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Sizing up pharmacotherapy for obesity.

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Obesity has increased over the last 20 years, from a condition affecting only a small portion of populations in developed countries, into a global pandemic.[1] The impact of obesity can be appreciated in the context of the populations at risk, and it is estimated that >1 billion adults worldwide are overweight (BMI >25 kg/m^2), 300 million of whom are clinically obese (BMI >30 kg/m^2).[2] In the United States, 65% of adults are overweight, and 32.2% of them are obese, a prevalence that has doubled over 20 years.[3] In industrialized countries, obesity rates have tripled, coinciding with adoption of a Western lifestyle.[4] Further, the growing worldwide rates of childhood obesity have reached epidemic values in developed countries.[5] This global obesity pandemic reflects genetic susceptibility, availability of high-energy foods, and decreased physical activity. Accelerating rates of obesity have profound health and economic consequences. Obesity is associated with a myriad of co-morbidities, including type II diabetes, coronary artery disease, obstructive sleep apnea, stroke, cancer, hypertension, osteoarthritis, and liver and biliary disease which collectively increase mortality.[6] Indeed, the health care impact of chronic obesity exceeds that of smoking or alcohol abuse.[7] National health care costs of obesity are $70-100 billion, and if this trend continues, in 15 years 20% of health care costs in the United States will be attributed to the chronic diseases associated with obesity.[8]

Collectively, these considerations underscore the health and economic imperative to develop novel therapeutic approaches to combat obesity and its

co-morbidities. In that context, overweight and obese individuals who receive assistance from their health care providers to lose weight are three times more likely to attempt weight loss.[9] The most common approach to medical weight management is counseling and lifestyle modification. However, while patients enrolled in these programs initially lose weight, they usually regain 30-35% of their lost weight within one year following treatment, and >50% of patients return to their baseline weight by five years.[10, 11] At present, only two drugs, orlistat and sibutramine, are approved for the long-term treatment of obesity. However, due to their inherent cardiovascular and gastrointestinal adverse effects, respectively, these drugs are often only utilized as rescue therapy for patients who fail diet and exercise. The scope of the obesity problem and the absence of available long-term solutions highlights the unmet clinical need for safe and effective pharmacotherapeutics to induce and maintain weight loss.

Endogenous Hormones

The adipose tissue-derived hormone, leptin, was one of the earliest endogenous hormones to be developed as an anti-obesity therapeutic. However, early leptin trials failed reflecting the evolution of leptin resistance in obese individuals. Recent insights into the molecular mechanisms underlying leptin signaling has revealed novel pharmacological approaches to increase receptor sensitivity, and leptin has re-emerged as a promising anti-obesity drug candidate. Indeed, chemical chaperones (4-phenyl butyric acid (PBA), tauroursodeoxycholic acid (TUDCA)), which resolve stress in the endoplasmic

reticulum, increase leptin sensitivity in mice[12]. Pramlintide, a synthetic analog of pancreatic amylin, also sensitizes mice to the effects of leptin, and pramlintide/metreleptin combination therapy is currently entering phase III trials after producing positive results in phase II testing.[13]

Glucagon-like peptide-1 (GLP-1) is an incretin secreted by the ileum and proximal colon which suppresses appetite in rodents and humans. In clinical trials, two proteolysis-resistant GLP-1 analogs (exenatide, liraglutide) induced weight loss. Further, a long-acting release formulation of exenatide (exenatide-LAR), injected once weekly, as well as nasal and transdermal formulations of exenatide, also are in early clinical development.[14] Moreover, testing of a long-acting GLP-1 analogue (NN9924), which utilizes sodium *N*-(8-(2-hydroxybenzoyl) amino) caprylate (SNAC) carrier technology to allow oral dosing, was initiated.[15]

Oxyntomodulin (OXM) is secreted post-prandially along with GLP-1 and has central anorectic effects. Repeated injections of OXM significantly reduced caloric intake and increased energy expenditure in overweight and obese subjects.[16, 17] A long-acting OXM analogue, TKS1225, has been developed.[18]

PYY is a satiety hormone secreted post-prandially by cells of the ileum and proximal colon which effectively reduces appetite in a dose-dependent manner.[19] Intranasal delivery of PYY (3-36) has been developed as an alternative delivery method to subcutaneous injection, and over 12 weeks of intranasal therapy PYY (200 μg, 600 μg) induced placebo-adjusted mean weight

losses of 1.4 kg and 2.3 kg, respectively. However, nausea and vomiting caused >50% of subjects receiving 600 μg PYY (3-36) to withdraw from the study.[20]

Ghrelin, secreted by the stomach, is the only known circulating orexigenic hormone. A vaccine comprising ghrelin conjugated to the hapten keyhole limpet hemocyanin decreased feeding and induced weight loss in rodent models.[21] An RNA spiegelmer, NOX-B11, which blocked the orexigenic activity of exogenous ghrelin[22], as well as small molecule ghrelin antagonists, are currently in early clinical and preclinical testing, respectively.[23]

Neuropeptide Signaling Modulators

Appetite and energy balance are primarily controlled by neuropeptide signaling within the hypothalamus. The arcuate nucleus is the principle signaling site for peripheral appetite-regulating hormones and contains neurons expressing the orexigenic neuropeptides, neuropeptide Y (NPY)/agouti-related peptide (AgRP) or the anorexigenic neuropeptide pro-opiomelanocortin (POMC).

The orexigenic activity of NPY is linked to signaling at Y1- and Y5-receptors, and an orally active Y5-receptor antagonist (MK-0557) has been developed. However, this drug did not induce clinically meaningful weight loss in a 1-year clinical trial.[24] Another Y5-receptor antagonist (S-2367) was modestly effective in clinical testing.[25] Since signaling at the Y1- receptor predominates in the appetite-stimulating effects of NPY, Y1-receptor antagonism or a combination

Y1/Y5-receptor antagonism may prove more effective in reducing appetite and inducing weight loss.

Due to their pre-synaptic inhibition of NPY release, Y2- and Y4-receptors, which are the targets of the satiety hormones PYY and pancreatic polypeptide, respectively, have been explored as molecular anti-obesity targets.[26] Currently, two drugs: obinepitide, a Y2/Y4- receptor agonist, and TM30339, a selective Y4 receptor agonist, are in phase I/II clinical trials.[27] Additionally, a specific AgRP inhibitor (TTT-435)[28], and BMS-830216, a pharmacological antagonist of signaling of the orexigenic neuropeptide, melanin-concentrating hormone, are in early clinical testing.[29]

Modulators of Monoamine Neurotransmission

Several monoamine neurotransmitters, including norepinephrine, dopamine, serotonin, and histamine, regulate appetite and energy balance. Bupropion, a norepinephrine and dopamine reuptake inhibitor currently marketed as an anti-depressant, induced long-lasting weight loss in normal and depressed obese patients.[30, 31] Thus, bupropion could be a useful therapeutic tool in the management of obese patients suffering from depression. Serotonergic drugs suppress appetite by stimulating central 5-HT_{2C} receptors.[32] Lorcaserin hydrochloride (ADP-356), a selective $5HT_{2C}$ agonist, effectively induced weight loss in phase II/III testing, and a New Drug Application (NDA) was recently filed for this agent .[33] Central histamine signaling also regulates appetite, and inhibition of H_1-histamine receptor signaling by antipsychotic

medications may underlie the weight gain commonly experienced with their use. H_3-histamine receptors regulate histamine signaling by inhibiting presynaptic histamine neurotransmission. Therefore, both H_1-receptor agonists and H_3-receptor antagonists are being developed as anti-obesity therapeutics.

Peripheral Modulators of Metabolism and Lipogenesis

Insulin resistance, commonly experienced by obese patients, may be an adaptive mechanism to prevent further fat accumulation, as insulin resistance is associated with a decreased risk of further weight gain. Thus, decreasing insulin signaling may be an effective means of inducing weight loss. Diazoxide, a potassium channel opener that inhibits insulin secretion, induced weight loss in clinical testing and may have utility as an anti-obesity therapeutic.[34] However, decreasing insulin secretion produces a serious risk of hyperglycemia, and the long-term safety of this agent must be defined.

The β3-adrenergic receptor (β3AR) is expressed by adipocytes, and its activation induces lipolysis and increases fat oxidation.[35] However, trials studying β3 agonists as potential anti-obesity drugs failed, likely reflecting the low expression levels of β3ARs in human adipocytes or the limited ability of these agents to activate β3ARs in adipose tissue. Trials investigating β3AR agonists for inducing weight loss are ongoing.

High circulating glucocorticoid levels produce the features of the metabolic syndrome, including central obesity and insulin resistance. In that context, 11β-Hydroxysteroid dehydrogenase type 1 (HSD1) converts inactive

cortisone to active cortisol in peripheral tissues. Selective 11β-HSD1 inhibitors are being developed to improve insulin sensitivity and induce weight loss.

Activated adipocytes produce a wide array of vascular growth factors and matrix metalloproteases to facilitate angiogenesis important for the growth of adipose tissue. Indeed, angiogenesis inhibition decreased weight gain in rodents[36] and may be useful in preventing the growth of adipose tissue in humans.

Finally, modulation of the transcription of genes involved in lipogenesis and cellular metabolism may be a productive strategy for inducing weight loss. Sirtuin-1 (SIRT1), an NAD-dependent deacetylase, binds to peroxisome proliferator-activated receptor-γ (PPAR-γ) in adipose tissue, repressing the transcription of genes involved in fat storage.[37] SIRT1 also enhances oxidative metabolism in brown adipose tissue, liver, and skeletal muscle by interacting with PGC-1a and inducing the expression of genes involved in mitochondrial oxidative metabolism.[38] SIRT1-activating drugs, which induce weight loss in rodents, are in early clinical trials to explore their utility in the treatment of obesity and metabolic diseases.

Combination Therapeutics

Combination therapy, which has been an effective strategy in the treatment of a variety of diseases, including hypertension, cancer, heart disease, and infectious diseases, may hold promise for the treatment of obesity. Three combination drugs, Contrave (bupropion + naltrexone), Empatic

(bupropion + zonisamide), and Qnexa (phentermine + topiramate), have shown great promise in clinical testing.[39] While most of these agents have proven individual efficacy, combination therapy amplifies clinical effects at lower individual drug doses, reducing the risk of adverse effects.

Conclusions

Molecular mechanisms controlling appetite, nutrient exposure, and energy balance are only beginning to emerge, and elucidation of these pathways will produce novel therapeutic targets for obesity.[40] Further, new technologies permitting more practical delivery methods, including oral, intranasal, and transdermal formulations, will allow drugs currently limited by their route of administration to achieve greater acceptance and patient compliance. The global health and economic consequences of obesity in the context of the ineffectiveness of lifestyle changes on producing durable weight loss highlight the critical unmet medical need for additional therapeutic approaches that achieve widespread integration into the clinical management of overweight and obese patients.

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