Energy Intake in Weight-Reduced Humans

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Abstract

Almost anyone who has ever lost weight can attest that it is harder to sustain weight loss than to lose weight. Maintenance of a 10% or greater reduced body weight is accompanied by decreases in energy expenditure to levels significantly below what is predicted solely on the basis of weight and body composition changes. This disproportionate decline in energy expenditure would not be sufficient to account for the over 80% recidivism rate to pre-weight loss levels of body fatness after otherwise successful weight reduction if there were a corresponding reduction in energy intake. In fact, reduced body weight maintenance is accompanied by increased energy intake above that required to maintain reduced weight. The failure to reduce energy intake in response to decreased energy output reflects decreased satiation and perception of how much food is eaten and multiple changes in neuronal signaling in response to food which conspire with the decline in energy output to keep body energy stores (fat) above a CNS- defined minimum (threshold). Much of this biological opposition to sustained weight loss is mediated by the adipocyte-derived hormone "leptin".

Keywords

Body Weight Regulation; Obesity; Energy Intake; Satiation; fMRI

Introduction

The strong heritability of body fatness and physiological/behavioral responses to alterations in body weight, coupled with the relative long-term constancy of body weight in adults despite substantial fluctuations in energy intake, indicate that body weight is "regulated". The average adult has been reported to gain from approximately 0.2 to 1.0 kg/year (an average of about 4000 kcal stored energy/year) (Du et al., 2009; Forouhi et al., 2009; Lewis et al., 2000); (Pietrobelli et al., 2002) despite ingesting between 800,000-950,000 kcal/year (Du et al., 2009; Forouhi et al., 2009), i.e., energy intake and output are "balanced" to within about 0.5% over time. This regulation does not preclude the increasing prevalence of obesity (Flegal, 2005; Ogden et al., 2003; Ogden et al., 2006) since even a small degree of weight

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gain (approximately 0.6 kg/year) will result in significant weight gain over time (2.0 kg/m^2/ decade for someone who is 1.75m tall and weighs 75kg).

The evolutionary basis for this regulation is defense of stored energy in service of reproductive integrity/fertility, and survival in circumstances of restricted availability of food (Leibel et al., 2001; Leibel, 2008; Prentice et al., 2008). More specifically, biological evolution would favor the defense of body fatness over that of body thinness while scientific evolution has created an environment in which any defenses against weight gain are fully engaged while defenses against weight loss are ready and waiting. The net result is a "bias" towards weight gain (Schwartz et al., 2003). In the current environment it is not infrequent for individuals to reach levels of adiposity which may in and of themselves compromise fertility or pregnancy (Mola, 2009; Yongev and Catalano, 2009). However, within the environment in which most of human evolution occurred, such opportunities would have been rare. Decreased fertility as a result of inadequate fat stores, plus inability to either sustain a pregnancy or breastfeed offspring should the food supply be even temporarily compromised, would have constituted more potent evolutionary pressures (Frisch, 1985).

Attempts to maintain a reduced body weight in are more difficult and less likely to succeed than actual dynamic weight loss (Wing and Hill, 2001; Wing and Phelan, 2005). Energy expenditure during maintenance of a reduced body weight is disproportionately (relative to body mass and composition) reduced, largely attributable to increased skeletal muscle work efficency (Goldsmith et al., 2010; Rosenbaum et al., 2003; Rosenbaum et al., 2005) in both lean and obese individuals (see Table 1). In addition, decreased sympathetic nervous system tone, circulating concentrations of leptin, thyroxine, and triiodothyronine and increased parasympathetic nervous system tone act coordinately to favor weight regain (Rosenbaum et al., 2005). The consequence of these coordinate changes in systems affecting energy output is that lean and obese subjects maintaining a 10% or greater weight loss over periods ranging from months to years demonstrate a significant decline in energy expenditure (approximately 300-400 kcal/day below that predicted from the changes in body composition) (Leibel et al., 1995; Rosenbaum et al., 2000; Rosenbaum et al., 2008a).

Based on the view that body energy stores, and in particular body fatness, are "defended" by the combined actions of systems regularly energy intake and output, one would predict that there is greater resistance to sustained weight loss (reduced-obese versus usual weight) than to weight gain (obese versus never-obese) and that individuals who are overfed following otherwise successful weight loss will gain weight more rapidly than those overfed at usual weight i.e., metabolic opposition to "weight regain" is less potent than the opposition to initial weight gain. Both of these predictions are correct. While there is little difference in 24 hour energy expenditure between lean and obese individuals who have been weight stable for at least 6 months once corrected for body composition (Cornier et al., 2004; Leibel et al., 1995; Rosenbaum et al., 1996) there is a significantly decreased 24 hour energy expenditure in sustained (> 6 months) reduced-obese compared to matched subjects at usual weight (Rosenbaum et al., 2008a). Furthermore, we have reported no significant differences in the rate of weight gain during overfeeding of lean versus obese individuals (Cornier et al., 2004; Leibel et al., 1995; Rosenbaum et al., 1996) whereas Cornier et al (Cornier et al., 2004) demonstrated significantly greater weight regain in the reduced-obese than weight gain in the never-obese subjects during overfeeding.

The decline in energy expenditure following weight reduction would have little consequence if energy intake were proportionately reduced. However, the relative long-term constancy of body weight in the setting of highly variable day to day caloric intake and activity suggests that energy intake and output are coupled such that they vary coordinately to maintain a relatively constant level of energy stores at usual body weight and vary discoordinately

during attempts to sustain reduced body weight in manner that favors weight regain. Here we discuss briefly the evidence indicating that the maintenance of a reduced body weight results in what could be termed "adaptive energy intake" that is leptin-sensitive.

Ingestive Behavior Following Weight Loss

Caloric intake, assuming that there is *ad libitum* availability of nutrients, represents the response to the sum total of multiple internal and external sensory inputs. These inputs include short-term (e.g., glucose) and longer term (e.g., leptin) internal "biological" signals regarding levels of energy stored, food anticipation (based in part on environmental stimuli such as the time of day), hunger, satiation, wanting of food, and liking of the food that is available (Finlayson et al., 2007); (Grill, 2010). These signals are then translated into how hard we will work for food, what type of food we will choose, how much we will eat, how fast we will eat, and when we stop eating (Guss and Kissileff, 2000; Hadigan et al., 1989; Kissileff et al., 1996; Kissileff and Guss, 2000; Kissileff et al., 2010; Wentzlaff et al., 1995; Yanovski et al., 1992).

Individuals maintaining a reduced body weight after non-surgical weight loss are inclined towards greater rather than diminished energy intake. Weight-reduced subjects report increased food craving (Chaput et al., 2007), a decreased perception of how much they have actually eaten (Rodriguez-Rodriguez et al., 2008), and an increased preference for calorically dense foods (Gilhooly et al., 2007). This imbalance wherein weight-reduced subjects tend to eat more calories than are needed to maintain their weight, persists even during overfeeding. Cornier et al (Cornier et al., 2004) compared pre- and post- meal ratings of hunger and satiation in never-obese and reduced-obese adults who were studied on a weight maintenance diet and again during 3 days of 50% overfeeding. While never-obese subjects demonstrated an approximate 35% decrease in pre-meal hunger ratings and 35% increase in post-meal satiety ratings during overfeeding compared to the weight-maintenance diet, reduced-obese subjects reported no changes in pre-meal hunger ratings, and only an 11% increase in post-meal satiety ratings during overfeeding. Following overfeeding, never-obese women, but not reduced-obese men or women, significantly reduced their *ad libitum* intake below weight maintenance needs. These data suggest that that reduced-obese subjects experience no change in hunger during overfeeding and only a small increase in satiation compared to very significant changes in both of these parameters in never-obese subjects. In addition, reduced-obese subjects do not appear to make any compensatory adjustments to resist sustained weight gain. While some studies have reported no significant changes in ratings of hunger or satiety in subjects who have achieved weight loss via pharmacotherapy (Valderas et al., 2010), this lack of decline in hunger or increase in satiation would, in the context of the hypometabolic state following weight loss (Chaput et al., 2007; Leibel et al., 1995), still favor the regain of lost weight.

The study of feeding behavior in humans following weight loss is, in general, complicated by a number of factors including the degree of stability of body weight at any testing period (or lack thereof), the composition and hedonic value of the diet consumed both prior to and during testing, and the difficulty in engendering the long-term successful weight reduction and subsequent weight stability that are necessary to the design of such studies. We have conducted a series of in-patient studies assessing elements of energy homeostasis in subjects studied before and after a 10% or greater weight loss and who remain on a monotonous liquid formula diet before, during, and after weight-reduction (Aronne et al., 1995; Kissileff et al., 2010; Leibel et al., 1995; Rosenbaum et al., 1996; Rosenbaum et al., 1997; Rosenbaum et al., 2000) over an approximately 9 month period. As discussed previously, lean and obese subjects maintaining a 10% or greater weight loss demonstrate a significant decline in energy expenditure (approximately 300-400 kcal/day below that predicted from

the changes in body composition) (Leibel et al., 1995; Rosenbaum et al., 2000; Rosenbaum et al., 2008a).

In a subset of initially obese subjects from this population, we found that despite the significant decline in energy expenditure in weight reduced subjects, actual meal sizes and numbers of calories required to achieve satiation are increased relative to rates of energy expenditure (i.e. subjects consume a significantly greater fraction of total daily energy expenditure at a single meal during reduced weight maintenance compared to the same subject at their usual weight), and the perception of how much food has been consumed are significantly diminished following weight loss (Kissileff et al., 2010). The delayed satiety and failure to decrease energy intake following weight loss are even more striking when one considers that subjects reported decreased "liking" of the monotonous liquid formula diet before their test meals following weight loss (Kissileff et al., 2010) (see Table 2). They consumed just as much of the formula despite liking it less, in contrast with subjects on a hedonically more enticing " *ad libitum* diet who report greater likeability of foods following weight loss (Cameron et al., 2008). It is important to note that liking was not different after they had eaten the food, but was reported to be lower before they ate it. Consequently, the liking, before eating, should be considered an overall attitude towards the food they were maintained on, rather than a specific response to the meal itself when it was consumed.

The behavioral changes favoring weight regain after weight loss are not reciprocated by a similar decline in ingestive behavior following weight gain. There is an asymmetry of control of energy intake such that when given open access to food there is a greater increase in energy intake following weight loss than decrease following weight gain. In contrast, Jebb et al (Jebb et al., 2006) reported that there was a highly variant and not overall significant changes in subsequent energy intake once overfeeding stopped.

Neuronal Activity Following Weight Loss

Brain regions involved in the regulation of energy intake have been identified largely through physical and, more recently, molecular lesioning of relevant CNS pathways (Gao and Horvath, 2007), as well as via pharmacological and electrophysiological manipulation (Berthoud and Morrison, 2008; Gottfried et al., 2003; Shizgal et al., 2001; Zheng and Berthoud, 2008). These regions are interconnected, receive multiple stimulatory and inhibitory inputs from gut peptides, GABA'ergic and dopaminergic neurons, short-term (e.g., GLP1) and longer term (e.g., leptin or adiponectin) signals of energy stores. (There are a number of excellent reviews of the molecular and biochemical physiology of these tracts and molecules (Batterham et al., 2007; Berthoud and Morrison, 2008; Gao and Horvath, 2007; Gottfried et al., 2003; Hohmann et al., 2000; Jo et al., 2005; LeMagnen, 1992; Shizgal et al., 2001; Zheng and Berthoud, 2008); a detailed description is beyond the scope of this manuscript.)

Functional magnetic resonance (fMRI) signals obtained as subjects are shown food (and non-food) items, indirectly reflect neuronal activity (using blood oxygenation as an index of blood flow) in brain regions mediating vegetative as well as hedonic and executive responses to food (Rosenbaum et al., 2008b). Using fMRI, we have examined obese subjects before and after a 10% weight loss using the same in-patient protocol and liquid formula diet described above.

Areas of the brain were more engaged in response to food vs. non-food visual cues prior to weight loss included regions associated with metabolic, autonomic, and neuroendocrine aspects of energy homeostasis (hypothalamus), emotional control of food intake (amygdala, parahippocampal gyrus, and cingulate gyrus), integrative cognitive control functions (hippocampus, middle frontal gyrus, inferior parietal lobule, fusiform gyrus, and

supramarginal gyrus), and motor planning (precentral gyrus) (Augustine, 1996; Beauchamp and Martin, 2007; Cota et al., 2006; Gao and Horvath, 2007; Killgore et al., 2003; Killgore and Yurgelun-Todd, 2007; Smith et al., 2009; Stephan et al., 2003; Tindell et al., 2006). Brain areas that were more active in responsive to visual food vs. non-food cues following weight loss included the limbic and reward systems (brainstem, culmen, ventral tegmental areas, and globus pallidus) as well as systems mediating aspects of executive and decision-making functions in the prefrontal cortex (inferior frontal gyrus, middle frontal gyrus, and lingual gyrus) and middle temporal gyrus (Augustine, 1996; Beauchamp and Martin, 2007; Gao and Horvath, 2007; Killgore et al., 2003; Killgore and Yurgelun-Todd, 2007; Smith et al., 2009; Stephan et al., 2003; Tindell et al., 2006). FMRI and positron emission tomography (PET) scan studies have shown that some of these same brain areas have been shown to be involved in the neuronal activation "signatures" in response to food of individuals who are successful at sustaining weight loss (DelParigi et al., 2004; DelParigi et al., 2007; Le et al., 2007) and individuals who are subjected to a prolonged fast (Delparigi et al., 2002; Wang et al., 2004).

Taken together, these patterns of decreased or increased neuronal activity during reduced weight maintenance suggest that the maintenance of a reduced body weight is accompanied by changes in the affective response to and rewarding properties of food, coupled with decreased "restraint" (emotional and cognitive control) (Rosenbaum et al., 2008b). These changes in neuronal activity are consistent with the increased wanting and delayed satiation noted in behavioral studies (see **Tables** 2 **and** 3).

The hypothalamus is of particular interest in these neuroimaging studies. As discussed below, it appears that many of the adaptive changes in thermogenesis and energy intake that oppose reduced weight maintenance are "reversed" by the administration of exogenous leptin (Kissileff et al., 2010; Rosenbaum et al., 2005; Rosenbaum et al., 2008b). The hypothalamus is the brain area with the highest rate of leptin uptake (Ziylan et al., 2009) and the arcuate nucleus of the hypothalamus contains the highest density of leptin receptors (Myers et al., 2008). Outflow tracts from the hypothalamus project to most, if not all, of other brain areas expressing the leptin receptor (Myers et al., 2008).

Hypothalamic nuclei and areas that are associated with regulation of energy balance include the arcuate, ventromedial, dorsomedial, paraventricular nuclei and lateral hypothalamic area. Neurons located in these regions produce molecules that stimulate or inhibit feeding behavior. The hypothalamus has afferent and efferent connections to the brainstem, midbrain, amygdala, hippocampus, and cortex, which, if selectively lesioned or stimulated, result in predictable alterations in feeding behavior (Meister, 2007). The observation that there is a net decrease in hypothalamic activity following weight loss, despite the fact that the hypothalamus contains neurons that mediate both hunger and satiety is consistent with studies demonstrating that in the basal state, the hypothalamus essentially functions as a catabolic "brake" on energy homeostatic systems that are otherwise biased towards weight gain (Schwartz et al., 2003). The hypothalamic restraints on metabolism and behavior that favor weight regain essentially prevents the engagement in constant unrestricted foraging behavior at the expense of reproductive integrity. In the weight-reduced state a decrease in hypothalamic activity would therefore, essentially "release" the brake with a net shift towards greater anabolism and decreased catabolism. The finding that overall hypothalamic activity in response to food cues is diminished in low leptin states (i.e., following weight loss) provides further support for this mechanistic view of the restraining role of the hypothalamus in energy homeostasis.

The role of leptin

The molecules that are capable of influencing ingestive behavior/energy expenditure number well over 50, and that number continues to grow. The cells in which these molecules are expressed (as well as adjacent microglia), and the connections among these cells, constitute a complex nexus that mediates what is apparent physiologically as the regulation of body weight. This nexus integrates short- (e.g. gut-derived hormones, glucose) and longer- (e.g leptin, insulin, FFA) term signals related to energy homeostasis (Korner et al., 1999; Korner et al., 2001; Korner and Aronne, 2003) (Schwartz et al., 2000). The hormone leptin, produced by adipose tissue in proportion to adipocyte volume and total fat mass, is clearly a central "player", but definitely not the only one, in systems regulating energy homeostasis. Leptin, along with other molecules, provides a signal to the brain - primarily via regions of the median eminence/arcuate nucleus and brain stem in which the blood brain barrier is "open" - regarding the status of energy stores (predominantly fat) (Oldendorf, 1981). Signals originating in leptin-sensitive brain regions and spreading throughout the brain influence neuroendocrine functions, autonomic efferents, and food-related behaviors (Korner et al., 1999; Korner et al., 2001; Korner and Aronne, 2003; Myers et al., 2008).

We, and others, have hypothesized that the major function of leptin is to signal CNS tracts regulating energy intake and expenditure that energy stores are below a critical level (for that individual). This "threshold" is determined by genetic, developmental and extant metabolic circumstance. A decline in circulating/CNS leptin concentrations below this critical level provokes "opposition" by energy homeostatic systems designed to "correct" the relative hypoleptinemia by increasing somatic fat stores (Ahima et al., 1996; Leibel, 2002). The physiological/behavioral responses to ambient leptin are, as predicted by the threshold model, highly asymmetrical and consistent with the observation that responses of energy expenditure and intake to elevations of circulating leptin - due either to obesity or exogenous administration - are minimal (Heymsfield et al., 1999). Based on this model, we hypothesized that restoring circulating leptin concentrations to pre-weight loss levels in humans who were in a state of relative leptin-deficiency as a consequence of weight loss would lead to changes in behaviors related to energy intake similar to those seen after leptin restoration in congenitally leptin-deficient animals and humans.

As predicted, the administration of "replacement doses" of exogenous leptin to subjects maintaining a 10% weight reduction reversed both the hypometabolism and the declines in satiation and perception of the quantity food eaten (Kissileff et al., 2010 ; Rosenbaum et al., 2005) (see **Tables** 1 and 2). Similarly, administration of exogenous leptin to weight-reduced subjects resulted in reversal of most of the changes that occurred in neuronal activity detected by fMRI (Rosenbaum et al., 2008b) (see **Tables** 1-3). These findings are consistent with the hypothesis that the brain perceives the weight-reduced state as one of relative leptin deficiency with resultant predictable changes in energy expenditure and behavior related to energy intake that favor the regain of lost weight. Of note, however, leptin did not reverse all of the alterations in behavior or in neuronal activity that were observed following weight loss. For example, weight-reduced subjects still did not like the monotonous formula diet, regardless of whether they received leptin or placebo (Kissileff et al., 2010) (see Table 2) and there was no significant effect of leptin administration on the reduction in activity of brain areas mediating taste sensitivity (globus pallidus and precentral and supramarginal gyri) that occurred as a result of weight loss (Rosenbaum et al., 2008b) (see Table 3).

The leptin-sensitive nature of the bioenergetic, behavior and neuronal activity changes that occur following weight loss is consistent with those occurring in congenitally leptin-deficient humans and rodents (Farooqi et al., 1999; Farooqi et al., 2002; Maclean et al., 2004; MacLean et al., 2006; Schwartz et al., 2000; Schwartz, 2001), who demonstrate

decreased energy expenditure and satiation, and increased hunger. Administration of exogenous leptin to congenitally leptin-deficient subjects reverses both the hypometabolism and hyperphagia that characterize that state (Williamson et al., 2005).

Conclusion

Our data suggest that the weight-reduced state is one of relative leptin deficiency, characterized by leptin-mediated behavioral and neuronal activity responses that favor energy conservation and increased food consumption. This bivalent defense of body weight, which creates the optimal circumstances for weight regain, makes evolutionary sense, but understandably defeats most therapeutic efforts against obesity. The physiological responses to maintenance of a reduced body weight should be regarded as important targets for "weight maintenance" as opposed to "weight loss" pharmacotherapy. The relevant molecules and their effective concentrations may be quite different for each of these two highly desirable therapeutic goals.

Acknowledgments

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Table 1

Effects of maintenance of a reduced body weight with and without leptin replacement on energy expenditure (Rosenbaum et al., 2005)

Phenotypes	Effect of Weight Loss	Effect of "Replacement" Leptin after Weight Loss
Energy expenditure per unit metabolic mass	Decreased, mainly due to decreased energy expended in physical activity and increased skeletal muscle work efficiency	Reversed
Neuroendocrine axes	Decreased circulating concentrations of bioactive thyroid hormones.	Reversed
Autonomics	Decreased SNS tone Increased PNS tone	Reversed Unaffected

Table 2

Effects of maintenance of a reduced body weight with and without leptin replacement on energy intake (Rosenbaum et al., 2005)

Feeding Behaviors	Effect of Weight Loss	Effect of "Replacement" Leptin after Weight Loss
Hunger	Possible small increase	Reversed
Satiety	Decreased	Reversed
Perception of how much food eaten	Decreased	Reversed
% total daily energy expenditure consumed at a single meal	Increased	Reversed
"Liking" of monotonous formula diet	Decreased	Unchanged

Table 3

Changes in neuronal activity following weight loss by fMRI and comparison of the same areas during administration of leptin or placebo in weight-reduced subjects (Rosenbaum et al., 2008b). Most of the changes in brain activity in response to food versus non-food cues following weight loss are "reversed" by the administration of "replacement" doses of leptin

Brain Region	Relative activity prior to weight loss versus during reduced weight maintenance	Relative activity in weight-reduced subjects receiving placebo or leptin
Hypothalamus	Usual Weight > Weight Loss	Leptin > Placebo
Cingulate Cortex	Usual Weight > Weight Loss	Leptin > Placebo
Caudate	Usual Weight > Weight Loss	*No significant difference*
Precentral Gyrus	Usual Weight > Weight Loss	*No significant difference*
Supramarginal Gyrus	Usual Weight > Weight Loss	*No significant difference*
Inferior Parietal Lobule	Usual Weight > Weight Loss	*No significant difference*
Amygdala	Usual Weight > Weight Loss	*No significant difference*
Brainstem	Weight Loss > Usual Weight	Placebo > Leptin
Middle temporal gyrus	Weight Loss > Usual Weight	Placebo > Leptin
Inferior frontal gyrus	Weight Loss > Usual Weight	Placebo > Leptin
Lingual gyrus	Weight Loss > Usual Weight	Placebo > Leptin
Insula	Weight Loss > Usual Weight	Placebo > Leptin
Ventral tegmental area	Weight Loss > Usual Weight	Placebo > Leptin
Globus Pallidus	Weight Loss > Usual Weight	Placebo > Leptin
Superior temporal gyrus	Weight Loss > Usual Weight	Placebo > Leptin