conducted from January 1, 1990 to April 30, 2006 reveals an overall weight loss at 38.5kg, or 55.9% excess body weight loss, and there are no significant differences among different bariatric surgeries (Buchwald et al., 2009). Bariatric surgery appears highly clinical efficient and cost effective in weight loss intervention compared with other non-surgical options (Picot et al., 2009; Devlin et al., 2008). Bariatric surgeries lead not only to weight reduction but also amelioration of obesity-associated diseases such as diabetes, hypertension, and hyperlipidemia (Buchwald et al., 2004; Ikramuddin et al., 2013; Sjöström et al., 2004). Studies
have also shown that these procedures could influence levels of hormones such as adiponectin, leptin, and ghrelin, which correlate with body fat and body weight (Faraj et al., 2003; Yannakoulia et al., 2003). For example, after a gastric bypass procedure, the levels of ghrelin, an orexigenic hormone, decline (Cummings et al., 2002), while the glucagon like peptide 1 (GLP-1) level increases, which improve glycemic control (Le Roux et al., 2006). Gut hormone modulation shows further regulation on body weight by promoting satiety and ameliorating other obesity-related illnesses through improving insulin sensitivity (Faraj et al., 2003). The weight reduction obtained did not show significant differences with respect to different time lengths of the study (Buchwald et al., 2004).

Many factors could affect the outcomes of bariatric surgery. Studies (Eric J. DeMaria et al., 2001) have shown that about 41% patients removed the devices 10 days to 42 months after the gastric adjusted banding surgery due to band leakage, infection or erosion. The failure rate of the gastric bypass is not ignorable as well. In a 5-year prospective study, 50% patients regained the weight they lost and 18.8% of patients failed in the super obese group at 48 months after surgery (Magro et al., 2008). Psychological disorder or binge eating disorders has been linked to a high failure rate. Behavior and psychology treatment can improve the successful rate of surgical procedure (Collins et al., 2009).

Contemporary Pharmacotherapy

Pharmacotherapy is a drug-based treatment and is less invasive and more commonly used compared to bariatric surgery. There are several FDA-approved drugs on the market that have different mechanisms of action focusing on appetite suppression, intestinal fat uptake inhibition...
and blocking hypoglycemic action. Some of the approved drugs have been withdrawn from the market in recent years because of the new findings of toxicity linking to increased incidents of cardiovascular events and strokes, based on the FDA 2017 report. Besides the group of drugs approved by the FDA for obesity treatment, there are drugs employed for off-label treatment of obesity. For example, liraglutide is a drug initially developed for treatment of diabetes but used as off-label for obesity treatment based on the observation of weight loss from the treated diabetic patients. In 2014, the FDA approved liraglutide for its use in obesity. The following is a brief summary of a list of drugs that are used in obesity treatment.

**Lorcaserin**

Lorcaserin is a potent 5-hydroxytryptamine (5-HT) receptor agonist that shows higher affinity to 5-HT\textsubscript{2C} subtype compared with 5-HT\textsubscript{2A} and 5-HT\textsubscript{2B} (Smith et al., 2008). In an in-vitro human receptor binding study, it was shown that the affinity of lorcaserin to 5-HT\textsubscript{2C} is 7.5-fold selectively higher than for 5-HT\textsubscript{2A} and also 11.6-fold selectively greater than 5-HT\textsubscript{2B} using the Ki value as an index. Additionally, the potency for lorcaserin to activate the human 5-HT\textsubscript{2C} receptor
Figure 6. Targeting organs of FDA-approved anti-obesity drugs

(Modified base on the Figure 1 of Barja-Fernandez et al., 2014)

Diagram of adipose tissue is taken from Figure 4 of Cao (2010). GI-tract and brain diagrams were retrieved on June 30, 2017 from http://www.anatomylibrary.us/

was greater than 5-HT$_2a$ and 5-HT$_2b$, at 18-fold greater potency and 104-fold greater potency, respectively (EC$_{50}$ as an index) (Thomsen et al., 2008).

The 5-HT$_2c$ receptor is a potent target for appetite control. The 5-HT$_2c$ receptor knockout mice model shows disordered eating (hyperphagic) that leads to obesity (Tecott et al., 1995). Lorcaner activaing the 5-HT$_2c$ receptors results in anorexigenic signaling (Sargent, et al., 1997; Walsh et al., 1994). The mechanism of a 5-HT$_2c$ agonist for appetite and satiety control is that activation of 5-HT$_2c$ receptors located on proopiomelanocortin (POMC) neurons induces the
syntheses of anorectic endogenous melanocortin agonist α-MSH in the arcuate hypothalamic nucleus (ARC) (Lam et al., 2008). α-MSH is an endogenous peptide hormone and neuropeptide of the melanocortin family, which acts at the melanocortin 4 receptor (MC4Rs) to reduce food intake (Fan et al., 1997). The MC4R null mice treated with the selective 5-HT2c agonist did not show a reduction in food intake (Lam et al., 2008). Lorcaserin regulates energy balance by reducing energy intake, perhaps without controlling energy expenditure (Martin et al., 2011). In the study by Corby et al, sleeping energy expenditure, respiratory quotient and fat, carbohydrate, and protein oxidation were measured for 24 h. They concluded that 24-h energy expenditure was lower in the lorcaserin treated group in the period during which the body composition was adjusting. After body composition adjusted, there was no difference between the two groups (Martin et al., 2011). Also in the selective 5-HT2c agonist study with a mouse model, the total activity and oxygen consumption did not differ from the placebo group (Lam et al., 2008).

Lorcaserin shows a weight loss improvement, reducing weight and body fat gain via appetite suppression in both preclinical and clinical studies (Higgins et al., 2014; S. R. Smith et al., 2009; S. R. Smith et al., 2010; Thomsen et al., 2008). In the clinical studies, the lorcaserin treated group was significantly different from the placebo group. A greater proportion of the patients in the lorcaserin-treated group lost about 5% or more of their baseline body weight in 1 year (47.5% vs. 20.3% for the placebo), and the loss was maintained for 2 years compared to the placebo group (67.9% vs. 50.3%, respectively) (S. R. Smith et al., 2010). Lorcaserin appears more appropriate for treatment of obesity patients with type-2 diabetes (O’Neil et al., 2012).
Locaserin avoids some side effects, such as serotonin-associated valvopathy and the risk of hallucination activated by 5-HT$_{2b}$ and 5-HT$_{2a}$ receptors (Connolly et al., 1997; Sachdev et al., 2002; S. R. Smith et al., 2009). However, side effects associated with locaserin such as headache, nausea, and hypoglycemia have been reported.

![Mechanism of action for Lorcaserin](http://www.anatomylibrary.us/)

**Figure 7.** Mechanism of action for Lorcaserin. Lorcaserin activation involved in the NPY/AGRP and POMC/CART system. Leptin and insulin are anorexigenic molecules that can inhibit NPY/AGRP release and activate the POMC/CART and induce the alpha mesh release, resulting in less food intake. Ghrelin shows the opposite effect. Lorcaserin, as a potent 5-HT$_{2c}$ agonist, has similar function to leptin and insulin, inducing an anorexigenic signal and then further controlling the feeding behavior. Source: Brain diagram, retrieved June 30, 2017 from [http://www.anatomylibrary.us/](http://www.anatomylibrary.us/). HT, hydroxytryptamine; NPY, neuropeptide Y; AGRP, agouti-related peptide; POMC, proopiomelanocortin; CART, cocaine- and amphetamine-regulated transcript; MSH, melanocyte stimulating hormone.
**Orlistat**

Orlistat is a lipase inhibitor that works in the gastrointestinal system and used for treatment of obesity. Orlistat is a potent and selective inhibitor for gastric and pancreatic lipases (Guerciolini, 1997). The enzyme is produced by pancreas and stomach that hydrolyzes dietary triglycerides in intestine to produce monoglycerides and free fatty acids, which are then absorbed as a major energy source. Inhibition of triglyceride hydrolysis blocks free fatty acid production and absorption, and thereby reduce calorie intake. Orlistat has little or no function on amylase, trypsin, chymotrypsin and phospholipases (Guerciolini, 1997).

The therapeutic effects of orlistat have been evaluated in clinical trial. In a randomized placebo-controlled trial, it showed that the orlistat treated patients lost more weight than those of placebo (10.2% vs. 6.1%, respectively) after a yearlong treatment and continued to show lower weight gain in the 2nd year (Sjöström et al., 1998). Another clinical trial confirmed this result, demonstrating that orlistat treatment, not only offering a better weight control but also bringing about improvement of the level of metabolic markers such as low-density lipoprotein, cholesterol and insulin (Davidson et al., 1999). However, orlistat causes several side effects including stomach pain, nausea, vomiting, and diarrhea and sometimes renal failure and precancerous lesion in the colon (Guerciolini, 1997). Even though orlistat is widely used and sold over-the-counter, the concerns on its safety limit its acceptance by general public.
Figure 8. Mechanism of action for Orlistat


**Liraglutide**

Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a gut hormone produced in the intestine and responds to meal ingestion. Liraglutide mimics the function of GLP-1, increases insulin release, decreases glucagon secretion and gastric emptying rate, promotes satiety, and suppresses appetite (Flint et al., 1998; Flint et al., 2001). Liraglutide was first approved by the FDA to treat type-2 diabetes in 2010. Significant weight loss observed in diabetic patients with liraglutide treatment led FDA approval in 2015 for its use as an off-label drug for treatment of obesity. In several previous clinical studies, liraglutide shows well-tolerated characteristics and sustains weight loss in both non-diabetic and diabetic obese patients (Astrup et al., 2011; Garber et al., 2009; Vilsboll et al., 2012).
Liraglutide affects energy intake more than energy expenditure (van Can et al., 2013) to induce weight reduction. It is due to combined effects on the gastrointestinal tract and the central nerve system (CNS). GLP-1 receptors are found in pancreatic alpha and beta cells, the central and peripheral nervous systems, and the GI tract (Drucker & Nauck, 2006). Liraglutide slows the rate of gastric emptying, as shown in 5-hour gastric emptying test compared to the placebo group (van Can et al., 2013). Gastric motility, such as gastric emptying, is an essential part of regulating satiation, hunger, and satiety by regulating the gastric tension and intestinal nutrients (Janssen et al., 2011). Satiety can be promoted and food intake can be reduced by the signal of slow gastric emptying and vagal motor outflow from the CNS. Liraglutide increases insulin secretion in beta cells and suppresses glucagon secretion in alpha cells. Glucagon release is reciprocally correlated with insulin secretion in glucose oscillation to mobilize hepatic glucose and maintain normoglycemia levels. GLP-1 receptors are also expressed in the hypothalamic paraventricular nucleus (PVN) and arcuate nucleus (ARC) areas, which can control energy homeostasis and appetite (Jin et al., 1988; Kanse et al., 1988). In this area, GLP-1 receptors are involved in the signal of increasing activity of Cocaine- and amphetamine-regulated transcript (CART) and suppressing the NPY/AgRP (neuronpeptide Y/agouti-related peptide) pathway (Secher et al., 2014).

In a two-year clinical study, liraglutide treatment at a dose of 3 mg per day, resulted in a total weight loss of 7.8 kg, with body fat decreased by 15.4% and lean tissue by 2.0%. Additionally, the metabolic syndromes of the participants were improved, with the prevalence of prediabetes and metabolic syndrome decreased by 52% and 59%, respectively (Astrup et al.,
The most common adverse events were mild to moderate transient nausea and vomiting (Astrup et al., 2012; Wadden et al., 2013).

**Phentermine/Topiramate combination**

Phentermine/topiramate is a combination agent that works with a mechanism of immediate release of phentermine and controlled-release of topiramate.

Phentermine is a drug of the substituted amphetamine and acts as an appetite suppressant for short-term use. In a mouse model, it increases accumulation of brain dopamine but not for serotonin releases (Balcioglu & Wurtman, 1998). It targets CNS-specifically in the ventral tegmental area (VTA) as an agonist for trace amine-associated receptor 1 (TARR1) on the dopaminergic neuron. The activation of the TARR1 would facilitate dopamine release into the synapse from the presynaptic dopaminergic neurons. Consistent results have shown that dopamine deficiency causes eating disorders. It was shown that D2 receptors were decreased in obese individuals in proportion to their BMI (Wang et al., 2001). The released dopamine activates the anorexigenic signaling by binding dopamine receptors, D1 and D2 subtypes on postsynaptic neurons in the nucleus accumbens.
Topiramate is the first approved drug for epilepsy treatment in children and adults. Most of the anti-epilepsy drug could induce body weight gain, while topiramate has an opposite effect. When using topiramate for anticonvulsant treatment, their baseline weight was reduced by 14% at one year (Ben-Menachem et al., 2003). Another study recruiting healthy obese patients in the treatment group also showed weight loss results, with the treatment group losing at least 5% of body weight compared with placebo (Bray et al., 2003). Topiramate treatment induces weight reduction in both epileptic and non-epileptic patients (Astrup et al., 2004; Bray et al., 2003; Dursun & Devarajan, 2001), but this treatment is correlated to baseline BMI. Obese individuals
experience greater weight loss than normal and overweight individuals (Ben-Menachem et al., 2003).

Topiramate induces weight loss by controlling energy intake and energy expenditure, but its mechanism has not been fully understood. Topiramate has been shown to decrease food intake in rats (Richard et al., 2000) and activate the inhibitory GABA neurons (Cowley et al., 2001). Topiramate may also involve attenuation of the glutamate signal by decreasing the activity of the voltage-gated calcium channel (Zhang et al., 2000) and voltage-gated sodium channel (Zona et al., 1997) on the presynaptic excitatory neuron and antagonizing NMDA/AMPA glutamate receptor on the postsynaptic neurons (Rawls et al., 2009). Stanley et al. have shown that direct injection of glutamate into the lateral hypothalamus in mice elicits excessive eating behavior (Stanley et al., 1993), suggesting that topiramate might suppress food intake by antagonizing glutamate receptors. Topiramate also can improve insulin and glucose, and leptin level (Liang et al., 2005; York et al., 2000). In a high fat diet induced experimental rodent model, high dose or repeated topiramate treatment increased the NPY/ NPY-galanin-like immunoreactivity level and corticotrophin-releasing hormone (CRH)-galanin-like immunoreactivities (Husum et al., 2003; York et al., 2000) and reduced NPY1 and Y5 receptor mRNA level in the hypothalamus tissue (York et al., 2000). CRH can inhibit NPY-induced feeding behavior (Heinrichs et al., 1993). CRH might override the function of NPY to suppress the appetite in rodent. Topiramate has an ability to stimulate thermogenesis, but the mechanism is not well understood (Richard et al., 2000). Although York et al., showed the uncoupling protein 1 mRNA level unchanged in brown adipose tissue (York et al., 2000), the lipoprotein lipase activity increased in brown adipose, skeletal and
cardiac muscles (Richard et al., 2000). It might explain the mechanism of energy expenditure stimulation.

![Figure 10. Mechanism of action of phentermine/topiramate combination](http://www.anatomylibrary.us/)

In a two-year Phase III extension study, the combination groups were assigned phentermine/topiramate in two different doses, 7.5 mg phentermine/46 mg topiramate or 15 mg phentermine/92 mg topiramate, with lifestyle modification. The participants’ body weight reduction was 9.3% and 10.5%, respectively. The treatment groups showed a significant and sustained weight loss compared with the control, which had only 1.8% weight loss (Garvey et al., 2012). Another 56-week clinical trial of phentermine/topiramate showed similar results.
Treatment groups with 3.75 mg phentermine/23 mg topiramate and 15/92 groups lost 5.1% and 10.9% of baseline body weight, respectively, while the placebo group had only 1.6% weight loss (Allison et al., 2012). The most common adverse events were dry mouth, paraesthesia, dizziness, constipation and dysgeusia, and around 8% patients had depression and anxiety adverse events (Gadde et al., 2011).

Table 2. Summary of the current drug treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorcaserin</td>
<td>Target: CNS 5-HT2c receptor agonist</td>
<td>Central Nervous System effects Gastrointestinal effects</td>
</tr>
<tr>
<td>Phentermine/ Topiramate</td>
<td>Target: CNS TARR1 agonist</td>
<td>Pulmonary hypertension Cardiac valvular disease Central Nervous System effects Gastrointestinal effects</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Target: CNS and Periphery GLP-1 receptor agonist</td>
<td>Thyroid cancer concerns Pancreatitis concerns</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Target: GI tract Intestinal lipase inhibitor</td>
<td>Steatorrhea Fecal incontinence</td>
</tr>
</tbody>
</table>
5. TREATMENT UNDER THE DEVELOPMENT

The principle of current pharmacotherapy is to tilt the energy balance in favor of weight loss and re-establish physiological homeostasis. The strategies employed in the past for development of anti-obesity drugs aim at appetite suppression, satiety promotion, lipid absorbance inhibition focusing on various targets in CNS, gastric intestinal tract and adipose tissues.

The arcuate nucleus of the hypothalamus (ARC) is a key area in brain for regulation of feeding behavior (Schwartz et al., 2000) and serves as a target for drug development research. Among many compounds under investigation, neuronpeptide Y (NPY), a 36-amino acid polypeptide that is widely distributed in the nervous system and involved in regulation of emotions, sexual behavior, and feeding behavior (Dube et al., 1994; Tatemoto, 1982), has attracted significant attention. Animal experiments showed that local administration of NPY could increase meal size, eating duration, and feeding frequency (Bivens, Thomas, & Stanley, 1998; Gray & Morley, 1986). Two NYP receptors have been identified, Y1 and Y5 (Gerald et al., 1996; Stanley et al., 1992). Y5 receptor antagonists have been tested in clinical trials in the U.S., including Velneperit (S-2367) from Shionohi and Mk-0557 from Merck. Obese patients with a daily treatment of Velneperit 800 mg with diet control for a year saw at least 5% weight loss. Compared with the placebo group, the weight loss percentage of the Velneperit treatment group
was almost three times higher than the placebo group (Smith et al., 2009). Mk-0557, another potent ligand, showed an ideal profile in a preclinical setting, but did not reduce significant weight loss in a phase II clinical trial (Erondu et al., 2006). Activation of the MC4R on the POMC neurons would stimulate anorexigenic signals. Another line of research focuses on MC4R. A few MC4R agonists have been developed and currently in clinical trials, including MK-0493 from Merck, RM-493 from Rhythm and AZD2820 from AstraZeneca. It was shown that RM-493 not only reduces food intake but also increase energy expenditure. RM-493 treatment of obese patients increased resting energy expenditure vs. placebo by 6.4%, or 111 kcal/24 hour, on average (Chen et al., 2015). RM-493 is now in a phase II trial for treatment of POMC-deficient patients. Cannabinoid receptor antagonists have also been investigated for their activity in suppressing appetite. Dietressa, a cannabinoid type 1 receptor antagonist, showed suppression of body weight gain in mice on a high-calorie diet with an ultra-low doses (Kheyfets et al., 2012). Dietressa is currently in a phase III clinical trial.

Following promising results from studies involving in GLP-1, oxyntomodulin (OXM), another gut hormone that can activate GLP-1R and glucagon receptors, has been studied. Similar to that of liraglutide, OXM suppresses appetite and decreases blood glucose. It also increases cAMP concentration. OXM analogues such as oxyntomodulin from Polor and MOD-6031 from Opko Biologics are in phase I clinical trials. In a four-week study, a body weight reduction of 2.3 ± 0.4 kg was obtained at a dose of 400 nmol OXM three times daily, compared with 0.5 ± 0.5 kg in the placebo group (Wynne et al., 2005). Another OXM analogue, MEDI00382 made by AstraZeneca, showed in mouse and nonhuman primates a longer blood half-life with full function on
GLP-1R and glucagon receptors. Interestingly, MEDIO0382 does not have an equal function between GLP-1 and glucagon receptors (Trevaskis et al., 2016). Gut hormones, such as amylin and pancreatic polypeptide with activities in regulating glucagon, appetite, and satiety, have also been considered for treatment of obesity. The examples include AC2307 (Tan et al., 2012) currently in clinical trials (Mack et al., 2010).

Despite the fact that a few anti-obesity drugs are already on the market, many anti-obesity compounds are at the stage of preclinical investigation in animals. For example, peroxisome proliferator-activated receptor (PPAR) agonists have been studied for obesity treatment for a long time due to their involvement in lipid metabolism. PPAR alpha (PPARα) is highly expressed in liver and muscle, stimulating fatty acid degradation. PPARs can be negative regulators of insulin resistance, dyslipidemia and inflammatory response, which could benefit obesity treatment as well. Oleylthanolamide is a high-affinity PPARα agonist and functions to regulate lipid level, satiety, and body weight. Mice with i.p. administration of oleylthanolamide at 10 mg per kg showed less food intake and reduced weight gain compared with the control group (Fu et al., 2003).
Table 3. Summary of selected anti-obesity drugs in clinical trials*

<table>
<thead>
<tr>
<th>Target</th>
<th>Mechanism</th>
<th>Drug</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>NPY blocker</td>
<td>Y5 antagonist</td>
<td>MK-0557</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Y5 antagonist</td>
<td>S-2367 (Veineperit)</td>
</tr>
<tr>
<td></td>
<td>Melanocortin receptor</td>
<td>MC4R agonist</td>
<td>MK-0493</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MC4R agonist</td>
<td>RM-493</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MC4R agonist</td>
<td>AZD2820</td>
</tr>
<tr>
<td></td>
<td>Cannabinoid receptor antagonist</td>
<td>cannabinoid type</td>
<td>Dietressa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 receptor</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>OXM</td>
<td>OXN mimicking</td>
<td>Oxyntomodulin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MOD-6031</td>
</tr>
<tr>
<td></td>
<td>PP</td>
<td>PP analog</td>
<td>PP1420</td>
</tr>
<tr>
<td></td>
<td>Amylin</td>
<td>Amylin mimicking</td>
<td>AC2307</td>
</tr>
</tbody>
</table>

* PP, pancreatic peptide; OXM, oxyntomodulin; MC4R, melanocortin 4 receptor
6. FUTURE DIRECTION

Two major forms of obesity treatment strategy are in practice: surgery and pharmacotherapy. Bariatric surgeries have high efficiency and efficacy in weight reduction and improvement of obesity related metabolic diseases, but patients face risk for procedure-associated negative consequences. The anti-obesity drugs currently on the market appear to have fewer risks, but still have some side effects or safety concerns with lower efficiency. Pharmacological drugs tend to target the mechanism of energy intake to achieve therapeutic benefits. Consequently, research aiming at energy expenditure may represent the direction for future development in treating obesity.

In humans, energy expenditure is achieved by physical activities, basal metabolism, and adaptive thermogenesis. Among the three, exercise is the most obvious choice for shedding extra pounds of fat in obese patients. For an obese individual, exercise alone, without restriction on food intake or combination of drug treatment, was not very effective, resulting in a mean 2.4 kg (2.7%) weight loss in six months and a mean 1.0 kg (1.0%) in 24 months (Franz et al., 2007). Exercise alone did not result in successful weight loss, though it did result in no further weight gain compared with other treatment (Franz et al., 2007). Utilizing compounds that enhance the basal metabolism and adaptive thermogenesis, such as lipolysis and white adipose tissue browning, may represent a new research direction for obesity treatment. For example, fibroblast
growth factor 21 (FGF21) is a hormone capable of inducing glucose uptake and lipolysis. Utilizing the FGF21 analogue could induce energy expenditure and lipolysis. Search for better structure and activity of hormone analogues may result in compounds with better affinity and potency. In fact, a new compound, Ly2405319, an FGF21 analogue, has been made and examined for its weight loss function (Gaich et al., 2013). In addition to drug discovery approach, a strategy of optimizing treatment by combination of different drugs focusing on more than one pathway could improve the therapeutical outcome. Development of multifunctional drugs is another strategy for improved efficiency. Glucagon-thyroid hormone conjugates have been shown in animals with activity in enhancing hepatic cholesterol metabolism and white fat browning (Finan et al., 2016). It was also shown in the same study that liver-directed thyroid action offsets the diabetogenic liability of glucagon (Finan et al., 2016). Glucagon-mediated delivery spares the cardiovascular system from the adverse T3 action (Finan et al., 2016). Overall, research progress made in the past has offered new opportunities for new approaches for treatment of obesity. Future research directions are likely to follow what are known about regulation of energy homeostasis and to find ways to tilting the balance on reduced energy intake or/and enhanced energy consumption. With rapid progress in understanding the cause of obesity and regulation of energy homeostasis, it is highly possible to reverse the trend of obesity development.
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