Published in final edited form as:
Cell Metab. 2014 October 7; 20(4): 565–572. doi:10.1016/j.cmet.2014.09.002.

A missing link in bodyweight homeostasis: The catabolic signal of the overfed state

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Abstract

Mammals regulate fat mass, so that increases or reductions in adipose tissue mass activate responses that favor return to one's previous weight: A reduction in fat mass activates a system that increases food intake and reduces energy expenditure, and conversely, overfeeding and rapid adipose tissue expansion reduces food intake and increases energy expenditure. With the identification of leptin nearly two decades ago the central circuit that defends against reductions in body fat was revealed. However, the systems that defend against rapid expansion of fat mass remain largely unknown. Here we review the physiology of the overfed state and evidence for a distinct regulatory system, which unlike the leptin-mediated system, we propose primarily measures a functional aspect of adipose tissue and not total mass *per se*.

In recent decades, mean body mass of populations in developed countries has increased, with the largest proportional increases occurring in individuals with the greatest weight (Flegal et al., 2012). However, most individual adults – irrespective of level of adiposity – maintain a relatively stable weight over long periods of time gaining or losing only a couple of pounds in any given year despite consumption of a million or more calories, suggesting that body mass is physiologically regulated (Passmore, 1971, 1982). Neumann at the beginning of the 20th century noted the remarkable stability of his own weight over more than a year, despite no conscious effort to balance energy intake with expenditure (Neumann, 1902). He inferred that beyond short term hunger and satiety signals, humans defend body mass against large perturbations and argued that the body compensates for excess caloric intake by increasing energy expenditure in the form of heat (a process which he termed "luxusconsumption"). Experimental evidence for such a system began to emerge

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in the middle of the 20th century with studies in both humans and rodents revealing that perturbations in weight lead to metabolic responses, particularly feeding responses, that favor returning to a previous stable weight.

The physiology of the weight-reduced state

To successfully study the effects of weight perturbations in humans requires control of food intake and careful monitoring to limit energy expenditure. Weight perturbation studies are challenging to perform because the responses alluded to above tend to cause a return to previous weight. To ensure compliance, especially with eating regimens, requires long-term monitoring, typically housing subjects for months in clinical settings in which metabolic measurements can be made. Keys, Brozek and their colleagues performed the first such studies, investigating the metabolic adaptation of lean, healthy conscientious objectors to the Second World War. By limiting food intake of study subjects until nearly all fat mass was lost, Keys and colleagues were able to measure the metabolic effects of reduced fat mass (University of Minnesota. Laboratory of Physiological Hygiene. and Keys, 1950). In this weight-reduced state, metabolic rate adjusted for body surface area and physical activity were reduced while subjective measures of hunger were markedly increased. Keys et al. established that in response to severely reduced fat mass in lean individuals, metabolism and behavior are modified to favor weight gain and restoration of previous weight. While the data were compelling, the extreme degree of weight/fat loss and the subjects all being young, lean healthy men limited the broader applicability of their findings. The study did not address whether more modest reductions in fat mass would cause reductions in energy expenditure and increase hunger, and it left open the question of whether obese and lean individuals respond differently to weight loss.

To investigate the effects of more modest weight loss in both obese as well as lean individuals, several inpatient studies were performed beginning in the 1980’s. The response to moderate weight loss mirrored the effects seen by Keys, and were surprisingly the same in obese and lean subjects (Leibel and Hirsch, 1984; Leibel et al., 1995). In both obese and lean individuals who maintained either a 10% or 20% reduced body mass, energy expenditure and behavior were altered in ways that favored restoration of previous weight (Rosenbaum et al., 2008b; Rosenbaum et al., 2003). Weight reduction (see Figure 1) lowered energy expenditure (EE) 15–20% below what could be accounted for by changes in body mass and composition, and increased hunger. These changes were also associated with reduced circulating concentrations of thyroid hormones, reduced sympathetic tone, and increased work (i.e. chemomechanical) efficiency of skeletal muscle (Rosenbaum et al., 2005). These metabolic adaptations do not subside over time, even if weight loss is maintained for years (Rosenbaum et al., 2008a), yet they are rapidly reversed if weight is regained. A meta-analysis of data from several weight loss studies also found that in formerly-obese patients who successfully maintain a reduced body weight there is a sustained reduction in metabolic rate (Astrup et al., 1999). Because lower resting metabolic rate predicts future weight gain (Ravussin et al., 1988), the metabolic response to weight loss is one that strongly favors weight regain. A minority of clinical studies have not detected a reduced energy expenditure associated with reduced fat mass, but the ability of these studies to detect significant differences may have been compromised by the sample

size and by not housing patients on a clinical research center for the duration of the studies (Amatruda et al., 1993; de Peuter et al., 1992).

However, weight reduction of rodents by food-restriction has consistently revealed an adaptive response that favors restoration of previous body fat similar to the human inpatient studies. Diet-induced obese (i.e. fed a high fat diet) and never-obese (i.e. fed a low fat diet) male mice that are weight-reduced to 20% below their initial body mass by hypocaloric feeding, have significantly lower energy expenditure (adjusted for body mass and body composition), increased food seeking behavior, and lower circulating thyroid hormone concentrations than never weight-reduced control animals (Ravussin et al., 2011). Not surprisingly, these weight-reduced animals rapidly regain lost weight once food deprivation is lifted (Ravussin et al., 2012). However, they never "overshoot;" rather, they gain fat mass to match the adiposity of *ad libitum* fed control animals ((Levin and Keesey, 1998) and reviewed in (Keesey and Hirvonen, 1997)). These observations suggest a system exists that also regulates the upper limit of fat mass.

The physiology of the overfed/weight-augmented state

During the 1960's, in studies that in many ways were the reciprocal of Keys' work, Sims and his colleagues overfed young male prisoners so that they gained and maintained weight (mean weight gain of 16.2kg) for more than 10 weeks, a condition they termed "experimental obesity". In response to an increase in body weight, appetite decreased and energy expenditure increased when compared to men of matched adiposity who were not overfed and weight augmented (Sims et al., 1973). As Sims noted, this response favored the loss of fat mass and the return to their original "pre-obese" body weight. Although the magnitude of changes in energy expenditure reported in the Sims studies have been debated (Sims et al., 1973), long-term inpatient studies confirmed that overfeeding and weight gain increase energy expenditure and reduce food intake in both lean and obese individuals (Leibel et al., 1995). In response to a 10% gain in body mass through increasing food intake, weight-stable lean and obese individuals increased energy expenditure and reduced muscle work efficiency (Rosenbaum et al., 2003).

Directly mirroring the human response to overfeeding, animals become hypermetabolic following periods of caloric excess. Overfeeding rodents through gastric feeding tubes or daily gavage augments fat mass and leads to a graded decrease in voluntary feeding (Cohn and Joseph, 1962), and an increase in energy expenditure (Rothwell and Stock, 1979). When overfeeding is stopped, animals eat fewer calories and expend more energy than *ad-libitum* fed controls until they reach the weight of never-overfed animals (Cohn and Joseph, 1962). Thus, complementary responses to the weight-reduced or - augmented state are consistent with the existence of homeostatic mechanisms that favor stability of fat stores in mammals.

Lipostatic model of weight regulation

Hetherington and Ranson (Hetherington and Ranson, 1940) and subsequently Brobeck and colleagues (Brobeck, 1957) ablated regions of the rat hypothalamus in functional neuroanatomical mapping studies. The nominally discrete lesions in the region of the ventral medial hypothalamus (VMH) induced responses similar to those observed in Keys' subjects:

increased food seeking behavior, hyperphagia and a reduction in metabolic rate. With free access to food, the VHM-lesioned rats rapidly became obese (Hetherington and Ranson, 1940). These animals behaved as if they were starved. Within hours of lesioning, animals were hyperphagic and quickly began to gain weight. While there was variation in the degree of hyperphagia and the rate of weight gain depending on the size and precise location of the lesion, all of the VMH lesioned animals became obese and subsequently defended (in response to food restriction) higher body weights. Conversely, electrical stimulation of the VMH inhibited food intake and induced weight loss (Hoebel and Teitelbaum, 1962).

In contrast to VMH damage, lesions to the lateral hypothalamus (LH) caused aphagia; these lesioned rats required special feeding protocols to keep them alive until spontaneous food intake was restored (Brobeck, 1957). Conversely, stimulation of this same region induced feeding behavior. Although there was variation in the quantitative responses, the qualitative effects were consistent across experiments, and magnitude correlated with lesion size (Anand and Brobeck, 1951).

These studies were interpreted to indicate that body weight is regulated by processes in which the hypothalamus “senses” weight via a “satiety center” located in the VMH, and maintains feeding by an “appetite center” in the LH. The identity of the signals sensed by the VMH remained a source of speculation for several decades. Mayer proposed that the weight-regulating signal was glucose or a glucose metabolite (Mayer, 1953), while Brobeck suggested that hypothalamic temperature, as a reflection of metabolic rate, was the central mediator (Brobeck, 1960). Kennedy, however, formulated a “lipostat” model of weight regulation in which he argued that an adipose tissue derived metabolite provided a measure of fat mass sensed by neurons in the VMH and the LH. He postulated that VMH-lesioned animals were insensitive to its effects (Kennedy, 1953b). He later suggested that such an adipocyte-derived signal might be a hormone (Kennedy, 1963). Woods and Porte subsequently proposed that fat mass was indeed sensed by the VMH but indirectly by circulating insulin concentrations which provided a measure of adipose tissue mass not derived from fat *per se* (Leibel, 1977; Porte and Woods, 1981).

Parabiosis experiments – in which animals are surgically joined to each other permitting exchange of circulating factors and cells (approximately a 3–5% exchange of blood per minute) – provided direct evidence for a circulating “satiety” signal. In a seminal series of parabiosis studies, in which rats with hypothalamic lesions were surgically joined to control animals, Hervey demonstrated that the circulation of obese VHM-lesioned animals contained a strongly anorexic/catabolic circulating factor(s). When parabiosed to VHM-lesioned animals, unlesioned rats in these studies markedly reduced food intake and lost weight, leading many to starve to death (Hervey, 1959)(see Figure 2).

Leptin as the regulatory signal of the weight-reduced state

Working at the Jackson Laboratory, Coleman recognized the similarity between VHM-lesioned rats and mice segregating for the autosomal recessive *obese (ob)* or *diabetes (db)* alleles. He performed parabiosis experiments with paired combinations of control lean and mutant *obese* and *diabetes* animals. He found that the effect of *diabetes* animals on a

control, parabiont mirrored the effect of VHM-lesioned rats, causing anorexia, weight loss and in some instances death from inanition (Figure 2). In contrast, the *obese* mice rapidly lost weight when parabiosed with either control or *diabetes* animals. Coleman concluded that *obese* mice lacked a circulating "satiety factor" and that *diabetes* mice lacked the ability to sense this factor. He proposed that the *obese* mice harbored a mutation in the factor or pathway required for its production and that *diabetes* mice were genetically deficient in its receptor. In the mid-nineties, the *obese* and *diabetes* mutations were mapped genetically, leading to the cloning of leptin (*Lep*) (Zhang et al., 1994) and its receptor (*Lepr*) (Chen et al., 1996; Chua et al., 1996; Lee et al., 1996).

Consistent with Coleman's hypothesis, leptin (the protein product of the *obese* gene) is an adipocyte-derived hormone that circulates at concentrations proportional to fat mass in weight stable rodents and humans (Leibel, 2008). Also in support of Coleman's hypothesis, the leptin receptor is highly expressed in the VMH (and elsewhere in the hypothalamus). Physiologic experiments confirmed a leptin-leptin receptor axis as providing a means for the periphery to communicate the size of fat stores to the central nervous system. Circulating concentrations of leptin decline rapidly in response to reduced body fat and food intake, providing a dynamic measure of existing fat stores and acute changes in energy balance (Ahima et al., 1996).

The relevance of the leptin axis to energy homeostasis in humans was quickly established. O'Rahilly and colleagues identified several obese children who were homozygous for inactivating mutations in leptin (Montague et al., 1997), and Clément and her coworkers described individuals with obesity due to leptin receptor mutations (Clement et al., 1998). Humans homozygous for these mutations are extremely hyperphagic with a phenotype that closely parallels those of the *obese* and *diabetes* mice.

Consistent with its role as a signal that mediates metabolic/behavioral responses to the weight (fat)-reduced state, leptin administration reverses many of these consequences of weight loss. Leptin administration to calorically restricted rodents with reduced circulating concentrations of leptin, increases energy expenditure to pre-weight loss or pre-fasted levels (Doring et al., 1998) and similarly reverses starvation-induced changes in gonadal, adrenal, immune and thyroid function (Ahima et al., 1996; Korner et al., 2001). Similarly, in humans, leptin reverses metabolic and behavioral changes that result from diet-induced reductions in fat mass; it increases energy expenditure, sympathetic tone, and thyroid hormones, while reducing hunger in obese and lean subjects who maintain a reduced body weight (Leibel et al., 1995; Rosenbaum et al., 2005; Rosenbaum and Leibel, 2010; Rosenbaum et al., 2002; Rosenbaum et al., 2008b). This ability to reverse metabolic phenotypes after weight loss, and its action on neurons central in the defense against reduced fat mass, established leptin as a key metabolic hormone in the defense against reduced fat mass: A reduction in the circulating concentration of leptin activates – primarily through the CNS - the metabolic and behavioral responses that favor weight regain (Ahima et al., 1996; Rosenbaum et al., 2005; Rosenbaum et al., 2002). Much effort is now focused on mapping the neuronal circuits responsible for leptin's actions (Myers and Olson, 2012; Vong et al., 2011).

Leptin is not the regulatory signal of the overfed/weight-augmented state

Kennedy originally imagined a single signal that would protect against large alterations in fat stores, responding to both caloric restriction and overfeeding (Kennedy, 1953a). Leptin has proven to be the critical signal of the weight-reduced state; as noted, decreased circulating concentrations of leptin activate central systems that increase feeding behavior and the efficiency of energy utilization (Kelesidis et al., 2010). However, despite initial predictions (and the naming of the hormone for the Greek word for “thin” or “fine”: *leptos*), leptin does not appear to be the signal that limits excess fat expansion.

In contrast to the ability of leptin to reverse many of the metabolic and endocrine effects of relative (i.e. weight reduced, fasted) or absolute leptin deficiency (i.e. genetic mutations) (Leibel, 2002), increases in circulating leptin do not mimic the overfed response. When rodents or humans at usual or increased weights are administered physiological doses of leptin they show minimal metabolic response (Mackintosh and Hirsch, 2001). Even supraphysiological doses of leptin (i.e. 10-fold elevations of plasma leptin concentrations) caused only modest weight loss (Heymsfield et al., 1999). Similarly, in rodents, pharmacological doses of leptin, which increase serum concentrations a thousand fold causes a modest and temporary reduction in food intake that is subject to rapid tachyphylaxis (Faouzi et al., 2007). This is in contrast to the effects of the overfed/weight-augmented state in which voluntary food intake is reduced and energy expenditure increased. These observations also suggest that the profound anorexia and weight loss seen in control animals parabiosed to either VMN-lesioned rats or *diabetes* mice is not simply due to hyperleptinemia but must require some other factor or set of factors.

The relative lack of response to exogenous leptin and high endogenous concentrations in obese individuals has been termed “leptin resistance” (Myers et al., 2012a). However, the metabolic/behavioral responses to leptin repletion following weight loss and/or fasting, even in obese individuals, suggest that leptin’s major physiological role is related to signaling body fat loss, rather than expansion. Furthermore, the apparent resistance or lack of effect of high concentrations of leptin seen in lean individuals (Heymsfield et al., 1999), indicates that obesity *per se* does not cause resistance to leptin action (Myers et al., 2012b). An asymmetric model of leptin function has been proposed in which decreased/low concentrations cause a strong anabolic response but increased/high concentrations cause only a relatively small catabolic response (Leibel, 2002). However, the fact that overfeeding leads to reduced food intake and increased energy expenditure - in lean and obese rodents and humans - suggests that there is a regulatory system that protects against rapid and excess fat expansion which is distinct from leptin.

Characteristics of an afferent catabolic signal that regulates the overfed/weight-augmented response

As outlined below, we infer from published data several characteristics of this putative catabolic factor that limits weight gain during periods of overfeeding. The molecule: (1) is elevated in the circulation of overfed animals, (2) requires intact leptin signaling for its effects (3) acts in both lean and obese individuals and (4) requires central integration and an

intact ventral medial hypothalamus. We further hypothesize that this catabolic signal originates from adipose tissue and is proportional to a functional aspect of the tissue. For simplification, we will refer to a single afferent "catabolic factor" produced in the overfed, weight-augmented state, but there may indeed be several factors that contribute to the metabolic effects of overfeeding. The term "weight-augmented" refers to an increase in weight that occurs through eating more than would voluntarily be eaten (i.e. overfed/force fed). Thus, both lean and obese individuals can be weight-augmented.

Catabolic signal circulates

Evidence that a circulating factor mediates the catabolic response to overfeeding derives most compellingly from parabiosis experiments. In the 1980s, Nishizawa and Bray studied the effects of overfeeding in parabiosed rats (Nishizawa and Bray, 1980). Consistent with the presence of a catabolic circulating factor in overfed/force fed animals, the parabiotic partner of overfed animals reduced food intake and after two weeks weighed less and had reduced fat mass than control parabiotic animals (Figure 2). Harris and colleagues confirmed the catabolic effect of parabiosing an overfed rat with one fed *ad libitum* (Harris and Martin, 1984).

In overfed animals, once the over-feeding is stopped and animals are given *ad-libitum* access to food, they remain hypophagic and even aphagic for up to several weeks, losing weight until they reach the weight of never-overfed controls (Cohn and Joseph, 1962). In contrast to the system that defends against reduced fat mass in which a reduction of circulating leptin is sensed and activates a central anabolic response, in overfed/weight-augmented animals, parabiosis data suggest that increases in the circulating concentrations of a catabolic factor results in weight loss (Harris and Martin, 1984; Nishizawa and Bray, 1980).

The catabolic signal action requires leptin

If the same molecule(s) is responsible for anorexia observed in parabiotic partners of VMN-lesioned, *diabetes* and overfed animals, then the catabolic molecule produced in the overfed state while distinct from leptin also requires central leptin signaling, i.e. the anorectic factor in the circulation of leptin receptor-deficient *diabetes* mice does not lead to severe anorexia in *diabetes* mice as it does in parabiotic partners of *diabetes* mice with intact leptin signaling. Consistent with this hypothesis, overfed obese Zucker rats (deficient in the *leptin* receptor*)* do not reduce caloric intake or lose weight once permitted to eat ad libitum (Harris and Martin, 1990). In contrast, similarly overfed control rats reduce their caloric intake, losing weight until they reach a body mass of never overfed animals (White et al., 2010). What is not clear is whether elevated (in proportion to fat mass) leptin concentration is required for the effects of a catabolic factor produced in the weight-augmented state. Nonetheless, that low leptin signal would predominate over any overfed signal makes evolutionary sense; the consequences of insufficient fat stores – infertility and potential starvation and death if food becomes scarce – are generally more consequential than excess fat stores. Hence, it is not surprising that a starvation signal - low [leptin] - predominates over any anorexic signal from an overfed/weight-augmented animal.

Catabolic signal regulates metabolism in lean and obese individuals

Although intact leptin signaling is required for the overfed response, obese individuals with intact leptin signaling do have a catabolic response to overfeeding. Indeed as discussed above, the catabolic response of increased energy expenditure and reduced food intake is comparable in overfed lean and obese individuals (Leibel et al., 1995). Furthermore, overfeeding rats until they become obese does not diminish the anorectic response once they are permitted to eat ad libitum. These observations suggest that identifying the catabolic factor and its downstream targets could provide effective therapies for obesity.

The parameters that might regulate release of a catabolic factor

Kennedy's lipostatic model of body weight regulation predicts that an afferent catabolic factor is produced in proportion to adipose tissue mass. One possibility is that the catabolic factor is produced and released in a manner analogous to leptin. By mechanisms that remain obscure adipocytes measure their lipid content and release leptin in proportion triglyceride stores (Zhang et al., 2002). That "system" could be used to similarly regulate the release of a catabolic factor.

Alternatively, the afferent catabolic factor may be released in response to a "functional" aspect of adipose tissue that is indirectly related to adipocyte volume/adipose tissue mass. Evolutionarily it makes sense that if adipocytes cannot accommodate additional lipid, they should provide a signal to limit further food intake and increase mobilization and oxidation of stored lipid. The origin of this catabolic signal could again be derived from adipocyte or indirectly from local adventitial cells or cells in distal organs affected by the reduced efficiency of lipid storage in adipocytes.

Originally, Kennedy proposed that a metabolite of adipose tissue that was altered by obesity might convey a signal to the VMH. With hypertrophy adipocytes become "less efficient" at storing lipids and ultimately release fatty acids and glycerol. Indeed both metabolites have been considered catabolic regulatory signals. Intravenous infusion of fatty acids lipid emulsions when administered with insulin in primates suppresses food intake (Woods et al., 1984). Glycerol infusion into rats decreased food intake (Glick, 1980) although attempts in humans revealed no effect on food intake or weight loss (Leibel et al., 1980). However, the use of highly specific β3 adrenergic receptor agonists that increase adipocyte lipolytic rates, do not reduce body mass in mice or humans (de Souza et al., 1997; Larsen et al., 2002). Some have suggested that the lack of effect is due to compensatory mechanisms blunting any anorexic effects. Nonetheless, these data would seem to argue that the release of fatty acids or glycerol alone is not sufficient to produce a catabolic effect.

Beyond the adipocyte, the presence of increased/excessive fat storage in an overfed state could be sensed locally by a non-adipocyte population of cells. Indeed, immune cells do respond to changes in lipid fluxes in adipose tissue (Kosteli 2010, Xu 2013). A key function of immune cells is monitoring the state of tissues for homeostatic perturbations. Expansion of adipose tissue in the setting of obesity activates a broad immune response. Despite more than a decade of study, our understanding of what regulates this response remains rudimentary. Nonetheless, it is known that as fat mass increases and the efficiency of storage

of TG in adipocytes is reduced, lipids accumulate in immune cells, especially a subset of CD11c+ adipose tissue macrophages (Kosteli 2010, Xu 2013). We have hypothesized that the immune response to expanding adipose tissue mass is partly adaptive, serving to provide storage for local excess lipids that cannot be accommodated by existing adipocytes (Kosteli 2010, Xu 2013). If this hypothesis is correct, then overwhelming this buffering function in overfed animals could lead to the release of a catabolic signal that reduces food intake and increases energy expenditure. This response would ultimately restore the ability of the immune system to adequately buffer lipids. Of course, activation of immune responses in other contexts (e.g. pathogen infections) reduces food intake and increases energy expenditure, providing a precedent for immune regulation of energy expenditure and intake.

Finally, a stress signal derived from an organ distinct from adipose tissue could drive expression of a catabolic factor. While excess lipids increase stress in adipocytes and local immune cells within adipose tissue, such accumulation also increases metabolic stress in other tissues. With a reduction in the adipose tissue's reserve capacity for lipid storage, neutral lipids and metabolic byproducts accumulate in muscle, liver and beta-cells of the pancreas. Although the focus of analysis of such excess lipids has been on local dysfunction, cellular stress responses are activated. These signal systems including atypical PKCs and ER-stress pathways within non-adipose tissues could regulate production and release of a catabolic factor (Varman 2010, Fu 2012).

Central sensing of the overfeed/weight-augmented response

Coordination of the behavioral and metabolic responses to nutritional status requires central integration. Leptin-regulated neurons and pathways and populations of neurons activated by weight reduction and caloric restriction have been intensively studied. Virtually nothing is known about pathways activated by overfeeding. Although many regions, including the VMH, LH, arcuate, PVN, and VTA, have been implicated in anorectic effects, none, to our knowledge, is implicated in receiving a catabolic factor of the overfed state.

Although the site(s) of action of a catabolic factor are not known it seems likely that it is sensed in a manner different from that used for leptin sensing in response to reductions in fat mass. Unlike leptin, which induces changes in behavior primarily in response to the decline of circulating concentration below a "threshold" (Leibel, 2008), the catabolic factor induced by the overfed state likely activates anorectic and hypermetabolic responses in the CNS in continuous proportion to increases in its concentration. Parabiosis experiments suggest this directly. The severe anorexia induced by parabiosis of rats to VMN-lesioned or *leptin receptor*-deficient animals argues that the action of the weight-augmented, overfed catabolic factor also requires intact VMH (or at least fiber tracts that pass through this anatomical region (Sclafani, 1971)), (Fig 2). More recent and technologically sophisticated studies are describing the neuronal circuits that directly integrate the various regions of the CNS that modulate hunger (Krashes et al., 2014; Wu et al., 2009).

Genetic and evolutionary evidence for an overfed/weight-augmented response

Have specific genetic variants been implicated in the development of obesity or part of the overfed, weight-augmented response? Without knowing the identity of components of this system it is not clear that any of the genes implicated either by genome-wide association studies or studies of extreme phenotypes are involved in the response to overfeeding. What would be the phenotype of an individual deficient in the response to the overfed state? As we have imagined the system, such people would not be unusually hungry or seek food but would rather not limit their intake during periods of hypercaloric feeding. Hence, unlike mutations that impair the leptin regulated system, genetic variants in the system that limit overfeeding may not be apparent in the absence of a second alteration, either genetic or environmental, that provides a stimulus to overeat.

While the evolutionary rationale for developing a system that defends against too little fat seems clear – with insufficient fat mass an animal risks infertility, dying or losing fetuses or suckling offspring - the evolutionary pressure to evolve a system that prevents excess adipose tissue mass is less apparent. Avoidance of predation at upper extremes of adiposity – presumably not readily achieved under most earlier environmental circumstances – would be one selective advantage. However, if as we imagine, the system works to limit expanding fat mass when doing so becomes inefficient or ineffective, there would be some evolutionary benefits; energy and efforts would be redirected to other evolutionarily beneficial behaviors, e.g. reproduction, caring for young, when ingesting more calories would not provide additional survival advantage.

A model for defense against deposition of excessive fat stores

We propose that the overfed/weight-augmented state activates a local stress response in adipose tissue that triggers release of a humoral catabolic factor. This catabolic signal is not leptin, although intact leptin signaling, is necessary for the action of the catabolic factor. We propose that the catabolic factor reports some aspect of adipocyte status that is related to the efficiency with which more triglyceride can be added to adipocytes (Figure 3). In our model, excess local triglycerides are partially buffered by immune cells. When this system's buffering capacity is exceeded, adipose tissue releases a circulating factor that acts within the CNS to reduce food intake and increase energy expenditure. The signal may be secreted directly by immune cells or by other local cells in response to the stress response of the immune cells. This model suggests that differences in either the ability of adipocytes to store excess calories and/or the function of adipose tissue immune cells to buffer excess lipids can affect the upper limits of rates of weight gain and absolute adiposity.

However, even if aspects of our model are incorrect, as surely they are, identifying components of the system that limits fat mass expansion in overfed animals will identify molecules and pathways that might be deployed for the prevention and treatment of obesity and its complications. A more detailed analysis of the physiology of the overfed state and identifying factors that circulate in high concentrations in leptin receptor-deficient and

VMN-lesioned animals provide rich opportunities to search for endogenous catabolic factors.

REFERENCES

Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS. Role of leptin in the neuroendocrine response to fasting. Nature. 1996; 382:250–252. [PubMed: 8717038]

Amatruda JM, Statt MC, Welle SL. Total and resting energy expenditure in obese women reduced to ideal body weight. The Journal of clinical investigation. 1993; 92:1236–1242. [PubMed: 8376583]

Anand BK, Brobeck JR. Hypothalamic control of food intake in rats and cats. Yale J Biol Med. 1951; 24:123–140. [PubMed: 14901884]

Astrup A, Gotzsche PC, van de Werken K, Ranneries C, Toubro S, Raben A, Buemann B. Meta-analysis of resting metabolic rate in formerly obese subjects. Am J Clin Nutr. 1999; 69:1117–1122. [PubMed: 10357728]

Brobeck JR. Neural control of hunger, appetite, and satiety. Yale J Biol Med. 1957; 29:565–574. [PubMed: 13443361]

Brobeck JR. Food and temperature. Recent Prog Horm Res. 1960; 16:439–466. [PubMed: 13804537]

Chen H, Charlat O, Tartaglia LA, Woolf EA, Weng X, Ellis SJ, Lakey ND, Culpepper J, Moore KJ, Breitbart RE, et al. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. Cell. 1996; 84:491–495. [PubMed: 8608603]

Chua SC Jr, Chung WK, Wu-Peng XS, Zhang Y, Liu SM, Tartaglia L, Leibel RL. Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science. 1996; 271:994–996. [PubMed: 8584938]

Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature. 1998; 392:398–401. [PubMed: 9537324]

Cohn C, Joseph D. Influence of body weight and body fat on appetite of "normal" lean and obese rats. Yale J Biol Med. 1962; 34:598–607. [PubMed: 13880343]

de Peuter R, Withers RT, Brinkman M, Tomas FM, Clark DG. No differences in rates of energy expenditure between post-obese women and their matched, lean controls. Int J Obes Relat Metab Disord. 1992; 16:801–808. [PubMed: 1330959]

de Souza CJ, Hirshman MF, Horton ES. CL-16,243, a beta3-specific adrenoceptor agonist, enhances insulin-stimulated glucose disposal in nonobese rats. Diabetes. 1997; 46:1257–1263. [PubMed: 9231648]

Doring H, Schwarzer K, Nuesslein-Hildesheim B, Schmidt I. Leptin selectively increases energy expenditure of food-restricted lean mice. Int J Obes Relat Metab Disord. 1998; 22:83–88. [PubMed: 9504315]

Faouzi M, Leshan R, Bjornholm M, Hennessey T, Jones J, Munzberg H. Differential accessibility of circulating leptin to individual hypothalamic sites. Endocrinology. 2007; 148:5414–5423. [PubMed: 17690165]

Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. JAMA : the journal of the American Medical Association. 2012; 307:491–497.

Glick Z. Food intake of rats administered with glycerol. Physiology & behavior. 1980; 25:621–626. [PubMed: 7192413]

Harris RB, Martin RJ. Specific depletion of body fat in parabiotic partners of tube-fed obese rats. The American journal of physiology. 1984; 247:R380–R386. [PubMed: 6431831]

Harris RB, Martin RJ. Site of action of putative lipostatic factor: food intake and peripheral pentose shunt activity. The American journal of physiology. 1990; 259:R45–R52. [PubMed: 2375428]

Hervey GR. The effects of lesions in the hypothalamus in parabiotic rats. J Physiol. 1959; 145:336–352. [PubMed: 13642304]

Hetherington AW, Ranson SW. Hypothalamic lesions and adiposity in the rat. Anat Rec. 1940; 78:149–172.

Heymsfield SB, Greenberg AS, Fujioka K, Dixon RM, Kushner R, Hunt T, Lubina JA, Patane J, Self B, Hunt P, et al. Recombinant leptin for weight loss in obese and lean adults: a randomized, controlled, dose-escalation trial. JAMA : the journal of the American Medical Association. 1999; 282:1568–1575.

Hoebel BG, Teitelbaum P. Hypothalamic control of feeding and self-stimulation. Science. 1962; 135:375–377. [PubMed: 13907995]

Keesey RE, Hirvonen MD. Body weight set-points: determination and adjustment. J Nutr. 1997; 127:1875S–1883S. [PubMed: 9278574]

Kelesidis T, Kelesidis I, Chou S, Mantzoros CS. Narrative review: the role of leptin in human physiology: emerging clinical applications. Ann Intern Med. 2010; 152:93–100. [PubMed: 20083828]

Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proc R Soc Lond B Biol Sci. 1953a; 140:578–596. [PubMed: 13027283]

Kennedy GC. The role of depot fat in the hypothalamic control of food intake in the rat. Proc R Soc Lond B Biol Sci. 1953b; 140:578–596. [PubMed: 13027283]

Kennedy GC. The Hypothalamus and Obesity. Proceedings of the Royal Society of Medicine. 1963

Korner J, Savontaus E, Chua SC Jr, Leibel RL, Wardlaw SL. Leptin regulation of Agrp and Npy mRNA in the rat hypothalamus. Journal of neuroendocrinology. 2001; 13:959–966. [PubMed: 11737554]

Krashes MJ, Shah BP, Madara JC, Olson DP, Strochlic DE, Garfield AS, Vong L, Pei H, Watabe-Uchida M, Uchida N, et al. An excitatory paraventricular nucleus to AgRP neuron circuit that drives hunger. Nature. 2014; 507:238–242. [PubMed: 24487620]

Larsen TM, Toubro S, van Baak MA, Gottesdiener KM, Larson P, Saris WH, Astrup A. Effect of a 28-d treatment with L-96568, a novel beta(3)-adrenergic receptor agonist, on energy expenditure and body composition in obese men. Am J Clin Nutr. 2002; 76:780–788. [PubMed: 12324291]

Lee GH, Proenca R, Montez JM, Carroll KM, Darvishzadeh JG, Lee JI, Friedman JM. Abnormal splicing of the leptin receptor in diabetic mice. Nature. 1996; 379:632–635. [PubMed: 8628397]

Leibel RL. A biologic radar system for the assessment of body mass the model of a geometry sensitive endocrine system is presented. J Theor Biol. 1977; 66:297–306. [PubMed: 886867]

Leibel RL. The role of leptin in the control of body weight. Nutr Rev. 2002; 60:S15–S19. discussion S68-84, 85-17. [PubMed: 12403079]

Leibel RL. Molecular physiology of weight regulation in mice and humans. Int J Obes (Lond). 2008; 32(Suppl 7):S98–S108. [PubMed: 19136999]

Leibel RL, Drewnowski A, Hirsch J. Effect of glycerol on weight loss and hunger in obese patients. Metabolism: clinical and experimental. 1980; 29:1234–1236. [PubMed: 7453567]

Leibel RL, Hirsch J. Diminished energy requirements in reduced-obese patients. Metabolism: clinical and experimental. 1984; 33:164–170. [PubMed: 6694559]

Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. N Engl J Med. 1995; 332:621–628. [PubMed: 7632212]

Levin BE, Keesey RE. Defense of differing body weight set points in diet-induced obese and resistant rats. The American journal of physiology. 1998; 274:R412–R419. [PubMed: 9486299]

Mackintosh RM, Hirsch J. The effects of leptin administration in non-obese human subjects. Obes Res. 2001; 9:462–469. [PubMed: 11500526]

Mayer J. Glucostatic mechanism of regulation of food intake. N Engl J Med. 1953; 249:13–16. [PubMed: 13063674]

Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997; 387:903–908. [PubMed: 9202122]

Myers MG Jr, Heymsfield SB, Haft C, Kahn BB, Laughlin M, Leibel RL, Tschop MH, Yanovski JA. Challenges and opportunities of defining clinical leptin resistance. Cell metabolism. 2012a; 15:150–156. [PubMed: 22326217]

Myers MG Jr, Heymsfield SB, Haft C, Kahn BB, Laughlin M, Leibel RL, Tschop MH, Yanovski JA. Challenges and opportunities of defining clinical leptin resistance. Cell Metab. 2012b; 15:150–156. [PubMed: 22326217]

Myers MG Jr, Olson DP. Central nervous system control of metabolism. Nature. 2012; 491:357–363. [PubMed: 23151578]

Neumann R. Experimentelle Beitrage zur Lehre von dem taglichen Nahrungsbedarf des Menschen unter besonder Berucksichtigung der notwendigen Eiweifsmenge. Arc Hyg. 1902; 45:1–87.

Nishizawa Y, Bray GA. Evidence for a circulating ergostatic factor: studies on parabiotic rats. The American journal of physiology. 1980; 239:R344–R351. [PubMed: 6159792]

Passmore R. The regulation of body-weight in man. Proc Nutr Soc. 1971; 30:122–127. [PubMed: 5113750]

Passmore R. Reflexions on energy balance. Proc Nutr Soc. 1982; 41:161–165. [PubMed: 7051013]

Porte D Jr, Woods SC. Regulation of food intake and body weight in insulin. Diabetologia. 1981; 20(Suppl):274–280. [PubMed: 7014326]

Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, Boyce V, Howard BV, Bogardus C. Reduced rate of energy expenditure as a risk factor for body-weight gain. N Engl J Med. 1988; 318:467–472. [PubMed: 3340128]

Ravussin Y, Gutman R, Diano S, Shanabrough M, Borok E, Sarman B, Lehmann A, LeDuc CA, Rosenbaum M, Horvath TL, et al. Effects of chronic weight perturbation on energy homeostasis and brain structure in mice. American journal of physiology. Regulatory, integrative and comparative physiology. 2011; 300:R1352–R1362.

Ravussin Y, LeDuc CA, Watanabe K, Leibel RL. Effects of ambient temperature on adaptive thermogenesis during maintenance of reduced body weight in mice. American journal of physiology. Regulatory, integrative and comparative physiology. 2012; 303:R438–R448.

Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, Gallagher D, Mayer L, Murphy E, Leibel RL. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. The Journal of clinical investigation. 2005; 115:3579–3586. [PubMed: 16322796]

Rosenbaum M, Hirsch J, Gallagher DA, Leibel RL. Long-term persistence of adaptive thermogenesis in subjects who have maintained a reduced body weight. Am J Clin Nutr. 2008a; 88:906–912. [PubMed: 18842775]

Rosenbaum M, Leibel RL. Adaptive thermogenesis in humans. Int J Obes (Lond). 2010; 34(Suppl 1):S47–S55. [PubMed: 20935667]

Rosenbaum M, Murphy EM, Heymsfield SB, Matthews DE, Leibel RL. Low dose leptin administration reverses effects of sustained weight-reduction on energy expenditure and circulating concentrations of thyroid hormones. J Clin Endocrinol Metab. 2002; 87:2391–2394. [PubMed: 11994393]

Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J. Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. The Journal of clinical investigation. 2008b; 118:2583–2591. [PubMed: 18568078]

Rosenbaum M, Vandenborne K, Goldsmith R, Simoneau JA, Heymsfield S, Joanisse DR, Hirsch J, Murphy E, Matthews D, Segal KR, et al. Effects of experimental weight perturbation on skeletal muscle work efficiency in human subjects. American journal of physiology. Regulatory, integrative and comparative physiology. 2003; 285:R183–R192.

Rothwell NJ, Stock MJ. A role for brown adipose tissue in diet-induced thermogenesis. Nature. 1979; 281:31–35. [PubMed: 551265]

Sclafani A. Neural pathways involved in the ventromedial hypothalamic lesion syndrome in the rat. Journal of comparative and physiological psychology. 1971; 77:70–96. [PubMed: 5166079]

Sims EA, Danforth E Jr, Horton ES, Bray GA, Glennon JA, Salans LB. Endocrine and metabolic effects of experimental obesity in man. Recent Prog Horm Res. 1973; 29:457–496. [PubMed: 4750591]

Keys, AB. University of Minnesota. Laboratory of Physiological Hygiene. The biology of human starvation. Minneapolis: University of Minnesota Press; 1950.

Vong L, Ye C, Yang Z, Choi B, Chua S Jr, Lowell BB. Leptin action on GABAergic neurons prevents obesity and reduces inhibitory tone to POMC neurons. Neuron. 2011; 71:142–154. [PubMed: 21745644]

White CL, Purpera MN, Ballard K, Morrison CD. Decreased food intake following overfeeding involves leptin-dependent and leptin-independent mechanisms. Physiology & behavior. 2010; 100:408–416. [PubMed: 20385158]

Woods SC, Stein LJ, McKay LD, Porte D Jr. Suppression of food intake by intravenous nutrients and insulin in the baboon. The American journal of physiology. 1984; 247:R393–R401. [PubMed: 6380317]

Wu Q, Boyle MP, Palmiter RD. Loss of GABAergic signaling by AgRP neurons to the parabrachial nucleus leads to starvation. Cell. 2009; 137:1225–1234. [PubMed: 19563755]

Zhang Y, Guo KY, Diaz PA, Heo M, Leibel RL. Determinants of leptin gene expression in fat depots of lean mice. American journal of physiology. Regulatory, integrative and comparative physiology. 2002; 282:R226–R234.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994; 372:425–432. [PubMed: 7984236]

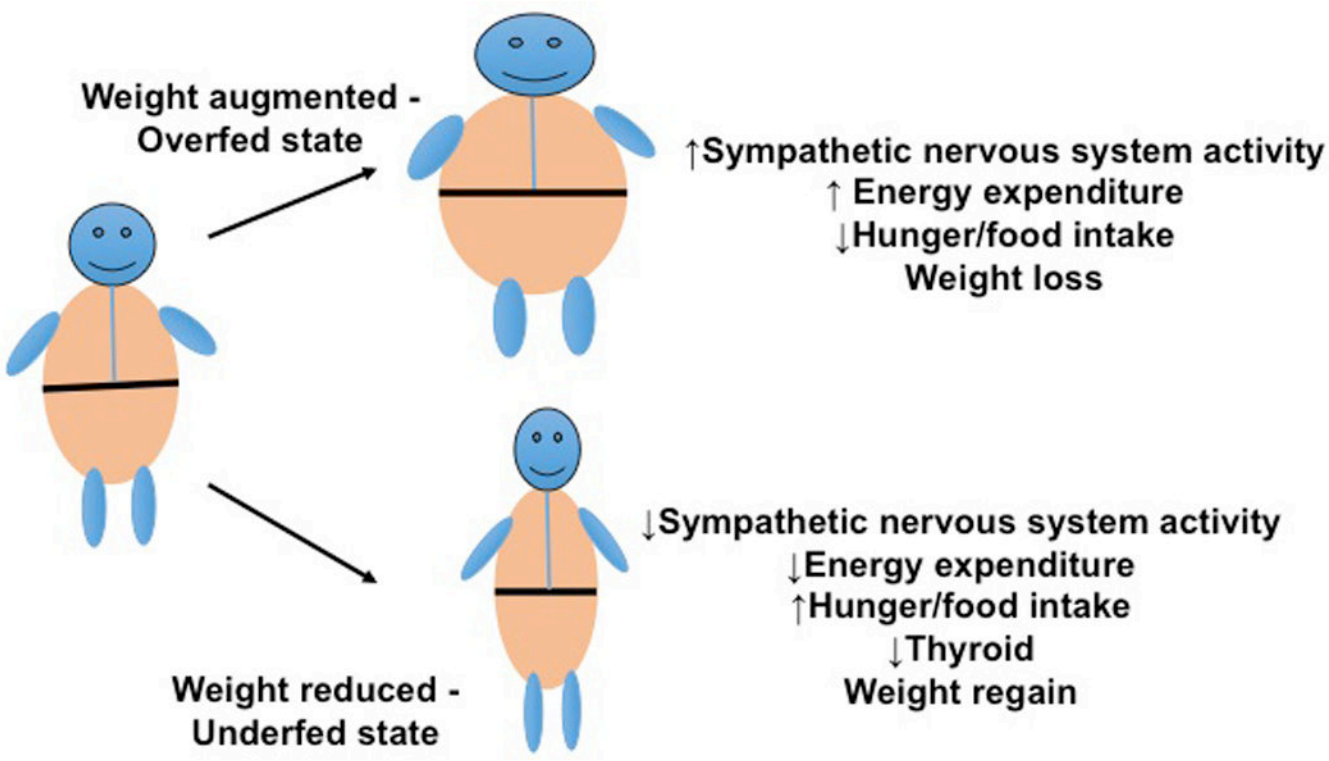

Figure 1. Physiological consequences of changes from body weight "set point"

Increases in body fat activate systems that favor a return to a lower fat mass. Conversely, reductions in fat mass activate a leptin-dependent system that favors a return to a higher fat mass.

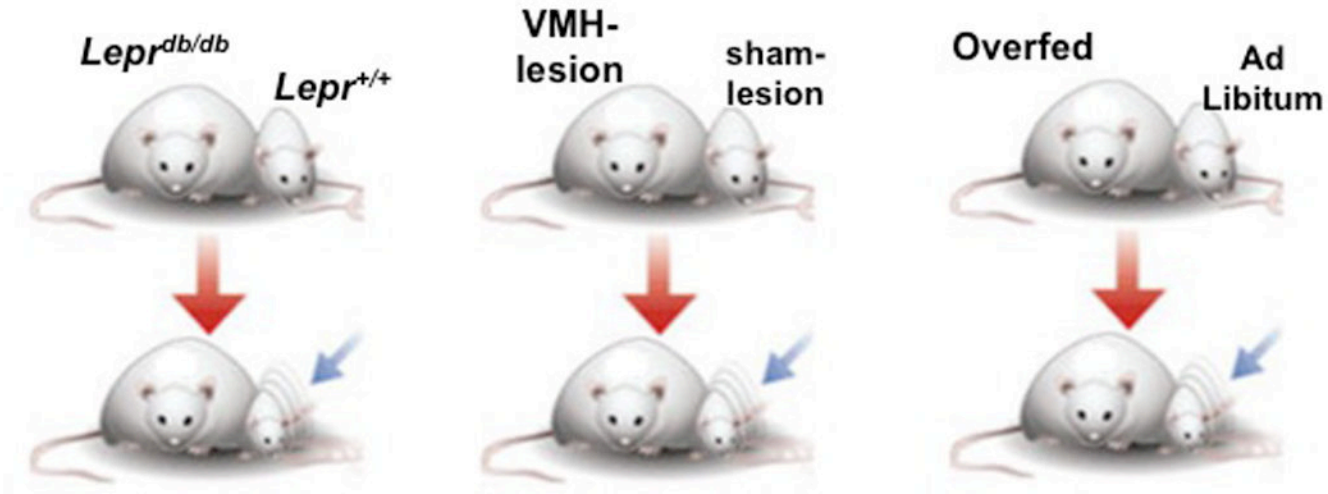

Figure 2. Evidence for a circulating catabolic factor in overfed animals

Diabetes animals (*Lepr*$^{db/db}$), that have a mutation in the receptor for leptin, and animals that have lesions that ablate their ventromedial hypothalamus (VMH) are hyperphagic, hypometabolic and rapidly become severely obese. Parabioses of *Lepr*$^{db/db}$ or VMH-lesioned animals to lean controls reduces food intake and induces weight loss of lean parabiotic partners, leading to starvation in a significant number of animals. Overfeeding animals (either via gavage or gastric tube) increases body weight of overfed animals and reduces voluntary food intake. Parabiosis of these animals with lean controls also decreases food intake and body fat in ad libitum fed parabiots.

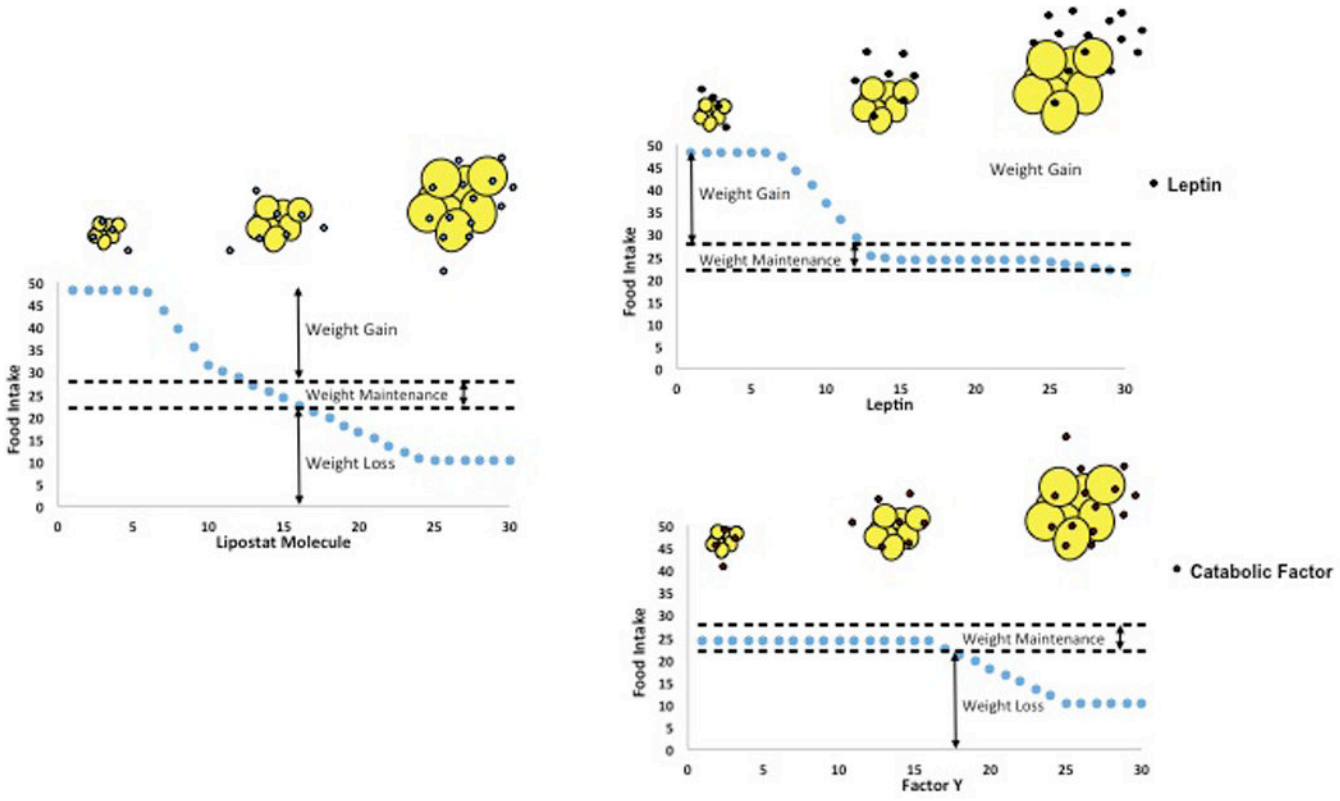

Figure 3. A dual component lipostatic model

(A) Kennedy proposed a single satiety factor capable of inducing catabolic and anabolic effects in response to weight loss and gain, respectively (B) Leptin, at reduced concentrations acts as a powerful anabolic factor regulating metabolic/behavioral responses to weight loss. (C) We propose that a catabolic factor similarly regulates the response to overfeeding, augmented weight and increased fat mass.