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Biologic Responses to Weight Loss and Weight Regain: Report From an American Diabetes Association Research Symposium

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On 26–28 April 2013, the American Diabetes Association convened an international group of experts in Washington, DC, for a research symposium titled "Biologic Responses to Weight Loss and Weight Regain." The speakers addressed the following topics: *1*) developmental processes and the prevention of weight gain, *2*) behavioral management approaches to weight loss, *3*) distinctions between the physiological mechanisms of weight loss and weight maintenance and the implications for treatment, *4*) the role of exercise in weight loss and maintenance, *5*) the physiological mechanisms and effectiveness of bariatric surgery, and *6*) pharmacological approaches to weight loss and maintenance. Both scientific and clinical perspectives were provided. The meeting concluded with an open session in which all the participants discussed emerging areas of investigation as well as unmet research needs. This discussion resulted in a series of recommendations for future research directions (Table 1). This Perspective article consists of summaries of the symposium sessions, by topic.

DEVELOPMENTAL PROCESSES AND THE PREVENTION OF WEIGHT GAIN

The rapid increase in the prevalence of childhood obesity has drawn attention to early life influences that may, in part, explain the increased susceptibility to weight gain for individuals and populations. This session featured investigators examining gestational factors and events early in intra- and extrauterine development that may predispose individuals to obesity later in life, such as the programming of the body weight "set point." These investigations may uncover developmental stages where behavioral or clinical interventions could be implemented to prevent or minimize excessive weight gain.

A propensity toward obesity may begin in utero. Over 40 studies have found a U-shaped relationship between birth weight and the risk for a variety of illnesses, including obesity, type 2 diabetes, and cardiovascular disease, with both high and low birth weights associated with greater risk. Susan Ozanne discussed animal research exploring the relationship between maternal nutrition and offspring health. In one study (1), researchers fed gestating mice either a 20% protein diet (normal control diet) or an 8% protein diet (low-protein diet). Offspring of mice fed the low-protein diet ate more and gained more weight in the early postnatal period than offspring of control mice, suggesting that gestational protein malnourishment programmed obesity in the offspring. The results were similar in leptin-deficient mice, suggesting that the effect was leptin independent (2). However, central resistance to the effects of insulin on the regulation of food intake in the offspring of the mice fed a low-protein diet was observed (S. Ozanne, unpublished data).

Patrick Catalano focused on how maternal weight before and during pregnancy affects birth weight and childhood obesity. In humans, birth weight is correlated with adiposity at age 8 (3), supporting the development of strategies that reduce excess birth weight. Maternal weight gain during pregnancy has been correlated with higher birth weights, and mothers are likely to retain excess weight after pregnancy (4). However, the strongest predictor for childhood obesity in one study was maternal prepregnancy BMI, which exceeded the impact associated with gestational diabetes mellitus and excess weight gain during pregnancy in humans (3). The Lifestyle in Pregnancy (LiP) study showed that obese women can safely reduce gestational weight gain; however, limiting gestational

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Table 1—Recommendations for research questions regarding biologic responses to weight loss and weight regain

- Studies aimed at understanding what determines the "defended weight" set point in humans, when it is established, and how it changes over the life cycle.
- Approaches to examine the impact of genetic vs. environmental influences on the defended weight set point, weight loss, and weight gain.
- Studies examining epigenetic factors that contribute to the establishment of the defended weight set point and the development of obesity, including the mechanisms underlying the establishment of epigenetic signals (maternal environment) and the downstream pathways that lead to obesity (in the offspring).
- Identification of biomarkers/genotypes that identify individuals at risk for development of metabolic disease.
- Studies aimed at understanding the mechanisms and pathways responsible for weight loss and maintenance as a result of bariatric surgery and how these pathways may be optimally manipulated (surgical and nonsurgical approaches) to favorably leverage these pathways for weight management. Examples include understanding how cell, tissue, metabolic, endocrine, and behavioral responses to dietary weight loss differ from weight loss imposed by surgery.
- Studies aimed at understanding how exercise impacts weight set points, weight loss, and weight regain, including the mechanisms by which muscle metabolism and structure change during weight loss and maintenance. Identification of the signals involved in communication of exercise activity from the periphery (skeletal muscle) to the brain is of particular interest and importance as these represent novel targets for enhancing weight loss and maintenance.
- Strategies to examine the effects of various combinations of therapies (with particular attention to pharmacotherapy combinations, but also behavioral, exercise, diet, and pharmacotherapy combinations) and to identify and characterize the mechanisms and pathways underpinning successful approaches to weight loss and maintenance of reduced body weight.
- Identification of individual differences, metabolic and genetic profiles, and biomarkers that predict responses to various therapeutic approaches for weight loss and maintenance.
- Examination of clinical strategies for the successful management of transitions from weight loss to weight maintenance and interventions specifically tailored for long-term weight maintenance.

weight gain with lifestyle intervention did not result in improved obstetric outcomes relative to a control group (5). Taken together, the evidence suggests that interventions during pregnancy may come too late, supporting a need to optimize maternal weight and/or diet during the preconception period.

Sebastien G. Bouret presented evidence from rodent experiments that hormones that are typically associated with feeding control also have a role in early brain development. The hypothalamus integrates hormonal signals, including insulin, leptin, and ghrelin, to control energy intake. Leptin and possibly ghrelin and other peptides also mediate aspects of the development of feeding circuits during the neonatal period. For example, leptin is neurotrophic in vitro, and leptin-deficient mice show altered patterns of synapses in hypothalamic pro-opiomelanocortin neurons that are involved in appetite regulation (6). In normal rodent development, leptin surges shortly after birth and then declines, while ghrelin levels, low at first, rise as leptin levels decline (7). Thus, the development of feeding circuits depends on the intercurrent metabolic and endocrine status. Disruption of hormonal signaling during neurodevelopment may result in changes that facilitate overfeeding.

Set-point theories suggest that maintaining a lower body weight is difficult because body weight is regulated at a predetermined level (or range) by altering energy expenditure and intake via a variety of feedback control mechanisms (8). Genetic factors clearly play an important role, as evidenced by studies of twin pairs that indicate 70% of the variance associated with BMI is heritable (9). However, the environmental factors that modify risk are poorly understood. Lori M. Zeltser observed that the BMI of very young children does not predict adiposity in adulthood (10), suggesting that there may be a critical period in early childhood that establishes the body weight baseline. To help define how set points are programmed, Ring and Zeltser (11) studied a leptin receptor knockout mouse, which exhibits early-onset hyperphagia and obesity that stabilizes with maturity. In an intervention study, the researchers restricted the food intake of the knockout mice in the first 10 weeks of life, after which they allowed the mice to eat ad libitum. The mice immediately began to overeat, matching the intake of a control group of mice that had eaten ad libitum throughout their lives. However, the mice reared on a restrictive diet continued to weigh less than the control group, suggesting that feeding restrictions in early life may lower set points. The lower weight was achieved by increased energy expenditure from brown fat thermogenesis (Fig. 1), not from an increase in locomotive activity or reduced energy intake (11). Some studies in different rodent models have similar findings, while others have conflicting results (12–14), demonstrating a need for more research on when and how set points are established.

BEHAVIORAL MANAGEMENT APPROACHES TO WEIGHT LOSS

Understanding how body weight control processes are established is critical for the prevention of obesity, but strategies are needed to safely and effectively reduce weight for the people who are already overweight and

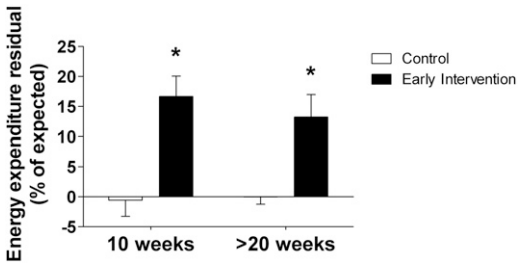

Figure 1—Increased energy expenditure after early food restriction leads to lower body weight (11). Leptin receptor (*Lepr*) knockout mice that were calorie restricted for the first 10 weeks of life (Early Intervention) exhibited decreased weight and increased energy expenditure compared with knockout mice allowed to eat ad libitum (Control). These differences persisted between the two groups of knockout mice even after both groups were allowed to return to ad libitum feeding after initial restriction (>20 weeks).

obese. Behavioral management and modification is one approach often used to achieve weight reduction. Research examining what behavioral approaches work best, including considerations for particular populations and emerging platforms that can deliver management programs to broad audiences in a cost-effective and efficient manner, is important.

Obesity in childhood has increased greatly in recent decades, and obese children are likely to become obese adults (15). Researchers continue to look for strategies that may help obese children lose weight and keep it off. Pediatric obesity is a particularly complex problem, including the influence of genetic and epigenetic variation, family, social networks, and the local food and physical activity environments. Family-based interventions that take external factors into account can produce significant treatment effects in the overweight pediatric population (16). Denise Wilfley highlighted the particular importance of early intervention with behavioral management approaches in the pediatric population. For example, overweight young children (ages 8–9) need to lose less weight to normalize their body mass/adiposity than older children (ages 12–13) (17). Interventions that involve the family and focus on children 8 years and younger may be particularly effective (18), although the long-term persistence of these effects is not yet known.

Losing weight in adulthood is no less challenging, but confers demonstrated health benefits, such as reducing the risk for developing type 2 diabetes and improving outcomes in those with the disease (19–24). Gary Foster described nutrition-based approaches to the behavioral treatment of obesity in adults. Habitually writing down food intake can facilitate weight loss (20). Another approach that can help limit caloric intake is the use of meal replacements, such as drinks or bars. Several studies have demonstrated that meal replacements enhance both initial and long-term weight loss (25,26). As far as what diet is optimal, net caloric restriction is essential, while differences in macronutrient composition do not appear to have a strong effect on the magnitude of weight loss in humans (27–29).

Determining the ideal weight-loss program is only part of the challenge; the mode of program delivery also influences efficacy. The emergence of technology into the daily lives of people worldwide may offer novel cost-effective opportunities, according to Deborah F. Tate. Phone-based interventions may provide a convenient approach to weight loss and weight maintenance, with efficacy in some studies matching in-person interventions (30). Internet-based weight-loss programs that provide structure and repeated contact result in significant weight loss (31). The addition of e-coaching, delivered in an automated format or by a human correspondent, further enhances the benefits of an Internet-based program (32,33).

Behavioral approaches to weight loss are an important component of weight management but are not sufficient to achieve and maintain weight loss in most people over the long term. Understanding how to integrate behavioral management approaches into broader programs of weight management that include diet, exercise, and pharmacological components is an important future direction.

DISTINCTIONS BETWEEN PHYSIOLOGICAL MECHANISMS OF WEIGHT LOSS AND WEIGHT MAINTENANCE AND THE IMPLICATIONS FOR TREATMENT

After losing weight, the work of weight maintenance begins. Weight maintenance is physiologically different from weight loss. After successful weight loss in a structured program, people on average regain 80% of the lost weight within 5 years (34) (Fig. 2), although it should be noted that around 15–20% of people maintain at least 10% of weight loss over the long term (35,36). A propensity toward weight regain is, in part, attributable to physiological changes that result from the initial weight loss. These changes include a decrease in salience of satiety signals, an increase in salience of hunger signals, and an increase in metabolic efficiency (37). Paul S. MacLean showed data on altered gene expression in adipocytes

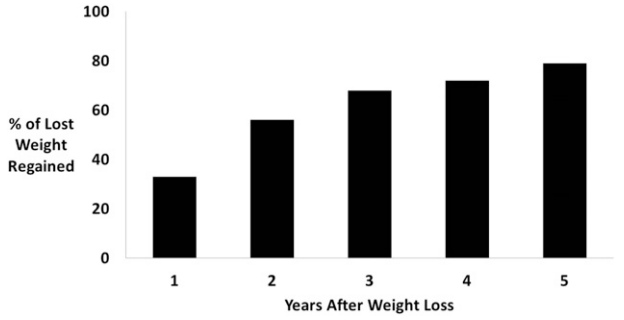

Figure 2—Propensity to regain weight after weight loss in response to hypocaloric diet (34). On average, weight regain occurs steadily following weight loss and approaches 80% by 5 years following successful weight loss.

during weight loss in rats, consistent with promoting the ability of the cells to take up nutrients (38,39). Exercise prevents adipocyte hyperplasia in animals (40), offering one mechanism by which physical activity may attenuate weight regain.

In an effort to address the question of the appropriate weight-maintenance diet, David S. Ludwig discussed the effects of dietary composition on energy expenditure. As obesity prevalence has increased in the U.S., the percentage of calories from fat has decreased, while the dietary glycemic index (GI)/glycemic load (GL) has increased (41,42). High-GI meals may be intrinsically less satiating. Despite having similar average body weights, rodents fed a high-GI diet have more body fat and less lean mass than those on a low-GI diet (43). In a large European study, a low-GL, high-protein diet was superior to higher-GL diets in both weight loss and weight maintenance (44). A low-GI/GL diet may have health benefits beyond weight, as well. Some evidence from epidemiological studies suggests that a low-GI diet may be associated with a decreased risk for gestational diabetes mellitus (45), myocardial infarction (46), liver steatosis (47), and breast cancer (48).

Data are scarce regarding the drivers of weight regain. J. Graham Thomas pointed out that participants in both the Diabetes Prevention Program (DPP) and Look AHEAD (Action for Health in Diabetes) regained weight slowly (20,26), while those in other studies with less provider contact regained weight more quickly. Data from the National Weight Control Registry, which includes people who have lost at least 30 pounds and kept it off for a year or more, suggest that long-term weight maintenance is associated with frequent self-weighing, high levels of physical activity, limited television viewing, and a low-calorie/low-fat diet (49). Behavioral programs that teach and reinforce these measures may be more successful in weight maintenance.

Together, these data suggest that overcoming obesity may require a reconfiguration of how weight loss and weight maintenance are perceived. One approach, according to Holly Wyatt, is to use a multistep strategy involving a weight-loss phase of 4–6 months, a short transition phase, and then a weight-maintenance phase. For weight loss, diet restriction may be the most important component, and then as one moves into the weight-maintenance phase of obesity treatment, physical activity becomes an important factor (50).

ROLE OF EXERCISE IN WEIGHT LOSS AND MAINTENANCE

Exercise is associated with numerous benefits and potentially creates a negative energy balance that can promote weight loss. While sustaining an increase in energy expenditure in the context of caloric restriction for extended periods to drive weight loss is difficult in practice, evidence suggests that physical activity and exercise are especially effective for preventing weight gain and weight regain following successful weight loss. The mechanisms underlying the effects of exercise in this context were discussed. Weight loss triggers skeletal muscle adaptations in human subjects that increase contractile efficiency, promoting weight regain (Fig. 3) (51). Michael Rosenbaum offered insight into possible interventions that may reduce these compensations. Weight loss in humans induces the expression of more chemomechanically efficient isoforms of myosin heavy chain; treating weight-reduced subjects with low doses of the hormone leptin reversed these effects (52,53). Preliminary studies of weight-reduced and non–weight-reduced subjects showed similar declines in skeletal muscle chemomechanical efficiency following resistance training (M. Rosenbaum, unpublished data) in both groups, suggesting that resistance training may be a useful adjunctive therapy to "reverse" some of the changes that occur in muscle as the result of weight reduction.

Bret Goodpaster described the effects of the loss of skeletal muscle on weight regain, which he presented as being complementary to MacLean's discussion of adipocyte adaptations. Skeletal muscle accounts for about 20% of resting energy expenditure and about 40% of body weight (54). Obese people have greater amounts of muscle and thus higher absolute resting and daily energy expenditures. However, weight loss tends to reduce skeletal muscle mass, with implications for long-term weight maintenance. Adding exercise to a weight-loss program can increase weight loss (55,56) and mitigate weight-loss–related reductions in muscle fiber size (57). Exercise also increases fatty acid utilization by human skeletal muscle (58) and increases brown fat in mice (59), factors that may account for some of the benefits of exercise, as well as the link between exercise and weight maintenance.

Exercise may also be helpful in the prevention of obesity. Silvana Obici presented evidence from rodent studies that exercise helps prevent diet-induced obesity

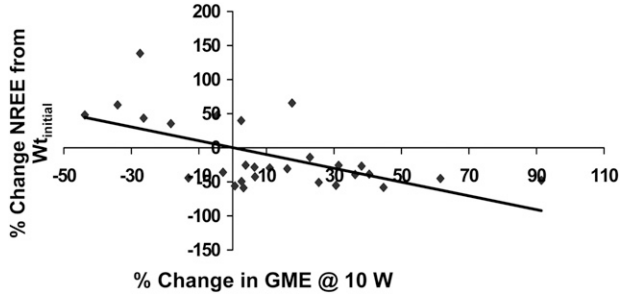

Figure 3—Relationship between changes in nonresting energy expenditure (NREE) and changes in muscle gross mechanical efficiency (GME) after weight change (51). GME is the increment in energy expenditure above resting energy expenditure to pedal a cycle ergometer to generate 10 W of power. Regression equations relating percent changes from $Wt_{initial}$ in GME to percent changes in NREE in subjects at $Wt_{+10\%}$ and $Wt_{-10\%}$ of initial showed that 35% of the variance in percent change in NREE at altered body weight was accounted for by changes in GME at 10 W ($P = 0.0008$).

by reducing central leptin resistance (60,61). To assess whether the melanocortin system mediates some of these effects of exercise, Obici studied wheel running in melanocortin-4 receptor (MC4R) knockout mice and rats. Wheel running lowered body and fat mass in MC4R knockout mice (62) and rats; however, voluntary wheel running and the expression of DeltaFosB, a protein associated with addiction, in nucleus accumbens (NAc) neurons were reduced in these animals (J.D. Mul, unpublished data), suggesting the rodents' reward system was affected. Despite decreased wheel-running activity, exercise did improve hyperlipidemia, hepatic steatosis, and glucose intolerance in MC4R knockout rats (J.D. Mul, unpublished data).

James A. Levine discussed nonexercise activity thermogenesis (NEAT), which may include domestic labor, work-related activity, stair climbing, and fidgeting, as another important component of energy expenditure. In people, reduction of NEAT due to an increasingly sedentary lifestyle may be associated with increasing obesity (63). Other studies suggest that NEAT may have effects on blood glucose as well; as anticipated based on the well-recognized effects of muscle contraction on glucose uptake (independent of insulin), walking after a meal was associated with significant reductions in postprandial glucose excursions in studies of patients with type 1 diabetes and healthy people (64). Biochemical manipulation of NEAT may also be possible; the neuropeptide orexin increases NEAT and reduces weight in rats (65).

PHYSIOLOGICAL MECHANISMS AND EFFECTIVENESS OF BARIATRIC SURGERY

The Swedish Obese Subjects (SOS) study is the most comprehensive long-term controlled bariatric surgery study to date, tracking weight change following Roux-en-Y gastric bypass (RYGB), laparoscopic adjustable gastric banding (LAGB), and vertical-banded gastroplasty (VBG) compared with conventional lifestyle intervention in 4,047 subjects (66). In the SOS study, all treatment arms reached maximal weight loss by 1 year and by 5 years had an average weight loss of 31% for RYGB and approximately 17% for both LAGB and VBG, representing nearly an order of magnitude greater weight loss than what was observed in an 8-year intensive lifestyle intervention (26). On average, weight loss remained significant over a 15-year follow-up, but weight did return toward baseline in all surgical groups, with 10-year average weight loss of 25%, 14%, and 16%, respectively. The primary end point of the study was mortality, and by the 16-year follow-up, a significant survival advantage was observed for patients who underwent RYGB compared with control subjects (66). There were 129 deaths in the control group and 101 deaths in the surgery group with an adjusted hazard ratio of 0.71 ($P = 0.01$). Decreased incidence of hard outcomes, such as diabetes (24% vs. 7% at 10 years) and myocardial infarction or stroke (199 in surgery vs. 234 in control group, adjusted HR 0.67, $P < 0.001$, median follow-up 14.7 years), and improvements in cardiovascular risk factors, such as HDL (13.6% increase in surgery vs. control group at 10 years) and triglycerides (14.8% reduction in surgery vs. control group at 10 years), were also associated with the surgical interventions (24,67). Improvements in risk factors were greatest at 2 years and, similar to weight loss, generally remained significant but returned toward baseline with longer follow-up (24).

A comparison between RYGB and LAGB showed significant variation in patient weight loss, with greater variation observed in the group with gastric banding (68). Weight-loss magnitude after surgery also appears to be related to several procedure-dependent factors, including degree of malabsorption and endocrine changes, such as ghrelin levels. An Australian study found that RYGB results in more rapid weight loss than LAGB, but that weight loss is similar over the long term (69). Duodenal switch, though more technically challenging than RYGB, may result in even greater weight loss (70). Variation may also be attributed to patient characteristics, including age, health status, behavior, and genetics. For example, older people and people with type 2 diabetes tend to lose less weight. Interestingly, the effects of bariatric surgery on weight loss appear to be dependent on MC4R in homozygous knockout animal models (71) and in humans with complete MC4R deficiency (72). However, patient heterozygosity for obesity-producing MC4R mutations does not affect the response to bariatric surgery (73,74). A better understanding of the different causes of the variability in weight loss may help identify patients who are best suited to specific bariatric surgeries and to predict their responses. The genetics of responses to bariatric surgeries will be an important area of investigation.

Vertical sleeve gastrectomy (VSG) is becoming a more popular choice for bariatric surgery, according to Randy J. Seeley, partly because it is technically simpler than RYGB. The procedure involves turning the stomach into a tube or "sleeve." VSG is often lumped in with LAGB as a purely restrictive procedure. However, physiologically, VSG may be more similar to RYGB. In patients with diabetes, the improvement in glycemic control and the amount of weight loss are comparable between VSG and RYGB (75). In rats, VSG and RYGB produce similar changes in food preferences and reductions in fat intake (76). It has been hypothesized that RYGB may improve insulin secretion because partially digested food encounters the small intestine more distally than it did before the surgery, leading to changes in the secretion of gut hormones, such as glucagon-like peptide 1 (GLP-1) and ghrelin. However, VSG does not rearrange the gastrointestinal tract, yet it has effects on insulin secretion similar to those of RYGB. VSG does indeed increase GLP-1 secretion in rodents, similar to what is observed with RYGB (77). The hunt is on for the potential molecular intermediaries for VSG. Ghrelin and GLP-1 receptor knockout mice still lose weight and experience improved glucose control after VSG, suggesting that neither ghrelin nor the GLP-1

receptor is a key mediator of these VSG benefits (77,78). Plasma levels of bile acids increase after VSG in rodents (79), activating farnesoid X receptor (FXR). In FXR knockout mice, VSG loses its capacity to lower weight and improve glucose control, suggesting bile acids and FXR activation may be one mechanism by which VSG exerts its beneficial effects (80). VSG-mediated microbiome changes may also be involved; after VSG, wild-type and FXR knockouts exhibit different microbiome signatures (80).

The benefits of bariatric surgery go beyond weight loss per se. Type 2 diabetes improves or resolves in many people who have bariatric surgery relatively early in the course of the disease, particularly those undergoing RYGB. What proportion of this improvement is the result of weight loss, hypocaloric intake, and/or changes in gut biology is an area of important scientific debate. The mechanisms for these metabolic improvements are poorly understood and apparently involve changes in brain, gut, and peripheral signaling pathways (81). While diet restriction prompts a strong counterregulatory response, such as hunger, some evidence suggests that RYGB may change body weight without potently triggering these responses (82). Though surgery may not entirely defeat a preprogrammed body weight set point (83), these observations suggest that gut hormones play a role in the physiological responses to bariatric surgery. Given the complexities of gut-brain signaling, Hans-Rudolf Berthoud believes it may be naïve to think that a single mechanism is responsible for the beneficial effects of RYGB. Many investigators have suggested that GLP-1 may play a role. However, in rat studies, blocking GLP-1 does not affect the response to RYGB (84). Peptide YY knockout mice do not significantly decrease body weight after bypass surgery (85), suggesting that the hormone has some role in RYGB benefits. However, a central blockade of signaling by Y2R, a receptor for peptide YY, had no effect on body weight in either RYGB or sham-operated rats (84). The vagus nerve does not appear to be relevant (86), nor is ghrelin required for VSG to be effective in mice (77). Together, these data suggest a complex set of interactions that will require further investigation to unravel.

The gut microbiome is emerging as another potential determinant of body weight. Lee Kaplan spoke about how gut microbes may mediate some of the benefits of bariatric surgery. When germ-free genetically obese mice or those obese due to a high-fat diet are colonized with microbiota from a lean donor they gain less weight than those colonized with microbes from an obese donor (87), suggesting that gut microbiota can influence adiposity. RYGB rapidly and selectively changes microbiota (88), independent of the associated changes in diet or weight loss. While diet-induced weight loss also triggers microbial changes, those changes are different from those observed after RYGB or other bariatric surgical procedures. Importantly, the transfer of post-RYGB microbiota into germ-free animal models results in weight loss and reduced fat mass (88). In addition, mice that receive the microbiota from the RYGB-treated animals have lower plasma leptin and lower adiposity despite greater food intake (88). A possible mechanism for these findings is that the microbiota from RYGB animals are able to stimulate increased energy expenditure in the recipient animals (A.P. Liou, unpublished data). Another potentially important observation is that RYGB-induced changes in microbiota increase propionate and decrease acetate in a mouse model (88). These short-chain fatty acids regulate metabolic signaling pathways and may contribute to the benefits conferred by RYGB.

PHARMACOLOGICAL APPROACHES TO WEIGHT LOSS AND MAINTENANCE

Emerging Treatments and Strategies

The development of pharmaceutical interventions for weight loss has been plagued by a number of factors, including a history of safety concerns (fenfluramine, rimonabant, and sibutramine), a generally modest impact on weight, the lack of a medical definition of obesity, and an unclear regulatory pathway for the development and approval of weight-loss medications. In the past decade, however, some of these barriers have been addressed and several new medications for weight loss have been approved, providing physicians with additional treatment options for their patients who need to lose weight. The evidence base supporting the use of these therapies alone, in combination, and as part of a comprehensive weight-management approach is growing and will continue to inform the optimal treatment of obesity.

Currently, the pharmacological agents approved for the treatment of obesity in the U.S. are orlistat, phentermine, phentermine/topiramate, bupropion/naltrexone, lorcaserin, and liraglutide. All of these agents are associated with a mean weight loss of around 5–10% (89) versus placebo control.

Lorcaserin activates 5HT2c receptors. A pivotal phase three trial, Behavioral Modification and Lorcaserin for Overweight and Obesity Management (BLOOM), found sustained weight loss and cardiometabolic benefits after 2 years; at 1 year, half of the participants achieved greater than 5% weight loss and 20% achieved greater than 10% weight loss versus placebo control (90). However, the clinical reality of the medication may be more nuanced, as nonresponders tend to drop out of these trials. Serotonergic drugs, such as lorcaserin, may improve glycemic control independent of weight effects. Participants with diabetes in the BLOOM trial were more likely to achieve an A1C of less than 7% and to reduce antidiabetes medication use (91). Similar beneficial effects were seen with phentermine/topiramate.

The emerging paradigm is that any weight-loss agent will have to be used indefinitely, similar to blood pressure and lipid medications; hence, long-term safety and efficacy will continue to be important considerations. Timing may be an unappreciated variable in the use of pharmaceuticals for treating obesity. Steven R. Smith discussed the utility of

the Edmonton Obesity Staging System, a tool that divides obesity into five stages (0–4), based on the extent of obesity-related medical, mental, and functional limitations, that can help health care providers determine when to treat obesity patients with pharmacotherapy (92).

Several avenues are being explored for the development of new weight-loss medications. A number of diabetes therapies have favorable weight effects, leading to their investigation for obesity. Pramlintide, an amylin analog that is currently approved for the treatment of diabetes, also reduces food intake in obese subjects (93), and in studies examining its efficacy for weight reduction, pramlintide led to sustained weight loss over a year (94). However, clinical development of pramlintide as a standalone weight-loss medication was discontinued in favor of combination approaches. Liraglutide, a GLP-1 receptor agonist that has been available as a diabetes medication since 2010, also has effects on satiety and food intake (95). Liraglutide was recently approved for the treatment of obesity. Beloranib, an inhibitor of methionine aminopeptidase 2 (MetAP2), is another molecule in late-stage clinical development for the treatment of obesity. MetAP2 is an enzyme that regulates angiogenesis and was initially identified as a therapeutic target for cancer (96). The mechanisms of action for the weight effects of beloranib are not well understood, however, they appear to be related not to angiogenesis but rather to the suppression of sterol regulatory element–binding protein activity and the attenuation of signaling through extracellular signal–regulated kinase pathways, resulting in decreased fat biosynthesis and stimulation of fat oxidation (96). Earlier in the development pipeline, the weight-loss candidate JD-5037 is a peripherally acting inverse-agonist of the CB1 cannabinoid receptor that has shown early efficacy in mouse studies. In contrast to brain-penetrant CB1 antagonists such as rimonabant, JD-5037 has little to no access to the brain, thus, in principle, limiting the adverse effects that have been associated with central CB1 blockade (97). The mechanisms of action for peripherally acting cannabinoid compounds are under investigation and may include modulation of leptin signaling (97), activation of brown adipose tissue (98), and effects on the sympathetic nervous system (99).

As multiple pathways appear to regulate weight loss, Paul T. Pfluger and Louis J. Aronne discussed the utilization of combination therapies for weight loss. Pfluger discussed strategies for potential combination therapies: coadministration of two hormones, such as pramlintide and leptin; coagonism of individual molecules with dual agonist activity, such as a GLP-1 and glucagon coagonists; and triagonism (100–103). In rodent and limited human studies, these combination therapeutic approaches led to increased weight loss with lower doses, suggesting that combining the action of endogenous hormones that coregulate glucose, lipid, and energy homeostasis may provide superior therapeutic outcomes. Such polypharmacy, ideally achieved by combining multiple agonist activities into single molecules, could help maximize efficacy by targeting multiple complementary pathways while preventing off-target adverse effects as a result of overstimulating a single pathway.

Aronne highlighted the treatment gap between the minor weight loss that occurs with lifestyle changes (5–7%) and the major weight loss that occurs with bariatric surgery (>15%). He suggested that pharmacotherapy may be able to fill in the gap. Combining lifestyle modification with weight-loss medications, including GLP-1 receptor agonists, may give better results in humans (104,105). The next question is can medication combinations with complementary mechanisms recreate the benefits of adding lifestyle modifications to a weight-loss drug? Promising combinations include the recently approved bupropion/naltrexone (106) and phentermine/topiramate (107). Other combinations have been explored in humans, such as pramlintide/phentermine (108) and pramlintide/metreleptin (in subjects with BMI <35 kg/m^2) (109), however, development programs on these combinations have been discontinued due to commercial considerations.

The efficacy of drugs in the induction of weight loss and maintenance of reduced body weight may differ (110). As maintenance of a reduced body weight is required for sustained beneficial effects of weight reduction, additional attention is needed in this area of pharmacology and in the regulations for the licensure of agents for the treatment of obesity. The hormone leptin, for example, is not an effective weight-loss medication in humans, even at very high doses (111), but can normalize energy expenditure and ingestive behaviors at very low doses in weight-reduced humans (53).

Central and Peripheral Targets

Brown adipose tissue, which expends energy, is emerging as a promising target in the development of weight-loss drugs. Li Qiang focused on using peroxisome proliferator–activated receptor γ (PPARγ) deacetylation to turn white adipose tissue, which primarily stores lipid, into metabolically active brown adipose tissue. Thiazolidinediones (TZDs), such as rosiglitazone, induce "browning" in white fat, as indicated by an increase in uncoupling protein 1 (UCP1), a marker of brown fat, both in vitro and in vivo (112,113). Cold exposure increases UCP1 in white fat as well but only in the presence of the deacetylase sirtuin 1 (SirT1), suggesting SirT1's browning function may be related to the deacetylation of PPARγ, the target of TZDs. Interestingly, SirT1 was found to interact with and deacetylate PPARγ in a TZD-dependent manner. Rosiglitazone potentiates PPARγ deacetylation by SirT1, suggesting that when SirT1 is inactive, PPARγ promotes energy storage and insulin resistance in adipose cells, while active SirT1 deacetylates PPARγ in the presence of ligand to promote energy expenditure and insulin sensitivity. The therapeutic implications are that a selective PPARγ agonist may induce deacetylation and browning to promote weight loss and mitigate type 2 diabetes.

Brown fat epigenomics may offer a new way to discover therapeutic targets for obesity and type 2 diabetes, according to Evan D. Rosen. The proteins that participate in histone modification operate in one of several ways—as "writers" that add modifications, as "erasers" that remove modifications, or as "readers" that recognize modifications. All of these alterations influence the expression levels of genes (114). Cellular differentiation is governed, in part, by epigenetic changes. By analyzing genome-wide histone modifications in mouse and human cells undergoing differentiation into adipocytes at multiple time points, researchers identified two regulators of adipogenesis: promyelocytic leukemia zinc finger protein (PLZF) and serum response factor (SRF) (115). The relationship was confirmed by experiments showing that a knockdown of PLZF or SRF enhances adipogenesis (115). An epigenomic scan also showed that interferon regulatory factor 4 (IRF4) is highly expressed in mature adipocytes. IRF4 is nutritionally regulated, with higher expression in the postfasting state than in the prefasting state (116). Fat-specific IRF4 knockout mice have increased adiposity as well as dysfunctional temperature regulation in a cold environment, suggesting a link to brown adipose tissue (116). Overexpression of IRF4 in brown adipose tissue promotes the expression of thermogenic genes and weight loss in mice (116).

The central role of the brain in weight regulation suggests that weight-loss medications that target the brain may prove particularly effective. Tamas L. Horvath discussed how hunger and appetite are complex goal-oriented behaviors, which require wakefulness, the ability to locate food, decision-making regarding the pursuit of food, the physical capacity to pursue food, and then the actual intake of food. Hypothalamic neurons that express neuropeptide Y (NPY) and agouti-related protein (AgRP), but not proopiomelanocortin, are essential for feeding in adult mice. Ablation of AgRP neurons leads to a cessation of food intake and death (117,118). Selectively eliminating SirT1 from AgRP neurons in mice results in reduced food intake and leaner animals (119). Horvath and colleagues (119) found that AgRP neurons regulate reward circuitry more generally, affecting dopamine neuronal plasticity. AgRP/SirT1 knockout mice are less interested in food and more interested in novel objects, suggesting that impaired AgRP neuronal excitability uncouples behaviors motivated by food from those not related to food.

In a related talk, Hongxia Ren explored the ability of G-protein–coupled receptor 17 (Gpr17) to activate AgRP neurons in the regulation of food intake. Paradoxically, the ablation of leptin (120) or insulin receptors (121) in AgRP neurons does not alter food intake in mice. Would targeting both pathways together create a greater response? The transcription factor FoxO1, which regulates metabolism by responding to hormonal cues and is highly conserved in AgRP neurons, is inactivated by both leptin and insulin signaling (122). Ablating FoxO1 in AgRP neurons may simultaneously confer increased insulin and leptin sensitivity. In support of this idea, mice with knockout of FoxO1 in AgRP neurons display reduced food intake, protection from weight gain from a high-fat diet, and improved glucose homeostasis (122). Gpr17 is highly abundant in AgRP neurons and is a FoxO1 target. Injecting mice with a Gpr17 agonist induces food intake, while a Gpr17 antagonist (cangrelor) reduces food intake. Inhibiting Gpr17 also increases leptin sensitivity, suggesting Gpr17 may be a potential drug target for weight-loss therapies. These novel directions underline the inherent complexity of the mechanisms governing food intake and energy balance but may form the foundation for a new generation of effective antiobesity medications.

Together, these talks highlighted the rapid pace of discovery in the central and peripheral control of body weight and the possibility of new targets that can be exploited to develop safe and effective pharmacotherapy.

SUMMARY

Obesity is an increasingly prevalent chronic disease that increases the risk of developing type 2 diabetes and cardiovascular disease. Obesity results in increased morbidity, mortality, and disability and represents a public health burden. Weight loss and maintenance are physiologically resisted, rendering them clinically difficult to achieve. Modest weight loss followed by weight regain is the norm (Fig. 2). While scientific and clinical efforts in recent years have led to the identification of important mechanisms that regulate body weight homeostasis, much remains unknown. Research to uncover and dissect new biological mechanisms of weight regulation will be required. To stimulate activity toward this end, the participants at the meeting discussed unanswered and emerging basic and clinical research questions in the field of body weight regulation, the answers to which should enhance our understanding of the biology of weight homeostasis and lead to the development of therapies and approaches to enhance the treatment of obesity and prevent type 2 diabetes (Table 1).

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