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Obesity: Current and potential pharmacotherapeutics and targets

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ABSTRACT

Obesity is a global epidemic that contributes to a number of health complications including cardiovascular disease, type 2 diabetes, cancer and neuropsychiatric disorders. Pharmacotherapeutic strategies to treat obesity are urgently needed. Research over the past two decades has increased substantially our knowledge of central and peripheral mechanisms underlying homeostatic energy balance. Homeostatic mechanisms involve multiple components including neuronal circuits, some originating in hypothalamus and brain stem, as well as peripherally-derived satiety, hunger and adiposity signals that modulate neural activity and regulate eating behavior. Dysregulation of one or more of these homeostatic components results in obesity. Coincident with obesity, reward mechanisms that regulate hedonic aspects of food intake override the homeostatic regulation of eating. In addition to functional interactions between homeostatic and reward systems in the regulation of food intake, homeostatic signals have the ability to alter vulnerability to drug abuse. Regarding the treatment of obesity, pharmacological monotherapies primarily focus on a single protein target. FDA-approved monotherapy options include phentermine (Adipex-P®), orlistat (Xenical®), lorcaserin (Belviq®) and liraglutide (Saxenda®). However, monotherapies have limited efficacy, in part due to the recruitment of alternate and counter-regulatory pathways. Consequently, a multi-target approach may provide greater benefit. Recently, two combination products have been approved by the FDA to treat obesity, including phentermine/topiramate (Qsymia®) and naltrexone/bupropion (Contrave®). The current review provides an overview of homeostatic and reward mechanisms that regulate energy balance, potential therapeutic targets for obesity and current treatment options, including some candidate therapeutics in clinical development. Finally, challenges in anti-obesity drug development are discussed.

Contents

Abbreviations: AgRP, agouti-related protein; α-MSH, alpha-melanocyte stimulating hormone; 2-AG, 2-arachidonoylglycerol; BDNF, brain derived neurotrophic factor; BOLD, blood-oxygen level dependent; CB1, cannabinoid-1; CB2, cannabinoid-2; CART, cocaine and amphetamine regulated transcript; CCK, cholecystokinin; CPP, conditioned place preference; DIO, diet-induced obesity; DA, dopamine; DAT, dopamine transporter; FXR, farnesoid X receptor; fMRI, functional magnetic resonance imaging; GLP-1, glucagon-like peptide-1; GHSR1A, growth hormone secretagogue receptor 1A; GABA, γ-aminobutyric acid; GPCRs, G-protein coupled receptors; ICV, intracerebroventricular; IP, intraperitoneal; MCH, melanin-concentrating hormone; MC4R, melanocortin-4 receptor; MetAP2, methionine aminopeptidase 2; NE, norepinephrine; NPY, neuropeptide Y; NTS, nucleus tractus solitarius; OEA, oleoylethanolamide; OLETF, Otsuka Long Evans Tokushima Fatty; POMC, pro-opiomelanocortin; PR, progressive ratio; pSTAT3, phosphorylated signal transducer and activator of transcription 3; PYY, peptide YY; 5-HT, serotonin; SC, subcutaneous; VTA, ventral tegmental area.

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1. Introduction

Obesity is a complex medical condition characterized by excessive, abnormal fat accumulation as a result of increased intake of energy-dense foods and decreased physical activity (WHO, 2015). The dramatic rise in obesity is attributed to genetic susceptibility, environmental factors such as availability of energy dense foods and sedentary life style lacking adequate physical activity. The prevalence of obesity in the Unites States during 2009–2010 was about 36% among adult men, 36% among adult women, and 17% among children and adolescents (National Health and Examination Survey, 2010). Projections based on current trends suggest an increase in obesity prevalence by 2050 to 60% in adult men, 40% in adult women and 25% in children (CDC Report, 2014). The rise in global obesity rates over the last three decades has been substantial, presenting a major public health epidemic in both developed and developing countries (Ng et al., 2014). A systematic analysis in 2013 of the global burden of disease revealed that more than 50% of the world's 671 million obese individuals live in 10 countries (ranked from most to least): United States, China, India, Russia, Brazil, Mexico, Egypt, Germany, Pakistan and Indonesia (Ng et al., 2014). Once considered a problem predominantly in western countries, obesity has become a global epidemic.

Obesity is a major contributor to the metabolic syndrome, a constellation of metabolic abnormalities including increased blood pressure, high blood sugar, excess body fat around the waist, high serum triglycerides, and low levels of high-density lipoproteins (Mokdad et al., 2001; Bloomgarden, 2002; Montani et al., 2002; Eckel et al., 2005; Grundy, 2005). The metabolic syndrome increases the risk for severe health problems including cardiovascular disease, type 2 diabetes and stroke (Eckel et al., 2005). Compared to non-obese women, obese women exhibit 60-fold greater probability of type 2 diabetes (Colditz et al., 1990). Overweight and obese men exhibit increased risk for ischemic and hemorrhagic stroke (Kurth et al., 2002).

In addition to the metabolic syndrome, obesity also increases risk for certain types of cancer. As examples, the contribution of obesity to cancer is as high as 40% for endometrial and esophageal adenocarcinoma (NCI, 2012). Current trends indicate that by 2030, there will be an additional 500,000 cases of cancer associated with obesity in the United States. Furthermore, the prevalence of neuropsychiatric disorders, particularly, dementia, depression and anxiety, is increased in obesity (Petry et al., 2008). Escalating rates of obesity and concomitant life-threatening disorders underscore the need for safe and effective strategies to treat this complex medical condition.

Multiple approaches and strategies are used for the treatment of obesity including lifestyle modifications (making healthy dietary choices and increasing exercise), bariatric surgery and pharmacotherapy (Polonsky & Klein, 2008). A healthy diet and increase in exercise are beneficial for both the prevention and treatment of obesity. Nonetheless, lifestyle modifications require self-discipline and persistence to ensure and maintain the necessary beneficial weight loss. Moreover, effective lifestyle management of obesity results from a partnership between a highly motivated patient and a committed team of health professionals that may include a physician, a psychologist, psychiatrist, physical and exercise therapists, dietitians and other sub-specialists, depending on the patient's comorbidities (Polonsky & Klein, 2008).

Importantly, lifestyle management is just one component of a comprehensive approach to treat obesity and associated metabolic abnormalities (Smith et al., 2011). Surgical approaches, such as bariatric surgery, produce significant weight loss and ameliorate associated cardiovascular complications and type 2 diabetes in morbidly obese patients (Abdeen & le Roux, 2015). However, surgical procedures are invasive, expensive and have their own inherent risks and side-effects, including increased alcohol use, which suggests that these procedures facilitate an addiction transfer or exchange of palatable food reinforcers for an alternate reinforcer such as alcohol (Lent et al., 2013; Polston et al., 2013). Durability of diabetes remission and incident relapse following bariatric surgery was assessed from 1995 to 2008 in a large, population-based study of three integrated health care delivery systems in the United States (Arterburn et al., 2013). Although bariatric surgery resulted in complete diabetes remission within five years in 68% of severely obese adults, one-third of the individuals undergoing surgery relapsed within five years of initial remission (Arterburn et al., 2013). Further investigation is needed to understand the mechanisms underlying the cardio-metabolic effects of bariatric surgery and the long-term efficacy and safety of these procedures.

Given the limitations of lifestyle interventions and bariatric surgery, pharmacotherapeutic approaches for the treatment of obesity are important options. During the past 20 years, several anti-obesity drugs have been discovered, marketed and subsequently withdrawn from the market. Despite showing efficacy during initial stages of treatment, therapeutics for obesity have been accompanied by adverse side-effects following long-term use. Nevertheless, robust escalations in obesity and associated health complications constitute major driving forces for the discovery of novel targets and for the development of safe and effective weight loss therapeutics. The current review discusses potential therapeutic targets for obesity and provides an overview of current FDA-approved anti-obesity drugs, as well as several therapeutic candidates under clinical investigation. With respect to the discovery of novel therapeutic targets, employment of powerful molecular and genetic tools has increased our knowledge of central and peripheral mechanisms underlying homeostatic energy balance. The current review discusses interactions between homeostatic and non-homeostatic hedonic mechanisms underlying excessive food intake. Centrally and peripherally derived factors that regulate homeostatic and non-homeostatic hedonic mechanisms underlying food intake are summarized in Fig. 1.

2. Homeostatic regulation of energy balance

Obesity results from a long-term positive energy balance, that is, increased food intake and decreased energy expenditure (Spiegelman & Flier, 2001). Homeostasis is the maintenance of equilibrium of energy balance through adjustments in physiological processes. Both central and peripheral mechanisms are involved in the maintenance of body weight set point. Set point is a descriptor of long-term weight maintenance that involves coordinated adjustments in both intake and expenditure of energy that serve to stabilize an individual's weight at a specified level and to resist displacement from this level (Keesey &

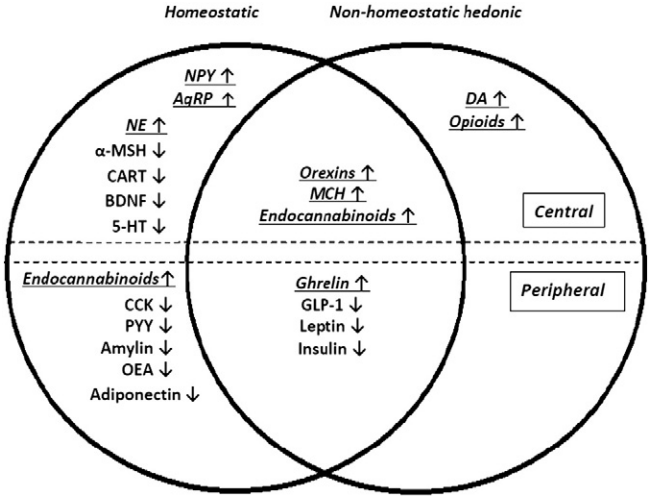

Fig. 1. Homeostatic and non-homeostatic hedonic factors that regulate food intake. Central and peripheral signals are provided above and below, respectively, the double line. "↑" indicates increases in food intake induced by orexigenic factors (also represented by the underline). "↓" indicates decreases in food intake induced by anorexigenic factors. Increased orexigenic signaling facilitates the development of obesity and increased anorexigenic signaling inhibits the development of obesity.