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Biological Mechanisms that Promote Weight Regain Following Weight Loss in Obese Humans

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Abstract

Weight loss dieting remains the treatment of choice for the vast majority of obese individuals, despite the limited long-term success of behavioral weight loss interventions. The reasons for the near universal unsustainability of behavioral weight loss in [formerly] obese individuals have not been fully elucidated, relegating researchers to making educated guesses about how to improve obesity treatment, as opposed to developing interventions targeting the causes of weight regain. This article discusses research on several factors that may contribute to weight regain following weight loss achieved through behavioral interventions, including adipose cellularity, endocrine function, energy metabolism, neural responsivity, and addiction-like neural mechanisms. All of these mechanisms are engaged prior to weight loss, suggesting that so called "anti-starvation" mechanisms are activated via reductions in energy intake, rather than depletion of energy stores. Evidence suggests that these mechanisms are not necessarily part of a homeostatic feedback system designed to regulate body weight or even anti-starvation mechanisms *per se*. Though they may have evolved to prevent starvation, they appear to be more accurately described as anti-weight loss mechanisms, engaged with caloric restriction irrespective of the adequacy of energy stores. It is hypothesized that these factors may combine to create a biological disposition that fosters the maintenance of an elevated body weight and work to restore the highest sustained body weight, thus precluding the long-term success of behavioral weight loss. It may be necessary to develop interventions that attenuate these biological mechanisms in order to achieve long-term weight reduction in obese individuals.

Keywords

Diet; BMI; Metabolism; Adipose; Endocrine; Brain; Neural; Metabolic

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Introduction

Forty-five million Americans attempt weight loss diets each year (1). Traditional cognitive-behavioral therapy-based "lifestyle change" diets often lead to weight loss and medically significant reductions in comorbidities (2). However, up to 50% of lost weight is typically regained by 1-year follow up, with nearly all remaining lost weight regained thereafter in the vast majority of individuals (3). This almost ubiquitous weight regain is witnessed in virtually every clinical weight loss trial, including those specifically aimed at improving weight loss maintenance (4, 5). Even the most well executed and empirically driven efforts to improve the sustainability of behavioral interventions have met with little success (5, 6). Without knowledge of the factors contributing to the long-term failure of behavioral approaches, investigators are limited in their ability to improve the sustainability of these interventions.

The focus of this manuscript is on biological pressures that may contribute to weight regain in obese or formerly obese individuals following behavioral weight loss. As behavioral weight loss remains the overwhelming treatment of choice for obese individuals (1), the discussion in this manuscript addresses the prototypical obese individual living in an industrialized nation who is able to achieve short-term success via energy restrictive diets, but is unable to maintain significant weight loss in the long-term. Factors contributing to initial weight gain, such as genetic predisposition and the food environment, are not discussed; however, it is important to note that the biological pressures to regain lost weight interact with these critical factors to determine the rate and amount of weight regain for each individual (7). Nonetheless, despite large inter-individual variability in genetic and environmental influences, the consistency of weight regain following behavioral weight loss in obese individuals suggests the influence of highly potent biological mechanisms that are consistent across nearly all individuals.

Conventional thought was that human biology included homeostatic feedback mechanisms designed to regulate body weight (8, 9). The average adult gains approximately 0.5 kg per year, which tranlates to approximately 3500 kcal surplus (10-13). Given average consumption of approximately 900,000 kcal per year (10, 11), this translates into only about 0.5% discrepancy, suggesting that homeostatic regulation of energy balance is relatively tight (14). However, the recent rapid spike in obesity rates calls into question the reliability of homeostatic regulation. With evidence that human biology evolved with a preference for energy intake and storage vs. expenditure (9, 15), it was recognized that these "regulatory" mechanims may reflect the same bias (9, 15, 16). As such, some investigators have proposed that these mechanisms may be more accurately described as "anti-starvation mechanisms" rather than regulatory mechanisms (17, 18). However, evidence in this manuscript suggests that the presence of adequate energy stores does not preclude the engagement of biological factors that contribute to weight regain. Thus, "anti-starvation mechanisms" may be as much of a misnomer as "regulatory mechanisms."

Only recently have there been attempts to identify these individual biologial mechanisms and how they may contribute to weight regain. The mechanisms to be discussed include adipose cellularity, endocrine function, energy metabolism, neurobiology, and addiction-like mechanisms. It should be noted that causal connections between these factors and weight regain following behavioral weight loss remain largely untested. Thus, this manuscript was written as a theoretical article, presenting *potential* mechanisms for weight regain. The primary goal of this discussion is to promote further study of the potential causal role of these factors in weight regain and encourage the exploration of treatments that may circumvent or counter these biological mechanisms to prevent them from undermining healthy weight loss in obese individuals.

Adipose Cellularity

Excess weight gain typically leads to changes in body composition, including significant alterations in adipose cellularity. Although increases in body mass index (BMI) do not directly predict an absolute increase in body fat content (19), elevated body weight is generally associated with an increase in the diameter of fat cells (hypertrophy), as well as greater amounts of fat (triglycerides) stored within (20, 21). Most literature points to adipocyte hypertrophy as the main feature of obesity; however, alterations in adipocyte number may also be important (22, 23). Upon reaching an upward critical limit in fat cell volume, enlarged adipocytes (fat cells) secrete paracrine factors that induce preadipocyte proliferation (hyperplasia) (24-26). Thus, excess caloric intake may lead to increases in fat cell size and subsequent increases in fat cell number (20, 26, 27). Recent evidence suggests that hyperplasia may occur in overweight (but not obese) individuals (28). However, the preponderance of evidence suggests that hyperplasia occurs primarily in clinically severely obese individuals (27, 29, 30). Thus, if hyperplasia is associated with weight regain, this effect may be relegated to weight regain following weight loss in [formerly] clinically severely obese individuals, for whom returning to a lean body weight through behavioral weight loss is exceedingly difficult (31).

With behavioral weight loss, adipocyte hypertrophy decreases; however, the hyperplasia remains (20, 29, 32-35). Thus, weight loss dieting may reduce the size but not the number of fat cells. A lack of programmed cell death may be responsible for the failure of reductions in fat mass via nonsurgical means to reduce adipocyte number (20, 33). Therefore, relative to never obese individuals, weight-suppressed [formerly] obese individuals (particularly clinically severely obese individuals) may be left with a significantly greater number of adipocytes, which cannot be reduced via behavioral weight loss (34). See Table 1. Liposuction is the only known treatment able to reduce adipocyte number, but carries high complication rates (36).

It is not yet definitively known whether hyperplasia encourages weight regain in weight-suppressed individuals. There is some evidence to suggest that the presence of smaller adipocytes may encourage weight regain by decreasing the overall rate of fat oxidation and increasing the retention of ingested fuel (37-41). Normally, during times of energy deprivation, lipid (fat) stores break down triglycerides into their individuals components, glycerol and free fatty acids (42), which generate energy for the cell. However, the rate of lipolysis (fat breakdown) appears to be related to adipocyte size and cellular surface area (43); smaller cells exhibit lower rates of basal lipolysis (44). Therefore, if size-reduced adipocytes are modified to break down less and store more fat, these cells may expand and promote further proliferation. Although still speculative, there is some evidence to suggest that these cells may be predisposed to reach a particular mean size, allowing them to store similar amounts of lipid as previously formed adipocytes (25, 34). However, small adipocyte number may be sufficient to observe a clinically significant effect in only a percentage of obese (i.e., clinically severely obese) individuals.

An additional line of evidence reports higher levels of insulin in newly size-reduced adipocytes (44, 45). Insulin, which is excreted from pancreatic beta cells in response to rising levels of glucose in the bloodstream, facilitates a preferential utilization of carbohydrates to meet the cell’s energy requirements (40, 46-48). In addition, insulin inhibits lipolysis (49) and stores triglycerides in adipocytes (lipogenesis) (50). Interestingly, although insulin sensitivity seems to improve in weight-reduced individuals, fat metabolism slows, potentially in an attempt to preserve energy stores (37, 38, 49, 50). As a result of these changes in carbohydrate and fat utilization, an abnormal accumulation of triglycerides may give rise to a higher net fat cell content and elevations in body weight (37, 38, 51-53).

Adipocyte size is also correlated with plasma leptin concentrations, which have been shown to affect weight loss maintenance (54). Relative to control, formerly obese weight suppressed participants were found to have reduced fat cell volume and serum leptin levels, despite almost identical percent body fat (35). Because smaller adipocytes in formerly obese individuals may be secreting less leptin following behavioral weight loss (28, 35, 37, 55), an association between increased number of smaller adipocytes and leptin insufficiency has been proposed (28, 35, 37, 55, 56). Although leptin levels are not entirely depleted in weight suppressed formerly obese individuals, their secretions are much more attenuated relative to lean subjects who undergo caloric restriction (35, 55). Thus, with reductions in leptin secretion, heightened appetite and excess food intake may lead to weight regain (28, 54). The potential role of leptin in weight regain is further discussed below.

Endocrine Function

Leptin

Leptin levels are reduced within 24 hours of energy restriction (57) and a number of studies report greater reductions of leptin than would be expected for given losses of adipose tissue (34, 35, 58). It has been suggested that leptin's primary role is the prevention of starvation, rather than weight regulation *per se*, questioning the notion of "leptin resistance" (18). Reductions in leptin levels appear to trigger a starvation defense response, despite the persistance of abundant fat stores (57). Evidence suggests that there may be a threshold below which the "anti-starvation" action of leptin is enacted, and this threshold is proposed to increase concurrently with increases in adipose tissue (57). Thus, weight loss dieting in obese individuals may lead to leptin depletion (sub-threshold levels), despite the persistence of relatively high levels of leptin. Sub-threshold leptin levels result in reductions in metabolic rate and physical activity (14), as well as increases in hunger and food intake (59). Thus, behavioral weight loss and weight loss maintenance are accompanied by physiological attributes that resemble those of a leptin-deficient animal: lower energy expenditure, increased hunger, reduced thyroid metabolism, and diminished sympathetic nervous activity (60, 61).

Other Neuroendocrine Signals

In addition to insulin and leptin, a number of hormones secreted from the gastrointestinal tract and adipose tissue have been implicated in the modulation of appetite, food intake, energy expenditure, and body weight (62). Ghrelin, for example, induces hunger (63), while peptide YY_{3-36} (PYY) and cholecystokinin (CCK) promote satiety (64). Both increases in the orexigenic hormone ghrelin, and decreases in the postprandial satiety signals PYY and CCK, have been observed in weight-reduced individuals (65, 66). Thus, weight loss could induce a simultaneous decrease in satiety and increase in hunger, potentially encouraging formerly obese individuals to overeat and regain lost weight (58). See Table 1. Less consistently, weight loss in obese individuals has been shown to reduce thyroid hormone levels (67, 68), while hypothalamic-pituitary-adrenal (HPA) axis activity is increased (69, 70). Because thyroid hormone is implicated in increasing metabolic rate (71), decreased thyroid hormone levels may also contribute to simultaneous decreases in fat breakdown and increases in fat storage. As the HPA regulates stress-related elevations in cortisol, increases in this type of hormonal signaling can lead to increased appetite, fat accumulation and potentially, weight regain (72). Finally, catecholamine (epinephrine, norepinephrine) release, indicative of sympathetic activity, may also play a role. Weight-suppressed obese individuals show reductions in muscle sympathetic nerve activity responsible for the regulation of energy expenditure (67, 73, 74). With less circulating epinephrine and norepinephrine, lipid oxidation could be compromised due to decreased heart rate, blood

flow, and oxygen delivery to muscle tissues. As suggested, this shift in metabolic activity (stunted triglyceride mobility) may encourage fat storage and weight regain.

Energy Metabolism

Behavioral weight loss necessarily results in the loss of metabolic tissue (both fat and lean mass), resulting in reductions in energy expenditure (60, 75). Although not unequivocal (76, 77), the majority of studies report that behavioral weight loss results in significantly greater reductions in resting and total energy expenditure than would be expected for given losses in metabolic mass, suggesting "metabolic adaptation" (60, 78-82). Thus, energy expenditure during weight loss maintenance may be disproportionately reduced relative to body mass and composition, which may be largely attributable to increased skeletal muscle work efficiency (83). In fact, increases in metabolic efficiency have been reported within hours of caloric restriction, prior to any loss of metabolic tissue (84). In order to overcome this metabolic adaptation, obese individuals would need to continually reduce energy intake and maintain energy intake below that of never obese individuals at the same BMI.

An additional theory points to changes in body composition that may result from the cycles of weight loss and regain endemic to most obese individuals. There is some evidence that the fat-to-lean ratio of mass regained during weight regain is higher than that of the mass lost initially during weight loss diet (85). Thus, with each successive "weight cycle," and individual's overall body composition may begin to favor fat vs. lean mass (86). Given the higher contribution of lean vs. fat mass to energy expenditure, such increases in the fat to lean tissue ratio would lead to a decrease in metabolic rate and increase the amount of surplus energy stored (87). Weight cycling has been shown to increase lipogenic enzymes and decrease leptin in rodents (87), but a causal connection with weight regain has not been established. In humans, mostly limited cross-sectional or single-cycle data has been collected, all of which are inconclusive in regards to weight cycling and enhanced weight regain (86, 88). Some prospective studies report associations between weight cycling and lower metabolic rate (89) and weight regain (90); however, the evidence is mixed (87, 91). Thus, the potential contributions of changes in energy metabolism to weight regain remain speculative. See Table 1.

Neural Responsivity

Food intake is primarily mediated by three interactive neural systems, the *homeostatic*, *reward-related* and *inhibitory* systems. The *homeostatic system*, comprised mainly of the hypothalamus, drives eating in response to caloric need in order to maintain energy balance. Alternatively, the *reward-related system* drives eating based on the perceived reward value of food, processed primarily through dopaminergic signaling in the mesolimbic pathway. The *inhibitory system*, comprised primarily of the dorsolateral prefrontal cortex, is associated with behavioral inhibition and processes attempts to inhibit excess food intake (i.e., dietary restraint) (92). Access to sufficient sustenance is commonplace in most industrialized nations, obviating the need for most homeostatic-driven eating (93). However, the homeostatic system serves to up-regulate the reward-system to increase the perceived reward value of food in response to energy restriction, encouraging the consumption of more high- vs. low- calorie foods and weight regain (94, 95). With energy surplus, there does appear to be an attempt to down-regulate reward-related signaling, which may combine with cognitive restraint represented by inhibitory signaling (95, 96). However, considerable evidence demonstrates that reward-related signaling easily overrides restrictive homeostatic and inhibitory signaling (97), driving food intake despite regulatory signals aimed at preventing excess caloric intake (93, 97). Thus, the hierarchical supremacy of the reward-related system illustrates the same biological bias towards the intake and storage of energy

(15). Importantly, it appears as though the neural propensity to consume more high- vs. low-calorie foods persists after behavioral weight loss (54, 98), and may contribute to weight regain. Further, there is some evidence to suggest that neural changes associated with behavioral weight loss may actually *increase* the neural drive to consume high-calorie foods (54), as discussed below.

Dietary restraint and inhibitory neural responsivity are acutely increased through behavioral weight loss treatment (54, 96, 99). The typical short-term success of behavioral interventions suggests that this increase in inhibitory responsivity (dietary restraint) is *temporarily* able to overcome the neurobiological drives to consume palatable high-calorie foods. However, decreases in dietary restraint typically follow the cessation of behavioral weight loss treatment are directly associated with weight regain (100), implicating post-treatment erosion of inhibitory neural responsivity in weight regain. Recent evidence also indicates that reward-related neural signaling is activated in conjunction with inhibitory signaling (101, 102), suggesting that reward-related neural responsivity may be increased concurrently with inhibitory responsivity during behavioral weight loss treatment. Increased reward-related responsivity to food cues is seen within hours of caloric restriction (94) and nonsurgical weight loss has been shown to increase reward-related responsivity to food cues (54). See Table 1. This increase in reward-related neural responsivity likely reflects the common increased desire for “forbidden foods” in dieting individuals (103), and illustrates a potential mechanism for the eventual erosion of dietary restraint and subsequent weight regain following behavioral weight loss.

Addiction-Like Neural Mechanisms

Obesity is associated with increased preference for, and consumption of, foods high in fat and sugar (104). It has been speculated that these foods may have addictive properties, similar to those of drugs of abuse (105). Whether the clinical and diagnostic features of addiction can be applied to chronic food intake is a topic of heavy debate (106-108). Withdrawal symptoms commonly seen in addicted mice deprived of their drug of choice have been seen in mice allowed to binge on sugar solutions and then deprived of it, including teeth chattering and head shakes (105). Humans trying to cut back on high-fat and sugar containing foods report unpleasant physical and psychological sensations commonly reported by substance abusers deprived of their drug of choice, including restlessness, insatiable cravings, fatigue and poor mood (109). Self-identified refined food addicts report eating to alleviate feelings of agitation, depression, anxiety, headache, stress and fatigue, which some interpret as psychological manifestations of withdrawal (109). When shown pictures of palatable foods, food addicts identified by the Yale Food Addiction Scale (110) showed activation in the same areas (anterior cingulate gyrus and amygdala) as cocaine addicts shown pictures of crack cocaine, which is proposed to represent the neural correlates of cravings (111). Recent evidence from rodent studies indicates that obesity causes potentially permanent changes in brain reward circuitry that may underlie the cravings and anxiety associated with food withdrawal (106). It is important to note, however, that the symptoms associated with withdrawal from substances of abuse and palatable food are not indistinguishable. For instance, opiate withdrawal is often accompanied by muscle aches/cramping, increased tearing, insomnia, runny nose, yawning, diarrhea, nausea/vomiting, goose bumps and dilated pupils, none of which have been reported in humans undergoing caloric restriction (110, 112-114). Further, it is unclear how many obese individuals would qualify for a diagnosis of food addiction, if it exists.

Regardless of whether food addition *per se* exists, chronic overeating also resembles substance abuse in several additional ways, such as its continued occurrence despite medical and health consequences (115). Analogous to chronic alcohol abusers who stand at higher

risks for liver and cardiovascular disease, obese individuals are at increased risk for a number of disorders, including hypertension, diabetes and cardiovascular disease (116). As with substance abusers who typically display frequent attempts to reduce usage, US adults attempt an average of seven weight loss diets in their lifetime (1). Furthermore, rates of weight regain in weight-reduced obese individuals are very reminiscent of the high relapse rates for drug addiction (117, 118), which may relate to the rewarding aspects of the substance (food or drug) and the potential for [neural] habituation to these rewarding aspects (2, 118), discussed below.

Importantly, studies consistently show progressive increases in the amount of substance consumed in chronic substance abusers (119). Similarly, portions sizes tend to increase with the development of obesity (120). Evidence suggests that this increase in usage may be due to habituation to the rewarding aspects of the food or drug (121, 122). Reward experienced from both substances of abuse and palatable foods is thought to result from striatal dopamine (DA) release from the ventral tegmental area to the nucleus accumbens within the dorsal striatum (123). Recent evidence suggests that that chronic stimulation of the dopamine D2 receptor results in reduced striatal DA terminal density (124, 125), and downregulation of the striatal D2 receptors (125). Evidence also suggests that both substance abusers and chronic overeaters increase usage (consumption) in order to make up for this habituation-induced deficit in reward (121, 122). Thus, chronic consumption of highly palatable foods may trigger addiction-like neuroadaptive responses in brain reward circuitries that drive compulsive and chronic overeating (121, 126).

Recent evidence suggests that reductions in experienced reward also persist in weight reduced formerly obese individuals (127), potentially contributing to weight regain. Interestingly, as alluded to in the previous section, users vs. non-users still show elevated reward responsivity *to cues* (i.e., wanting) associated with drugs and palatable food (122), potentially due to superconsolidation of the initial associations between the substance of abuse and resulting feelings of pleasure (122). Thus, chronic substance users and overeaters appear to be hyper-responsive to drug/food *cues*, but hypo-responsive to drug/food *intake* (128), both of which appear to persist after periods of non-use and may encourage recidivism. See Table 1. There is also evidence to suggest that chronic substance abusers display deficits in inhibitory signaling, which may contribute to the eventual failure of attempts to abstain (129); however, it remains unclear whether this is in-born or develops as a consequence of chronic overconsumption. Nonetheless, disinhibition, or the loss of control following consumption of a small amount of the pleasurable stimuli, is endemic to both substance abusers and chronic overeaters (130). Finally, recent evidence in rodents suggests that the permanent changes in reward-related neurocircuitry resulting from chronic overconsumption may be related to overconsumption-related increases in the permeability of the blood brain barrier, allowing potentially damaging elements to enter the brain (131). However, this hypothesis remains speculative until further studies can be conducted.

Discussion

Changes in adipose cellularity and addiciton-like neural habituation result from chronic overconsumption and appear irreversable via behavioral weight loss (24, 34, 122, 129). Thus, these factors are not activated to prevent weight loss but serve to encourage preservation of highest sustained body weight, and may actually promote indefinite increases in energy storage. Alterations in endocrine function (e.g., decreases in leptin and increases in ghrelin), decreases in energy expenditure, and increases in neural responsivity to high-calorie food cues all occur within 24 hours of caloric restriction (Table 1) (57, 84, 132). Regardless of when these mechansism are activated, each has the potential to exert a [neuro]biological influence that may reduce an obese or formerly obese individual's ability

to maintain behavioral weight losses and promote weight regain at least to the individual's highest sustained lifetime weight. These influences also carry the expected weight regain promoting behavioral correlates. Weight-reduced vs. never-obese subjects report increased food craving (133), a decreased perception of amount eaten (134), decreased postprandial satiety (135) and an increased preference for calorically dense foods (136). With these additional biological influences encouraging the consumption and storage of energy, it is not surprising that weight regain following behavioral weight loss occurs at a faster rate than initial weight gain (135, 137).

These mechanisms appear not to be part of a highly sensitive homeostatic feedback system designed to regulate body weight at any particular "set point," but mechanisms either aquired via excess weight gain or enacted almost immediately via reduced caloric intake. Importantly, these mechansims operate irrespective of the adequacy of energy stores. Thus, these mechanisms may be more accurately described as anti-weight loss mechanisms, rather than anti-starvation mechansims *per se*. Regardless, these systems are engaged with very rare exception, and appear not to descriminate by sex, BMI or even genetic makeup. Thus, the consistency of the influence of these mechanisms appears to mirror the consistency of weight regain in weight reduced [formerly] obese individuals (138). Discussion of these factors illustrates the importance of obesity prevention efforts. This is particularly true for children and adolescents, where rates of obesity have seen disproportionately high increases in recent years (139).

Ultimately, the biological forces to maintain highest body weight, resist weight loss and regain lost weight appear insurmountable for most individuals attempting to lose weight through behavioral interventions (138). The presence of these biological forces may explain why relatively drastic surgical procedures (e.g., Roux-en-Y gastric bypass) are the only form of intervention for obesity demonstrating long-term efficacy. Further, it may not be a coincidence that significant changes in several of these mechanisms (e.g., endocrine function (140) and neural responsivity (141)) have been reported following obesity surgery (142). Thus, it may be necessary to circumvent at least some of these biological mechanisms in order to achieve sustainable weight loss.

It is important to note that the hypothesis presented in this paper does not propose to account for individual differences in weight gain over the lifespan. Nor does it attempt to explain the rapid increase in obesity rates in the past 30 years. These issues have been discussed at length in other published work, which are typically explained by differences in genetic makeup and changes in the food environment, respectively (143, 144). The focus of this paper was intentionally relegated to the biological mechanisms consistent across all individuals that may contribute to weight regain. Thus, the concepts discussed here do not explain obesity or individual differences in weight gain, but attempt to offer some potential explanation for the astounding consistency of weight regain following weight loss in obese or formerly obese individuals. We believe that the evidence suggests that the biological pressures discussed here would be more accurately described as pressures to sustain sufficient caloric intake to maintain homeostasis (weight stability) at an individual's highest sustained body weight, rather than to regain lost weight *per se*.

Most obese individuals are able to utilize current behavioral techniques, which have been honed through decades of research and experimentation to maximize their effectiveness, to overcome these biological pressures *for a relatively short time* (typically a few months) and lose some (typically 5-10% initial) weight (2, 4, 145). Eventually, however, these biological pressures win out, as so called "diet fatigue" sets in and individuals are no longer able to maintain the level of cognitive and behavioral discipline necessary to overcome unyielding (and potentially mounting) biological pressures to return to their highest sustained body

weight. However, we feel it vital to stress the importance of the necessary interaction between these biological pressures, genetic makeup and the food environment. Although nearly all obese and formerly obese individuals regain weight following behavioral weight loss, some do not (99, 146). Further, those that do regain lost weight, do so at different rates (5). This may be explained by a myriad of different psychological and social factors but is most likely explained by individual differences in genetic makeup and the food environment.

Part of the purpose of this review was to incite further thought and research, as several questions naturally stem from the evidence and theories presented. For example, how might the food environment moderate the effects of these responses, how long do these regulatory responses persist, and can these mechanisms be "reset" so the body defends a healthy (or even just overweight) vs. obese body weight? We would suggest that a toxic or "obesogenic" food environment, such as that currently seen in the US, is neither necessary nor sufficient for weight regain but is a very potent contributing (moderating) factor that makes weight regain much more likely. Few would argue against the notion that a toxic food environment contributes to weight gain, regardless of whether it was preceded by weight loss. However, further research may determine whether this effect is more or less strong for weight suppressed vs. never obese individuals. The evidence presented in this review seems to suggest that these biological pressures toward weight regain persist until caloric intake returns to the level it was at when the individual was at their highest maintained body weight. There is some speculation that gastric bypass (and possibly sleeve gastrectomy) surgery may "reset" some of these mechanisms so that they either do not operate to drive weight regain or at least not operate to the same extent to which they would following behavioral weight loss (147). For example, gastric bypass surgery has been shown to dramatically alter gut peptide signaling (140, 142, 148) and neural responsivity (141, 149, 150), both of which have been shown to be associated with decreased desire to eat calorically-dense foods following surgery (150, 151). Other recent evidence suggests that bypass surgery vs. behavioral weight loss results in greater decrease in circulating amino acids, which may contribute to improvements in glucose homeostasis and sustained weight loss (152). We will look to current and future research to lend support for or refute these hypotheses.

Future Directions

The weight regain promoting actions of the mechanisms discussed in this manuscript remain largely speculative, as evidence demonstrating causal relations between these factors and weight regain is lacking. Future research should seek to elucidate and quantify the contribution of each of these factors, with the goal of developing ways to circumvent those with the greatest contribtion to weight regain. One possibililty may be to identify how bariatric surgery alters some these mechanisms and attempt to replicate this action through nonsurgical means (141, 153). Other factors are likely involved and require more study, particularly the potential moderating effects of the food environment. Additional important factors may include the potential for increased drive to eat, decreased drive to be physically active, altered sympathetic/parasymphathetic tone, and altered gut microflora (154). Future work should also address the possibility that these mechansims act syngeristically to create a biological profile for which weight regain in weight reduced obese individuals is almost inevitable. Finally, future research may also look to determine how long an elevated body weight must be maintained before these biological mechanisms begin to defend that weight.

Conclusion

We have presented evidence that the likelihood of weight regain in weight suppressed obese and formerly obese individuals may be increased by a confluence of biological mechanisms,

including increased metabolic efficiency, changes in neuroendocrine signaling (e.g., decreased satiety signaling), and changes in neural responsivity to both food cues (e.g., increased reward-related or decreased inhibitory anticipatory responsivity) and food intake (e.g., decreased consummatory reward through habituation to the rewarding aspects of palatable food). These biological pressures that may undermine weight loss efforts and promote weight regain are almost immediately enacted in obese individuals attempting even modest and healthy weight reduction. Further, these mechanisms operate invariably and appear to defend an individual's highest sustained body weight. Thus, it is the opinion of these authors that these mechanisms would be more accurated describe as anti-weight loss mechanisms rather than anti-starvation mechanisms. Regardless, obese individuals face an extreme uphill battle in having to overcome powerful biological drives that appear insurmountable via behavioral interventions, illustrating the critical importance of obesity prevention efforts for normal and overweight individuals. This may be particularly pertinent to parents of overweight children, who are significantly more likely to become obese adults (155). It is our hope that future research will further elucidate these mechanisms and provide the opportunity for the development of interventions that counter these mechanisms and enable long-term behavioral weight loss maintenance.

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Highlights

- Reviews evidence of biological mechanisms contributing to weight regain after diet
- Presents original hypothesis about action of these mechanisms
- Suggests mechanisms not part of regulatory system & enacted prior to weight loss
- Suggests mechanisms enacted irrespective of energy stores
- Suggests reframing as anti-weight loss vs. anti-starvation mechanisms

Table 1

Biological Influences Contributing to Weight Regain following Behavioral Weight Loss

Biological Influence	Change with Obesity	Mechanism of Action	Change with Weight Loss	Time of Engagement	Weight Regain Promoting Action
Adipose Cellularity	↑ cell size, ↑ cell number	Secretion of growth factors by adipocytes upon reaching upward limit in size	↓ cell size, unchanged ↑ cell number	↑ cell number occurs with development of obesity	↓ lipolysis, ↑ triglyceride synthesis
Endocrine Function	↓ ghrelin, ↑ leptin, ↑PYY, ↑CCK	↓ adipocyte secretion of leptin and gut secretion of PYY, CKK; ↑ gut secretion of ghrelin	↑ ghrelin, greater than anticipated ↓ leptin, ↓PYY, ↓CCK	Within 24 h of caloric restriction	↑ hunger, ↓ satiety
Energy Metabolism	↑ energy expenditure, ↑ fat mass, ↑ lean mass	↑ metabolic tissue	↓ energy expenditure, ↓ fat mass, ↓ lean mass	↓ energy expenditure within hours of caloric restriction	↓ lean mass > ↓ fat mass, ↓fat oxidation
Neural Responsivity	↑ reward responsivity & possible ↓ inhibitory responsivity to food cues	Possible superconsolidation of positive associations with palatable food intake	Hypothalamic upregulation of ↑ reward responsivity; temporary ↑ inhibitory responsivity	Hypothalamic ↑ reward responsivity within hours of caloric restriction	↑ expected reward from food; subsequent ↓ inhibitory system activation
Addiction-Like Neural Mechanisms	↓ dopamine response to food intake	Habituation to rewarding effects; down-regulation of D2 receptors	↓ neural reward from food intake	↓ dopamine response occurs with obesity	Increased consumption to make up for deficit in reward