Immunotherapeutic Approach to the Treatment and Prevention of Obesity

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Abstract

Clinical availability of anti-obesity drugs is limited, and their inadequate effectiveness and safety concerns sometimes discourage widespread use. A therapeutic vaccine has the potential to be an attractive tool for preventing and treating obesity, because of the possibility of prolonged therapeutic effect and low frequency of administration. Experimental investigations have shown that vaccines targeting endogenous molecules that promote obesity could be a viable alternative. Recent novelties in drug-delivery systems and biotechnology will support further progress in vaccine development. This chapter provides an overview of recent advances in the area.

Keywords

Adenovirus 36 · Adipocyte · Glucose-dependent Insulinotropic Polypeptide · Ghrelin · Immunotherapy · Somatostatin · Vaccine

Introduction

The worldwide prevalence of obesity has markedly increased (nearly tripled in 40 years) (Flegal et al. 2013; Wilson et al. 2002; WHO 2020), and it is predicted that the condition will cost the U.S. healthcare system $48–$66 billion a year by 2030 (Wang et al. 2011). To combat the cardiometabolic comorbidities of obesity and their economic burden, global strategies for obesity prevention and treatment are required.

Lifestyle Interventions

Lifestyle initiatives targeting energy intake and physical activity are generally the first approach to weight reduction (Bray et al. 2016). They can trigger a 5–8% reduction in body weight (Heymsfield and Wadden 2017). However, obese persons often lack the motivation to continue with lifestyle management for weight reduction, because obesity is usually asymptomatic. Therefore, long-term weight management in obese persons remains a difficult task, and weight regain is a common problem following weight loss intervention (Heymsfield and Wadden 2017).

Pharmacological Management

The following prescription agents are approved by the U.S. Food and Drug Administration: phentermine (sympathomimetic amine), orlistat (lipase inhibitor), phentermine–topiramate (sympathomimetic amine and an antiepileptic drug), lorcaserin (5-HT2c receptor agonist), naltrexone–bupropion (opioid antagonist and aminoketone antidepressant), and liraglutide (glucagon-like peptide-1 [GLP1] receptor agonist). Yet relatively few patients receive sustained pharmacologic therapy for reasons that encompass insufficient weight loss, side effects, and prompt recurrence of obesity after treatment be interrupted (Heymsfield and Wadden 2017).

The Role of Vaccines

A therapeutic vaccine may be a potential candidate for improving treatment adherence. In general, a vaccine has prolonged therapeutic effects and low frequency of administration, when it succeeds in inducing neutralizing antibodies against a target molecule (Table 22.1).

Features of Therapeutic Vaccines

Therapeutic vaccines for the treatment of chronic diseases have the potential to increase treatment adherence, reduce healthcare costs, and offer enhanced specificity for target molecules. When administration of a therapeutic vaccine successfully induces antibodies that bind to the target self-molecule and inhibit its

Table 22.1 Potential vaccines targeting obesity

Target	Antigen	Species/References	Effect
Ghrelin	Ghr1 (1–10 a.a.)—KLH Ghr2 (13–28 a.a.)—KLH Ghr3 (1–28 a.a.) KLH	Male Wistar rat (Zorrilla et al. 2006)	No change in food intake 20% reduction in weight gain (Ghr1, Ghr3)
	Ghrelin (1–10 a.a.)—BSA	Male/female piglet (Vizcarra et al. 2007)	15% reduction in food intake 10% reduction in weight gain
	Ghrelin–NS1 (VLP-based)	DIO male C57BL6/J mouse (Andrade et al. 2013)	Decrease in food intake Increase in energy expenditure No change in weight gain
Adipocyte	Pig adipose tissue	Male/female human adult (Bourinbaiar and Jirathitikal 2010)	No change in body weight 7.6% reduction in waist size 25.9% increase in HDL-C
	Mouse adipocytes	Male/female Sprague Dawley rat (Lai et al. 2010)	About 50% reduction in weight gain
Somatostatin	Somatostatin-CAT	DIO male C57BL6/J Mouse (Haffer 2012)	12–13% reduction in body weight No change in food intake
Adenovirus 36	Inactivated Ad36	Ad36-infected C57BL6/J mouse (Na and Nam 2014)	No change in food intake 17% reduction in weight gain 20% reduction in epididymal fat

BSA, bovine serum albumin; DIO, diet-induced obesity; KLH, keyhole limpet hemocyanin; NS1, non-structural protein 1; VLP, virus-like particle

function, the vaccine should have a long-term therapeutic effect. In the case of hypertension vaccines, three doses of a peptide vaccine targeting angiotensin II type 1 receptor reduced blood pressures for 24 weeks after final immunization in hypertensive rats (Azegami et al. 2012), and a DNA vaccine targeting angiotensin II decreased blood pressure for at least 6 months in rats (Koriyama et al. 2015). The prolonged therapeutic effects of such vaccines will mean a low frequency of administration and may result in increased treatment adherence and savings in medication costs.

In addition to their prolonged effect, therapeutic vaccines have the potential to have greater specificity to target molecules compared with conventional low-molecular-weight drugs (Hansel et al. 2010). In general, high specificity to the target tends to result in few off-target effects and low rates of drug–drug interaction, and it may reduce the incidence of side effects (Hansel et al. 2010). Therapeutic vaccines also have some advantages over monoclonal antibody therapy, including lower production costs, no possibility of inducing anti-drug antibodies, and less frequent dosing (Hansel et al. 2010).

Ghrelin Vaccines

The especial feature of the ghrelin peptide is the *O*-acylation at the Ser^3 residue. It uniquely stimulates food ingestion with diminished energy expenditure (Kojima et al. 1999; Nakazato et al. 2001; Tschop et al. 2000; Wortley et al. 2004). Peripheral ghrelin, which is produced mainly in the gastric X/A-like cells, modulates the nucleus tractus solitarius via the vagus nerve. This results in an increase in noradrenaline in the arcuate nucleus of the hypothalamus and consequent appetite stimulation (Date et al. 2006). *O*-acylation at Ser^3 with octanoate, which is mediated by ghrelin *O*-acyltransferase (GOAT), provides the orexigenic action of ghrelin (Yang et al. 2008); unacylated ghrelin negatively impacts appetite and body weight (Asakawa et al. 2005).

Laboratory experiments demonstrate that antagonization of ghrelin ameliorates obesity. Genetic deletion of ghrelin increases energy

expenditure and locomotor activity in mice, which are less prone to diet-induced obesity (Wortley et al. 2005). Genetic deletion of ghrelin receptor (growth-hormone secretagogue receptor: GHSR), GHSR antagonists, and GOAT inhibitors attenuate diet-induced obesity in mice (Zigman et al. 2005; Maletinska et al. 2011; Barnett et al. 2010). However, as of 2019, no anti-obesity drug that targets ghrelin function—such as a ghrelin inhibitor, GHSR antagonist, or GOAT inhibitor—has been clinically available.

Vaccine Against Synthetic Ghrelin Peptides

Zorrilla et al. (2006) synthesized three ghrelin peptides (Ghr1, Ghr2, and Ghr3) for vaccine development in 2006. Keyhole limpet hemocyanin (KLH) and a couple of adjuvants were attached, and antigen-specific antibodies were elicited. Only Ghr1-KLH and Ghr3-KLH induced weight reduction (by 20%) (Zorrilla et al. 2006).

Also in a porcine model, vaccine comprising the N-terminal residues (1–10) of porcine ghrelin, combined with additional molecules, diminished appetite and weight accrual in piglets (Vizcarra et al. 2007).

Virus Like Particles (VLPs)

VLPs are viral proteins that reliably self-assemble and exhibit antigenic epitopes (Kushnir et al. 2012). Clinical trials in other areas have confirmed the concept (Maurer et al. 2005; Ambuhl et al. 2007). Also a ghrelin VLP vaccine was arranged and, in rodents, diminished appetite however not body weight (Andrade et al. 2013). More extensive studies are necessary in the area.

Nanogel-based vaccine

Advances in nanomaterial development have also been applied to the development of innovative anti-obesity vaccines. To avoid the risk of localized skin adverse events and psychological and physiological stress, when vaccines are administered by using injectable delivery methods, nanoparticle drug delivery to mucosal surfaces is an option (Lamichhane et al. 2014). Nanometer-sized polymer hydrogels (nanogels) can incorporate various proteins through hydrophobic interactions and subsequently allow their release in their native form (Azegami et al. 2018). The cationic type of cholesteryl-group-bearing pullulan (cCHP) nanogel is adequate for local application and interaction with nasal dendritic cells (Nochi et al. 2010). A recombinant fusion protein based on mouse ghrelin and PspA (pneumococcal surface protein A), paved the way for an intranasal vaccine using cCHP nanogel. In mice, serum IgG antibodies were elicited and weight gain was reduced (by 7%). Mitochondrial uncoupling protein 1 in brown adipose tissue was upregulated (Azegami et al. 2017).

Glucose-dependent Insulinotropic Polypeptide (GIP) Vaccines

GIP, as one of incretins, promotes pancreatic insulin secretion in a glucose-dependent manner (Sadry and Drucker 2013), and increases adipose tissue (Miyawaki et al. 2002). In animal experiments, a GIP receptor antagonist attenuated diet-induced obesity and subsequently improved glucose metabolism (McClean et al. 2007). GIP combined with bacteriophage Qβ VLPs allowed the development of a vaccine. In a mice model, weight gain was inhibited (by 35%), without hyperglycemia. The anti-obesity response was attributed to elevation of energy expenditure (Fulurija et al. 2008).

Adipocyte Vaccines

A small clinical trial with oral tablets of pig adipose tissue was conducted for 3 months (Bourinbaiar and Jirathitikal 2010). Waist circumference decreased (by 7.6%), however not

body weight. In turn, an intraperitoneally injected xenogeneic adipocyte vaccine in rats was followed by adipocyte apoptosis and 50% amelioration of weight increase (Lai et al. 2010).

Somatostatin Vaccine

Pharmacological supplementation with growth hormone (GH) decreases body fat in obese adults (Kim et al. 1999); however, the clinical applications of GH are limited by its very short half-life. Vaccine inhibition of somatostatin, which blocks GH secretion, was attempted by means of intraperitoneal immunization with somatostatin and carrier protein chloramphenicol acetyltransferase. Weight reduction (by 12–13%) and IgG production were achieved (Haffer 2012).

Adenovirus 36 (Ad36) Vaccine

In some large series, many obese persons tested positive for antibodies against Ad36 (Atkinson et al. 2005), and animals respond to Ad36 challenge with increased adiposity (Dhurandhar et al. 2002). An Ad36-based vaccine in mice was successful in preventing body fat elevation (Na and Nam 2014).

Future Possibilities

As therapeutic vaccines elicit the production of antigen-specific antibodies to neutralize biomolecules that promote weight gain, not only ghrelin, GIP, adipocytes, and somatostatin, but also other endogenous molecules can be targeted. The therapeutic vaccine approach is feasible for pathways with which no small-molecule drug has yet been able to interact. Brain and intracellular molecules that cannot be reached by neutralizing antibodies would not be suitable targets. In addition, enhancement of the immune reaction is a trade-off between preferable humoral immune responses and undesired autoimmune reactions.

Better selection of epitope sequences from self-antigens and adjuvants designed to elicit Th2 activity will help to induce Th2-dominant humoral immune responses. Enhanced drug-delivery systems and biotechnology will also help to develop effective and safe vaccines.

References

Ambuhl PM, Tissot AC, Fulurija A, Maurer P, Nussberger J, Sabat R et al (2007) A vaccine for hypertension based on virus-like particles: preclinical efficacy and phase I safety and immunogenicity. J Hypertens 25(1):63–72

Andrade S, Pinho F, Ribeiro AM, Carreira M, Casanueva FF, Roy P et al (2013) Immunization against active ghrelin using virus-like particles for obesity treatment. Curr Pharm Des 19(36):6551–6558

Asakawa A, Inui A, Fujimiya M, Sakamaki R, Shinfuku N, Ueta Y et al (2005) Stomach regulates energy balance via acylated ghrelin and desacyl ghrelin. Gut 54(1):18–24

Atkinson RL, Dhurandhar NV, Allison DB, Bowen RL, Israel BA, Albu JB et al (2005) Human adenovirus-36 is associated with increased body weight and paradoxical reduction of serum lipids. Int J Obes 29(3):281–286

Azegami T, Sasamura H, Hayashi K, Itoh H (2012) Vaccination against the angiotensin type 1 receptor for the prevention of L-NAME-induced nephropathy. Hypertens Res 35(5):492–499

Azegami T, Yuki Y, Sawada S, Mejima M, Ishige K, Akiyoshi K et al (2017) Nanogel-based nasal ghrelin vaccine prevents obesity. Mucosal Immunol 10 (5):1351–1360

Azegami T, Yuki Y, Nakahashi R, Itoh H, Kiyono H (2018) Nanogel-based nasal vaccines for infectious and lifestyle-related diseases. Mol Immunol 98:19–24

Barnett BP, Hwang Y, Taylor MS, Kirchner H, Pfluger PT, Bernard V et al (2010) Glucose and weight control in mice with a designed ghrelin O-acyltransferase inhibitor. Science 330(6011):1689–1692

Bourinbaiar AS, Jirathitikal V (2010) Effect of oral immunization with pooled antigens derived from adipose tissue on atherosclerosis and obesity indices. Vaccine 28(15):2763–2768

Bray GA, Fruhbeck G, Ryan DH, Wilding JP (2016) Management of obesity. Lancet 387(10031):1947–1956

Date Y, Shimbara T, Koda S, Toshinai K, Ida T, Murakami N et al (2006) Peripheral ghrelin transmits orexigenic signals through the noradrenergic pathway from the hindbrain to the hypothalamus. Cell Metab 4 (4):323–331

Dhurandhar NV, Whigham LD, Abbott DH, Schultz-Darken NJ, Israel BA, Bradley SM et al (2002) Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. J Nutr 132 (10):3155–3160

Flegal KM, Kit BK, Orpana H, Graubard BI (2013) Association of all-cause mortality with overweight and obesity using standard body mass index categories: a

systematic review and meta-analysis. JAMA 309 (1):71–82
Fulurija A, Lutz TA, Sladko K, Osto M, Wielinga PY, Bachmann MF et al (2008) Vaccination against GIP for the treatment of obesity. PLoS One 3(9):e3163
Haffer KN (2012) Effects of novel vaccines on weight loss in diet-induced-obese (DIO) mice. J Anim Sci Biotechnol 3(1):21
Hansel TT, Kropshofer H, Singer T, Mitchell JA, George AJ (2010) The safety and side effects of monoclonal antibodies. Nat Rev Drug Discov 9(4):325–338
Heymsfield SB, Wadden TA (2017) Mechanisms, pathophysiology, and management of obesity. N Engl J Med 376(3):254–266
Kim KR, Nam SY, Song YD, Lim SK, Lee HC, Huh KB (1999) Low-dose growth hormone treatment with diet restriction accelerates body fat loss, exerts anabolic effect and improves growth hormone secretory dysfunction in obese adults. Horm Res 51(2):78–84
Kojima M, Hosoda H, Date Y, Nakazato M, Matsuo H, Kangawa K (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402 (6762):656–660
Koriyama H, Nakagami H, Nakagami F, Osako MK, Kyutoku M, Shimamura M et al (2015) Long-term reduction of high blood pressure by angiotensin II DNA vaccine in spontaneously hypertensive rats. Hypertension 66(1):167–174
Kushnir N, Streatfield SJ, Yusibov V (2012) Virus-like particles as a highly efficient vaccine platform: diversity of targets and production systems and advances in clinical development. Vaccine 31(1):58–83
Lai QG, Jiang BQ, Zhou XH, Xu X, Gao ZN, Yuan KF (2010) The effects and mechanism of xenogeneic adipocyte vaccine for the prevention of obesity in rats. J Int Med Res 38(5):1700–1707
Lamichhane A, Azegami T, Kiyono H (2014) The mucosal immune system for vaccine development. Vaccine 32 (49):6711–6723
Maletinska L, Matyskova R, Maixnerova J, Sykora D, Pychova M, Spolcova A et al (2011) The Peptidic GHS-R antagonist [D-Lys(3)]GHRP-6 markedly improves adiposity and related metabolic abnormalities in a mouse model of postmenopausal obesity. Mol Cell Endocrinol 343(1-2):55–62
Maurer P, Jennings GT, Willers J, Rohner F, Lindman Y, Roubicek K et al (2005) A therapeutic vaccine for nicotine dependence: preclinical efficacy, and Phase I safety and immunogenicity. Eur J Immunol 35 (7):2031–2040
McClean PL, Irwin N, Cassidy RS, Holst JJ, Gault VA, Flatt PR (2007) GIP receptor antagonism reverses obesity, insulin resistance, and associated metabolic disturbances induced in mice by prolonged consumption of high-fat diet. Am J Physiol Endocrinol Metab 293(6):E1746–E1755
Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H et al (2002) Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med 8 (7):738–742
Na HN, Nam JH (2014) Proof-of-concept for a virus-induced obesity vaccine; vaccination against the obesity agent adenovirus 36. Int J Obes 38(11):1470–1474
Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K et al (2001) A role for ghrelin in the central regulation of feeding. Nature 409(6817):194–198
Nochi T, Yuki Y, Takahashi H, Sawada S, Mejima M, Kohda T et al (2010) Nanogel antigenic protein-delivery system for adjuvant-free intranasal vaccines. Nat Mater 9(7):572–578
Sadry SA, Drucker DJ (2013) Emerging combinatorial hormone therapies for the treatment of obesity and T2DM. Nat Rev Endocrinol 9(7):425–433
Tschop M, Smiley DL, Heiman ML (2000) Ghrelin induces adiposity in rodents. Nature 407 (6806):908–913
Vizcarra JA, Kirby JD, Kim SK, Galyean ML (2007) Active immunization against ghrelin decreases weight gain and alters plasma concentrations of growth hormone in growing pigs. Domest Anim Endocrinol 33 (2):176–189
Wang YC, McPherson K, Marsh T, Gortmaker SL, Brown M (2011) Health and economic burden of the projected obesity trends in the USA and the UK. Lancet 378 (9793):815–825
WHO (2020). https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
Wilson PW, D'Agostino RB, Sullivan L, Parise H, Kannel WB (2002) Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 162(16):1867–1872
Wortley KE, Anderson KD, Garcia K, Murray JD, Malinova L, Liu R et al (2004) Genetic deletion of ghrelin does not decrease food intake but influences metabolic fuel preference. Proc Natl Acad Sci U S A 101(21):8227–8232
Wortley KE, del Rincon JP, Murray JD, Garcia K, Iida K, Thorner MO et al (2005) Absence of ghrelin protects against early-onset obesity. J Clin Invest 115 (12):3573–3578
Yang J, Brown MS, Liang G, Grishin NV, Goldstein JL (2008) Identification of the acyltransferase that octanoylates ghrelin, an appetite-stimulating peptide hormone. Cell 132(3):387–396
Zigman JM, Nakano Y, Coppari R, Balthasar N, Marcus JN, Lee CE et al (2005) Mice lacking ghrelin receptors resist the development of diet-induced obesity. J Clin Invest 115(12):3564–3572
Zorrilla EP, Iwasaki S, Moss JA, Chang J, Otsuji J, Inoue K et al (2006) Vaccination against weight gain. Proc Natl Acad Sci U S A 103(35):13226–13231