The History of Obesity Research

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Abstract
Perhaps the most unexpected development in pediatric endocrinology in the past 50 years has been the recognition of obesity as an endocrine/metabolic disorder rather than a life choice or moral failing. The history of obesity research is disjointed, having followed two separate paths in the 20th century, based on two independent yet overlapping paradigms. Proponents of the "Energy Storage" hypothesis point to data implicating monogenetic disorders, the ventromedial hypothalamus, insulin, cortisol, and the adipocyte itself in the pathogenesis of obesity. Alternatively, proponents of the "Energy Balance" hypothesis point to data implicating increased caloric intake, decreased caloric expenditure, gastrointestinal hormones, and microbiome changes as being critical for obesity. These two separate lines of research merged somewhat with the discovery of leptin in 1994, as leptin established a major hormonal role in weight control. Leptin has explained some of the dichotomy and has proved essential in understanding the importance of developmental programming and epigenetics. However, the mystery of leptin resistance remains unsolved. Despite all our collective knowledge, we appear no closer in solving the obesity puzzle today than we were 50 years ago.

Introduction
The Venus von Willendorf, a 13-inch bust of an obese woman's torso, sitting in the Natural History Museum of Vienna, carbon dates back to 24,000 BCE (Fig. 1). Obesity has been around for a long time, although in ancient times it was a rare occurrence. Throughout the Middle Ages and the Renaissance, obesity was considered a status symbol of affluence (e.g., Rubenesque body types). The focus on childhood obesity is much more recent and only gained public attention approximately 40 years ago, when it was noted that a stable childhood obesity prevalence curve morphed into a parabolic one. Currently, 19.7\% of American children [1] and 5.7\% of European children [2] are obese. Similarly, the number of academic articles on obesity has exhibited a similar parabolic climb over the last 20 years [3].

Despite its increasing incidence, prevalence, and severity, we have limited understanding of what causes obesity and an even poorer understanding of best approaches to management. Perhaps the most blatant example of our confusion is that to this day, we still don't know to what extent, for the vast majority of individuals, obesity is due to a defect in energy storage, which is primarily endocrine in etiology, or due to a defect in energy balance, which is primarily nutritional in etiology. Indeed, in the 20th century, the history of obesity research had taken two divergent paths, with various adherents subscribing...
to one or the other hypothesis. Table 1 provides an integrated chronological timeline of research progress, underscoring proponents of each hypothesis.

**The Energy Storage Hypothesis**

In exploring the energy storage hypothesis of obesity, genetic and endocrinologic constructs have provided the primary key insights into the determinants of obesity. Organs involved include the brain, the adrenal gland, the pancreas, and the adipocyte itself.

**The Ventromedial Hypothalamus and Obesity**

The seminal illustration of the energy storage hypothesis is the clinical syndrome of hypothalamic obesity. The first description dates back to 1840, when a 57-year old woman developed massive obesity within a year of her death, and an autopsy demonstrated a tumor at the base of the brain [4]. The notion that obesity could have a neuroendocrine (i.e., either brain or hormone) origin dates back to 1900, when Babinski [5] and Frohlich [6] independently described children who were normal weight until the development of a tumor at the base of the brain, which led to massive obesity that was unresponsive to any intervention. However, both ascribed the obesity to dysfunction of the pituitary. By 1921, Bailey and Brenner [7] showed that stereotactic lesioning of the same area in rats led to massive obesity. In 1937, Harris [8] localized the hypothalamus as the brain area regulating energy metabolism and other hormonal secretions. In 1940, Hetherington and Ranson [9] lesioned the ventromedial hypothalamus (VMH) without damaging the pituitary and recapitulated the same increase in adiposity, and in 1943, Brobeck et al. [10] demonstrated that these animals developed severe hyperphagia, thus postulating (incorrectly) that the VMH was the brain’s “satiety center”. However, this was disproven in 1975 when Bray and Gallagher [11] demonstrated that on a calorically restricted diet in-hospital, these patients still gained weight. Rather, in the 1970s, studies in rats by the Bray lab in the USA [12] and Rohner-Jeannelaud and Jeannelaud [13, 14] in France showed that either VMH lesions or vagal stimulation increased insulin secretion from the pancreas and resultant hyperphagia, both of which could be blocked by vagotomy. These findings have argued for a VMH-vagus-pancreas-adipose axis that regulates energy storage [15].

**Cortisol and Obesity**

In 1912, Cushing described his experience with the now-famous “Minnie G.” and seven other patients with pituitary basophilic adenoma, “painful” obesity, headache, and hypertension [16]. Subtemporal decompression reversed many of the symptoms (as well as the obesity), for a time, but most of the patients died years later. However, within the next 2 decades, it became clear that many patients with “Cushing’s Disease” did not have a pituitary
tumor but rather an adrenal adenoma [17], and that unilateral adrenalectomy would reverse the obesity, suggesting an adrenal hormonal etiology. By 1936, the Kendall lab had isolated cortisone from bovine adrenal glands [18], and by 1946, Sarett had succeeded in synthesizing cortisol for pharmaceutical use [19]. While cortisol turned out to be a “wonder drug” for various inflammatory diseases, its side-effects were undeniable, especially weight gain [20].

Numerous studies of adrenal function in general obesity have demonstrated increased absolute daily urinary cortisol excretion; however, when corrected for body mass index or fat mass, these differences are mitigated [21]. Further investigation, using transgenic mice bearing a mutation in the gene encoding \( \Delta \)-hydroxysteroid dehydrogenase-1, which prevents the conversion of the active hormone cortisol to the inactive precursor cortisone,

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**Table 1. Chronology of major discoveries in the field of obesity and relationship to origin of obesity hypotheses**

| Year       | Obesity milestone                                                                 | Author(s)                                    | Relationship to origins of obesity hypotheses |
|------------|----------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------|
| Antiquity  | Description of obesity                                                           | Hippocrates                                  |                                               |
| 1901       | Hypothalamic obesity                                                              | Babinski [5], Frohlich [6]                   | ES¹                                          |
| 1916       | Calories in specific foods                                                        | Atwater [59]                                | EB²                                          |
| 1921       | Lesioning of VMH results in obesity                                               | Bailey and Brenner [7]                      | ES                                           |
| 1921       | Discovery of insulin                                                             | Banting and Best [28]                       | ES                                           |
| 1922       | Hypophysectomy for Cushing’s disease                                              | Cushing [16]                                | ES                                           |
| 1930       | Theory of energy balance                                                          | Newbergh [60]                               | EB                                           |
| 1941       | Physiologic dissociation of hypothalamus from pituitary                          | Hetherington et al. [9]                     | ES                                           |
| 1943       | VMH lesions cause hyperphagia                                                     | Brobeck et al. [10]                         | ES                                           |
| 1956       | Reduced activity in obese humans                                                  | Mayer et al. [66]                           | ES                                           |
| 1960       | High insulin in type 2 diabetes                                                   | Yalow and Berson [34]                       | ES                                           |
| 1964       | Weight loss reduces adipocyte size, not number                                    | Hirsch et al. [44, 45]                      | ES                                           |
| 1973       | Parabiosis of db/ob and db/db mice                                                | Coleman [108]                               | ES                                           |
| 1975       | Hypothalamic obesity gain weight even when food restricted                        | Bray and Gallagher [11]                     | ES                                           |
| 1982       | Discovery of Peptide YY3-36                                                       | Tatemoto [79]                               | EB                                           |
| 1986, 1990 | Heritability of BMI in twins                                                      | Stunkard et al. [52, 53]                    | ES                                           |
| 1987       | Glucagon-like peptide-1 stimulates insulin                                        | Holst et al. [88], Mosjov et al. [89]        | EB                                           |
| 1987       | Bariatric surgery reverses diabetes                                               | Pories et al. [74]                          | EB                                           |
| 1990       | Insulin stops fat oxidation                                                       | Bonadonna and DeFronzo et al. [40]          | ES                                           |
| 1990       | SGA infants and adult chronic disease, beginning of DOHaD                        | Barker [48]                                 | ES                                           |
| 1992       | Isolation of Exendin-4                                                            | Eng et al. [94]                              | EB                                           |
| 1994       | Cloning of leptin                                                                | Zhang et al. [109]                          | ES                                           |
| 1995       | Weight loss reduces resting energy expenditure                                    | Leibel et al. [69]                          | EB                                           |
| 1997       | Leptin treatment in leptin deficiency                                             | Farooqi et al. [112]                         | ES                                           |
| 1997       | Congenital leptin deficiency                                                      | Montague et al. [110]                       | ES                                           |
| 1998       | Melanocortin-4 receptor mutation                                                  | Yeo et al. [56]                             | ES                                           |
| 1998       | Leptin receptor mutation                                                          | Clement et al. [111]                        | ES                                           |
| 1998       | PPAR-gamma is a transcriptional regulator of subcutaneous fat                     | Spiegelman et al. [85]                      | ES                                           |
| 1999       | Recombinant leptin ineffective in adult obesity                                    | Heymsfield et al. [115]                     | ES                                           |
| 2001       | Discovery of ghrelin                                                              | Cummings et al. [62]                        | EB                                           |
| 2001       | Dutch Winter Famine research                                                      | Roseboom [47]                               | ES                                           |
| 2004       | Discovery of microbiome (fetal transplant)                                        | Bäckhed et al. [99]                         | EB                                           |
| 2004       | Leptin rewires the hypothalamus                                                   | Pinto et al. [126]                          | ES                                           |
| 2005       | Liposuction does not improve metabolism                                           | Klein et al. [27]                           | ES                                           |
| 2006       | Peptide YY3-36 is a satiety signal                                                | Ballantyne [80]                             | ES                                           |
| 2007       | Leptin extinguishes reward in leptin deficiency                                   | Farooqi et al. [113]                        | ES                                           |
| 2008       | Fat cell number fixed by age 2                                                    | Spalding et al. [46]                        | ES                                           |
| 2009       | Lipodystrophy treated with leptin                                                | Mulligan et al. [114]                       | ES                                           |
| 2009       | GWAS studies show 36 loci associated with body weight                             | Loos [58]                                   | ES                                           |
| 2013       | Gut microbiome and leptin resistance                                              | Schéle et al. [124]                         | ES and EB                                    |
| 2015       | Dietary fat reduction resulted in reduced body fat                                | Hall et al. [71]                            | EB                                           |

¹ ES, energy storage. ² EB, energy balance.
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by the Flier lab in 2001, demonstrated an increase in visceral obesity and metabolic syndrome [22]. In another set of transgenic studies, the Zukowska lab in 2007 showed that acute adrenergic activation of the visceral adipose tissue depot resulted in lipolysis, while chronic activation resulted in lipogenesis, due to the adrenergic-blocking effects of the co-localized Neuropeptide Y [23].

In clinical studies, increased stress and HPA axis activity have been noted in patients with visceral adiposity [24, 25]. These findings support a role for stress, chronic adrenergic activation, and cortisol in the growth of the visceral fat depot, exclusive of the subcutaneous fat depot, and with an increased risk for chronic metabolic disease. Conversely, in 2002, the DeFronzo lab showed that thiazolidinediones (TZDs), by binding to the peroxisome proliferator-activated receptor-gamma (PPARγ) increase subcutaneous fat development but not visceral fat, and cause weight gain yet improve insulin sensitivity and reduce risk for metabolic syndrome [26]. Apparently, the converse is also true, as Klein et al. [27] demonstrated in 2005 that liposuction of subcutaneous fat only did nothing to improve the metabolic dysfunction of obese subjects.

Insulin and Obesity

Insulin is a prerequisite for energy storage in adipose tissue. It has long been known that type 1 diabetics lose significant weight and fat mass before succumbing to diabetic ketoacidosis. In 1921, Banting et al. [28] discovered insulin; shortly thereafter, patients with type 1 diabetes worldwide started receiving exogenous insulin injections, and it became apparent that recipients rapidly increased their adiposity by shunting glucose and lipid into adipocytes [29]. Furthermore, studies of patients who manifested increased endogenous insulin release (e.g., congenital hyperinsulinism, Beckwith-Wiedemann syndrome, insulinoma) also had increased adiposity [30, 31].

In 1939, Himsworth [32] first postulated the concept of insulin resistance; this was borne out in 1951 when Bornstein and Lawrence [33] first measured insulin levels in patients with type 2 diabetes. In 1959, Yalow and Berenson [34], in developing the concept and procedures for the radioimmunoassay, showed consistent hyperinsulinemia in those with type 2 diabetes. In 1983, Reaven et al. [35] demonstrated that the majority of, but not all, obese persons without diabetes also had increased fasting insulin levels; those that did had associated insulin resistance [36], and that they manifested the cluster of signs (“diseases”) which he termed “Syndrome X,” but “metabolic syndrome” was the term that stuck. However, for decades, this paradox of high insulin levels and low insulin effect was explained by the postulate that obesity induced insulin resistance. Furthermore, Knowler et al. [37] showed in 2002 that weight loss improved insulin sensitivity and reduced risk for disease.

More recent research argues that insulin is a primary driver of weight gain. Johnson et al. have demonstrated that transgenic animals deficient in insulin secretion gain less adipose tissue and manifest increased longevity [38]. In humans, the Ludwig lab showed in 2008 that the Quebecois, who exhibit an increased insulin release in response to glucose, manifest increased weight gain in response to a high-carbohydrate diet [39]. Bonadonna et al. [40] showed that insulin inhibits fatty acid beta-oxidation, thus preventing energy utilization. Robert Lustig et al. [41, 42] suppressed insulin secretion using octreotide and demonstrated weight loss, first in 1999 in patients with hypothalamic obesity, and then in a sub-cohort of obese adults in 2006. These and other revelations have supported the carbohydrate-insulin hypothesis of obesity [43]; that is, increased carbohydrate diets stimulate insulin release, resulting in energy storage and increasing adiposity.

The Adipocyte and Obesity

Many other hormones affect adipocyte growth (e.g., estrogens, androgens, thyroid hormone), but first those adipocytes have to develop – and once they do, they don’t go away. In 1964, Hirsch and Goldrick [44, 45] demonstrated that weight loss reduces fat cell size but not fat cell number, suggesting that obese individuals have aberrant adipose tissue development. Spalding et al. [46] in 2008 showed that adipose tissue number was set by age 2 years in humans, putting the focus on the fetal and neonatal period. Indeed, documentation of the relationship of small for gestational age with adult obesity and cardiovascular disease started with studies of the Dutch Hunger Winter during World War II and its aftermath. Data on adults born to women exposed to rations of less than 1,000 kcal/day during different periods of gestation identified small size at birth for third trimester exposure with abnormalities of glucose tolerance as adults, while first trimester exposure resulted in increased size at birth with atherogenic lipogenic profile as adults [47]. These studies supported Barker’s 1990 postulate of the Developmental Origins of Health and Disease (DOHaD) [48]. We now have data that the in utero environment modulates the risk of obesity and metabolic disease into childhood and adulthood [49].

The DOHaD paradigm applies to environmental chemical exposures, including obesogens, which can also...
lead to obesity later in life, and even across generations [50]. For example, the U.S. government in 1972 banned the insecticide dichlorodiphenyltrichloroethane (DDT), composed of o,p′-DDT and p,p′-DDT, of which the latter is metabolized to the long-acting p,p′-DDE, which was shown in 2021 to be associated with obesity and earlier age of menarche in the grandchildren of the exposed grandmothers [51]. These findings demonstrate that there is a window of neural, chemical, and hormonal vulnerability during the fetal and neonatal period, during which risk for obesity can be programmed.

Genetics and Obesity

In 1975, Stunkard et al. [52, 53] examined the variance in BMI in mono- and dizygotic twins and estimated the heritability of obesity at 40–70%. Further strong evidence of the heritability of BMI came from a study of identical twins separated at or near birth and brought up in different environments. The study demonstrated that as adults, BMI was highly correlated between identical twins but showed little correlation with that of their adoptive parents or siblings. In the mid-1990s, the melanocortin system, consisting of the pro-hormone proopiomelanocortin (POMC) and its metabolites (α-melanocyte stimulating hormone [α-MSH], β-MSH, γ-MSH, and ACTH), as well as the five G-protein melanocortin receptors and their antagonists (e.g., Agouti-related peptide [AgRP]), was associated with feeding behavior and energy homeostasis [54]. The system acts as a key mediator of a variety of physiologic functions, including adrenal growth and hormone development, erectile responses, natriuresis, melanogenesis, as well as energy homeostasis [55]. However, despite the physiologic significance of this system and the recognition of its derivation from the POMC gene (as well as the identification of numerous other genes associated with obesity), these genetic loci have had only a limited impact on the epidemic of obesity due to the small numbers of individuals affected by single gene defects. The melanocortin-4 receptor (MC₄R) is of greatest epidemiologic significance, being involved in approximately 2.5% of those morbidly obese [56]; however, all the other monogenetic disorders in the energy balance pathway combined account for less than another 1%. Furthermore, GWAS studies suggest that a minority of weight gain is attributable to other genetic loci. The FTO gene, which encodes alpha-ketoglutarate dependent dioxygenase, is the most prevalent genetic association found thus far (in 14% of children) only accounts for 3.3 kg in extra weight [57]. While a total of 39 different genes demonstrate linkage with obesity, their collective contribution to the prevalence of obesity is quite small [58]. Nevertheless, their recognition has led to an enhanced understanding of the physiology of obesity with the interaction of peripheral factors and central factors controlling appetite and energy metabolism.

The Energy Balance Hypothesis

The energy balance hypothesis has been around for just as long, and encompasses both control of energy intake and rates of energy expenditure, including thermogenesis. Relevant organs include the liver, muscles, and GI tract.

Energy Intake and Obesity

The conservation of energy by the human body was first posited by Atwater [59]. He related the unit of combustion, the “calorie”, to the nutrient value of foods, and demonstrated that each calorie consumed was either stored, burned, or excreted. Newburgh and Johnston [60] in 1930 proposed that obesity was a simple matter of excessive intake relative to energy expended. He proposed that “All obese persons are, alike in at least one fundamental respect – they literally overeat.” This hypothesis has become a central tenet of obesity management, leading to the focus on dietary restriction as the primary intervention [61].

Cummings et al. [62] pursued the idea of obesity as an endocrine problem identifying ghrelin, its pre-prandial rise, and role in meal initiation. Ghrelin levels are elevated in patients with Prader-Willi syndrome [63] and low in patients with simple obesity [64], confounding the idea that abnormalities in ghrelin explained general obesity. To date, ghrelin remains one of a limited number of identified orexigenic hormones, but one without a disease attached to its excess or deficit.

Energy Expenditure and Obesity

The notion that energy expenditure might be dysfunctional in obese individuals was codified by Mayer [65], who in 1953 noted that obese mice were more sedentary than controls; a finding he expanded to humans by 1956 [66], suggesting that “calories out” played a major role in obesity. This started the “exercise” craze for weight loss in an attempt to balance the “calories in” part of the equation.

However, implementation of this approach to obesity management has demonstrated that weight loss and weight maintenance are difficult to achieve [67, 68]. Metabolic adaptation to change from baseline weight through changes in energy expenditure during the process of weight loss or gain was demonstrated by Rudolph Leibel
et al. [69] and shown to persist during weight maintenance by Camps et al. [70].

Several approaches to understanding metabolic adaptation have been undertaken. One effort has focused on the value of carbohydrates versus fat or protein for the adaptive response. The questions remain, is a calorie a calorie? And which is better – low fat or low carbohydrate diets? Numerous studies have explored these questions. In a 2015 in-patient metabolic balance study, Hall et al. [71] demonstrated that a 30% caloric restriction with stable protein but decreased carbohydrate content of the diet resulted in increased oxidation of fat but decreased carbohydrate oxidation and no appreciable change in body fat; whereas decreasing the fat content of the diet resulted in decreased body fat, suggesting that dietary fat was a greater contributor to body fat because of its calories. These findings were supported by a systematic review and meta-analysis of randomized control trials [72].

Nevertheless, the proponents of the energy storage hypothesis have argued that obesity is the result of high-carbohydrate diets, which stimulate insulin release, driving fat into cells for storage, decreasing lipolysis, and producing obesity [61]. As a result, they argue that the emphasis should be on diet composition rather than calorie counting and energy balance, with the hypothesis that the etiology of obesity is fundamentally an endocrine problem affecting metabolism [73].

GI Hormones and Obesity

Bariatric surgery as a modality for severe obesity was introduced as early as 1950. Pories et al. [74] were able to demonstrate in 1987 not only weight loss but also control of type 2 diabetes by this procedure, and, in 1992 documented, long-term diabetes remission with up to 10-year follow-up [75]. Furthermore, improved control of diabetes occurred within days after bariatric surgery and therefore was not likely due to weight loss [76], making the initial hypotheses of the metabolic benefit of this procedure due to restriction [77] and malabsorption [78] less likely as the sole mechanism.

Exploration of mechanisms that might explain this rapid change in diabetes control after bariatric surgery involved analysis of the effects of the procedure on gut hormone secretion including peptide YY (PYY) and glucagon-like peptide 1 (GLP-1). PYY had been initially identified in porcine intestine in 1980 and shown to inhibit exocrine pancreatic secretions [79]. Secreted by the L-cells of the intestine, PYY is thought to exert its primary effect by acting on the central nervous system to induce satiety by binding to the Y2 receptors on POMC neurons in the VMH [80]. Obese subjects appear to have reduced PYY secretion and decreased sense of satiety [81]. After bypass surgery, baseline PYY levels decrease, yet respond better to stimulation by food [82]. Though PYY is clearly a satiety hormone, its role in obesity management remains an area of ongoing investigation [83, 84].

Glucagon-like peptide-1 (GLP-1), a 31-amino acid polypeptide secreted primarily by the L-cells of the intestine [85], is a splice product of proglucagon [86, 87], which was shown in 1987 to be a potent stimulator of insulin release [88, 89]. Nauck et al. [90] showed the GLP-1-induced insulin response to be glucose-dependent and absent below a glucose threshold of 4.3 mM. As with PYY, GLP-1 acts both centrally [91] and peripherally [92] to inhibit food intake. GLP-1 is secreted in response to nutrients [93] with a short half-life of activity due to cleavage by dipeptidyl peptidase-4 (DPP-4) and renal clearance. However, with the isolation of Exendin-4 (a long-acting analog of GLP-1) from the Gila monster [94], a new world of therapeutics (first for diabetes, then for obesity) began with GLP-1 receptor agonist therapy [95].

The Gut Microbiome and Obesity

The gastrointestinal tract is home to trillions of microorganisms collectively known as the microbiome [96]. Differences in the microbial populations are noted between normal weight and obese individuals [97], with less microbial diversity described in those with obesity [98]; however, it is still not clear whether this is a cause or effect. The Gordon lab was able to show that germ-free mice receiving a fecal microbial transplant (FMT) from conventional mice gained weight despite increased energy expenditure and decreased energy consumption [99]. By transplanting microbiota from genetically obese ob/ob mice into germ-free mice, they were able to demonstrate a 2% increase in energy deposition over calories actually consumed. As a result, they hypothesized that the microbiota of obese animals might more efficiently extract energy [100]. Several investigators have demonstrated changes in the microbiome paralleling changes in the diet [101, 102], suggesting that one way diet affects obesity is by altering the microbiome. Thus, the animal model has provided direct evidence that a “predisposed” microbiome might increase the energy intake of individuals with obesity. However, data from humans have been inconsistent [103].

Dietary efforts to manipulate this system have focused on prebiotics, “a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bac-
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teria in the colon, and thus improves host health” [104]. For instance, in 2006 Cani et al. [105] administered the indigestible carbohydrate oligofructose to animals, resulting in improved insulin sensitivity, and to humans, resulting in increased satiety and decreased energy intake [106], possibly by altering GI hormones. Prebiotics, probiotics, and postbiotics remain an active area of investigation in the treatment of obesity [107].

Putting It All Together: The Leptin Era

Throughout the 20th century, these two investigative paradigms seemed destined to continue to disagree about the etiology and pathogenesis of obesity. But two mice solved the conundrum that is obesity – or so one thought. Coleman was the first to postulate hormonal feedback from the adipose tissue to the brain. In 1973, he joined the circulations of an ob/ob and a db/db mouse in a parabiosis experiment; the ob mouse lost weight, while the db mouse did not [108]. This suggested a circulating factor present in the db mouse and a functional receptor present in the ob mouse. Positional cloning by Friedman’s lab led in 1994 to the identification of the adipocyte hormone leptin [109].

Leptin Clinical Studies

In 1997, the O’Rahilly lab identified the first leptin-deficient child [110], and in 1998, the first leptin receptor-deficient patient was identified by Clement et al. [111]. Farooqi et al. [112, 113] showed in 1999 that leptin therapy worked well in promoting weight loss and in reducing appetite and reward in children with congenital leptin deficiency, and Mulligan et al. [114] in 2009 showed similar results in adult patients with lipodystrophy (who also manifest leptin deficiency). But unfortunately, leptin proved to be ineffective in generalized obesity [115] because these patients are leptin resistant.

Leptin Resistance

The first clue to the pathogenesis of leptin resistance was gleaned in 1995 by Leibel et al. [69], who showed that obese patients who lost weight also reduced their energy expenditure, as they became leptin deficient in addition to being leptin resistant. Thereafter, Levine et al. [116] demonstrated one reason why this occurs; patients who gain weight easily have decreased levels of nonexercise activity thermogenesis (NEAT; otherwise known as fidgeting) due to their leptin resistance. However, Rosenbaum et al. [117] performed a seminal experiment which showed that in response to weight loss, obese patients regained sensitivity in response to exogenous leptin injection. These findings suggested that some factor was reversibly antagonizing leptin action in the obese patient.

That factor was identified in 2001, when Niswender and Schwartz [118] documented overlap and crosstalk among insulin, the insulin receptor, and the leptin receptor in the hypothalamic POMC neuron. Lustig et al. [119] demonstrated increased leptin sensitivity upon insulin suppression. Also, the Bruning lab [120] and Nazarians-Armavil et al. [121] demonstrated that hyperinsulinemia is at least a cause, if not the only cause, of leptin resistance. The question is why?

Leptin is a necessary signal to the VMH for the initiation of high-energy processes such as puberty and pregnancy [122]. Indeed, both puberty and pregnancy are insulin-resistant states; leptin levels increase acutely; in adulthood or post-partum, insulin levels fall, weight stabilizes or is lost, and leptin levels return toward the baseline state. Insulin antagonism of leptin signal transduction is likely an integral control mechanism to insure reproductive competence. If leptin signaling could not be modulated, the weight accrual required for reproductive competency during puberty and pregnancy would be compromised [123].

The gut microbiome may also play a role in leptin resistance. In an experiment using only mice otherwise resistant to obesity, Schéle et al. [124] compared mice raised germ-free to conventionally raised mice. The conventionally raised mice had decreased expression of GLP-1 and brain-derived neurotropic factor (BDNF) in both the hypothalamus and brain stem, as well as decreased expression of orexigenic peptides POMC and CART (cocaine- and amphetamine-regulated transcript), and increased expression of the orexigenic peptides NPY and AgRP in the hypothalamus. Furthermore, the conventionally raised mice had inherent leptin resistance, as leptin administration caused less suppression of NPY and AgRP and less weight loss than in the germ-free mice, a clear signal that the gut microbiota influences central feeding mechanisms.

Leptin and DOHaD

Leptin also exerts effects in the prenatal period. Leptin-deficient mice (ob/ob) exhibit maldevelopment of hypothalamic architecture, with aberrant projections of neurons from the arcuate nucleus (the site of leptin receptors) to the paraventricular nucleus (the site of the melanocortin-4 receptors) [125]. However, a single leptin injection at birth can restore normal hypothalamic development and neurotransmission [126]. This effect of neonatal
leptin is also seen in a rat model of maternal undernutrition. Offspring of pregnant rats placed on food restriction during gestation are small for gestational age, insulin resistant, and leptin deficient at birth. However, with adequate nutrition after the neonatal period, these animals become obese as adults, particularly when placed on high-fat chow after weaning [127], suggesting that the neonatal leptin overrode a developmental programming signal for future obesity.

Conclusions

Despite the knowledge of the insulin-leptin connection, and despite multiple efforts of diet, pharmacotherapy, and surgery to promote weight loss, obesity, insulin resistance, and chronic metabolic disease continue to predominate in the population. Only 12% of adults are metabolically healthy [128], and obesity prevalence and severity continue to increase in children, occurring earlier and earlier [129]. Genetics can increase predisposition to obesity but do not explain this health care debacle. Whether this is due to processed food, reduced activity, stress, addiction, mitochondrial dysfunction, obesogens, developmental programming, epigenetics, microbial dysbiosis, or a combination thereof, remains unclear. One hypothesis is that obesity is a syndrome with different patients manifesting different etiologies for their obesity, and therefore likely responding to different therapies. But what is clear is that none of these etiologies are the patient’s fault – no one chooses to be obese, especially not children. Obesity and its overlapping disease entities are not a personal health issue, but rather a public health crisis, and will ultimately require a rational public health response.

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Statement of Ethics

Dr. Lustig and Dr. Fennoy declare no financial or material conflict of interest with respect to this manuscript.

Conflict of Interest Statement

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