GENE-ENVIRONMENT INTERACTIONS CONTROLLING ENERGY AND GLUCOSE HOMEOSTASIS AND THE DEVELOPMENTAL ORIGINS OF OBESITY

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hemoglobin A1C of ≥6.5%, or fasting plasma glucose of ≥126 mg/dl, or a plasma glucose concentration of ≥200 mg/dl 2 h after a 75 g oral glucose tolerance test or a random plasma glucose measurement ≥200 mg/dl (www.diabetes.org). There are currently estimated to be around 382 million individuals worldwide that have diabetes. In the United States (US) alone, 25.8 million individuals (8.3% of the population) have diabetes. It was estimated that diabetes caused at least 548 billion dollars in health expenditure in 2013, and this figure is set to continue growing (International Diabetes Federation). Understanding the factors driving this increase is therefore of great economic and social importance.

B. Prevalence and Associated Morbidity and Mortality of Obesity

The prevalence of obesity and overweight in the United States is high. In 2007–2008, 32% of US men and 36% of US women were obese, and an additional 40% of men and 28% of women were overweight (149). In 2010, more than one-third of US children and adolescents were overweight or obese (368). About 5% of Americans have a class III obesity, i.e., a BMI of >40 kg/m^2 (149). The prevalence of obesity and overweight has increased by 134 and 48%, respectively, since 1976–1980 (492). While overweight and obesity trends among women have remained stable, rates in men have continued to rise (149) with a 50 and 25% long-term risk of developing these conditions, respectively, in the Framingham study (531). These figures vary widely among sex, ethnic, and racial groups (149), as does the relationship between BMI and disease risk such that obesity prevalence is not a definite predictor of the degree of disease risk.

In general, obesity reduces life expectancy by 6–20 yr depending on age and race (152, 397), particularly among adults below the age of 65 (4, 114, 151, 152, 422). Cardiovascular disease, T2DM, cancer, and respiratory diseases are the leading causes of death in obese individuals (422). It is less clear whether being overweight carries the same increased mortality risk (4, 151, 286, 397, 422). The association between overweight/obesity and mortality risk, however, varies by sex, ethnicity, and age, which may be why data are mixed (71, 188, 229, 320, 497, 519). Being overweight or obese is associated with an increased risk of coronary heart disease (52, 91, 555). T2DM is strongly associated with obesity or overweight in both men and women (191), and a BMI of >25 kg/m^2 was associated with a 2.2-fold greater risk of death from diabetes, a greater association than with any other cause of death (422). However, as with other diseases, the relationship between BMI and T2DM risk also varies by ethnicity (314, 499). Other diseases associated with obesity include various types of cancer (70, 112, 201, 433), ischemic stroke (358, 501, 579), heart failure (245), dementia (202), venous thrombosis (7), gallstones (489), gastroesophageal reflux disease (386), renal disease (145), sleep apnea (570), and osteoarthritis (83). Particularly pertinent to this review, maternal obesity is associated with gestational complications and adverse fetal and neonatal health outcomes (348, 513). However, there remains a controversy as to the higher rate of mortality among the overweight and obese, particularly using self-reported BMI (244). Some report the so-called obesity paradox whereby the overall mortality was lower among those with T2DM and cardiovascular comorbidity and weight loss but not weight gain was associated with increased mortality and morbidity (124, 125).

C. Genes × Environment Interactions: Imprinting (Epigenetics) as a Concept

Although a number of common genetic susceptibility loci for obesity and T2DM have been identified over the last decade, the rapid rise in prevalence of these conditions in the last two decades, a time frame which is not compatible with a change in our genetic make-up, suggests that the environment in which we live is an important determinant of obesity risk. Environmental factors that have been attributed to this rapidly increasing prevalence of obesity include increased consumption of highly processed foods that are high in saturated fat and refined carbohydrates as well as reduced physical activity (421). However, the wide variation in BMI among individuals living in the same "obesogenic" environment has led to the opinion that obesity risk is determined by a complex interaction between our genes and the environment in which we live. How these interactions could occur at the molecular level through epigenetic mechanisms and how there may be critical time periods during development when this is more likely to occur will be discussed in more detail below.

D. Historical Background

1. Early concepts of energy homeostasis regulation

In 1940, Hetherington and Ranson (209, 210) first demonstrated that lesions of the ventromedial hypothalamus caused rats to massively overeat and become obese. As later became apparent, to produce the massive obesity associated with the "classic" VMH lesion, damage usually extended to a quite large area including both the ventromedial (VMN) and arcuate (ARC) nuclei (127, 249, 462). However, it was not until several years after this fact became evident that the importance of the ARC and its resident proopiomelanocortin (POMC) and neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons in the regulation of energy and glucose homeostasis were recognized (38, 42, 43, 189, 467). Later, it was shown that large lesions of the lateral hypothalamic area (LHA) produce profound anorexia and weight loss (15), which led Stellar (493) to put forward the dual center hypothesis whereby the VMH was the "satiety center" and

the LHA was the "feeding center." This concept held sway for many years and led to the largely hypothalmocentric view of energy homeostasis control that still dominates the thinking and research of many investigators. However, we now recognize that such control resides within a distributed network of sites within the brain (183, 184) and that lesions in one part of this network can alter the defended level of body weight and adiposity (242). The observation that the level of defended body weight can be altered by lesions of areas such as the VMH and LHA led to the idea of a set-point whose level is set depending on the neural substrates as well as internal and external environments (242).

However, it was obvious that the brain required some means of monitoring the metabolic status of the periphery to enable it to control overall energy homeostasis. Kennedy (247) was among the first to suggest that body fat storage might be the source of such feedback. He suggested that adipose tissue produces a signal, in proportion to its mass, that is sensed by the brain to regulate changes in intake or expenditure, and this keeps body fat within a predefined set-point. This negative-feedback system has been termed the "lipostatic" hypothesis (247). In fact, the lipostatic factor postulated by Kennedy was eventually shown to be leptin, a hormone produced by adipose tissue in proportion to its overall mass (577). However, the basic concept of a set-point remains highly controversial, and extensive tomes have been written in defense (243) and rebuttal of this concept (396, 488, 558). What does seem clear is that in most humans, and some rodent strains that become obese, the defended body weight can be moved upward fairly easily while long-term attempts to move them below their higher body weight by caloric restriction is met with failure in upwards of 90% of individuals (288, 292, 302). The underlying reason for this observation remains unknown, but its existence serves as the main focus for most research which attempts to find treatments for obesity.

2. The discovery of leptin and how it changed things

In 1949, investigators at the Jackson laboratory in Bar Harbor reported a colony of mice showing severe obesity (223). These mice were first distinguishable from littermates at 4 wk of age but became four times heavier than wild-type littermates as adults. Offspring of heterozygous matings demonstrated the 3:1 ratio characteristic of a recessive gene, which was subsequently designated ob (now Lep) (223). In 1966, a second mouse strain with severe obesity syndrome was identified by Coleman and colleagues (220). Mice homozygous for the mutation were designated diabetes (*db*) and displayed early-onset obesity, hyperphagia, and diabetes. These fortuitous observations represented a major breakthrough in the field of the genetics of obesity, although the nature of the defective gene(s) remained to be discovered. Prior to the era of sophisticated transgenic approaches, Coleman and colleagues went on to perform heroic parabiosis experiments. They surgically connected the circulatory system of either wild-type or obese *ob* mice with diabetic *db* mice and found that it produced weight loss and hypophagia in wild-type and *ob* mice without affecting *db* mice. Based on these observations, Coleman and colleagues (220) proposed that *ob* mice lacked a circulating satiety factor and that *db* mice overproduced that circulating factor but could not respond to it. In 1994, Friedman and collaborators (577) cloned the defective gene of the ob mouse. Using positional cloning, they found that the *ob* gene encode a 4.5-kb RNA secreted by adipose tissue in proportion to its mass (577). As predicted, administration of the recombinant OB peptide reduced body weight and food intake of obese mice (73, 197, 399). Based on these physiological effects, Friedman named the peptide "leptin" from the Greek root leptos for "thin." However, *db* mice were insensitive to the weight loss-inducing effect of leptin, suggesting that the *db* locus encodes the leptin receptor, which was subsequently cloned in 1996 (82, 283). Leptin appears to act primarily on the brain to mediate its effects on feeding and metabolism because central administration of leptin has a marked effect on feeding (73), and the strongest expression of leptin receptor occurs in the hypothalamus (283, 527). In fact, leptin fulfills all of the predicted "lipostatic" properties proposed by Kennedy in 1953 (247). Moreover, the observation that leptin is one of the first major metabolic hormones to appear during embryogenesis (215) suggests a role for leptin in perinatal development.

3. Early studies implicating the perinatal environment in the pathogenesis of obesity and diabetes

Some of the earliest evidence in support of the importance of the early life environment in determining long-term health came from studies in the United Kingdom and Sweden in the 1930s demonstrating that, within any one age group, death rates were most affected by the date of birth and not the year of death (248). Further support for the importance of the neonatal environment on long-term health emerged almost 50 years later in studies in Norway by Forsdahl (155) demonstrating that geographical variations in atherosclerotic disease were not associated with current mortality rates but correlated strongly with past infant mortality rates. The earliest evidence that nutrition during neonatal life could influence long-term metabolic health came from the study of individuals who were born during the Dutch Hunger Winter that occurred in the western part of the Netherlands at the end of World War II. These data suggested that low nutrient intake during early postnatal life actually reduced the risk of obesity at age 19 (428). These observations were supported by pioneering studies in rats by Kennedy (246) where he altered the plane of nutrition during the suckling period through manipulation of litter size. Rats reared in small litters where there is little competition for the mother's milk gain more weight during lactation and remain fatter and heavier throughout life even when fed a standard laboratory chow diet. In contrast, rats reared in large litters receive less milk and conse-

quently gain less weight during suckling. These animals remain smaller and leaner throughout life. Importantly, it was demonstrated that if nutrient restriction was initiated for the same length of time post-weaning, rats rapidly caught up in weight (552). On the basis of these findings it was suggested that appetite was determined during the suckling period and that the hypothalamus played an important part in mediating these effects (553). These findings were supported in studies by others in subsequent decades (252, 377, 392, 413). More recent findings from animal models demonstrating the importance of the early postnatal period are discussed below.

Focus on the potential importance of the fetal environment arose from studies by Barker and colleagues (198) demonstrating a strong association between birth weight and subsequent risk of development of T2DM and other features of the metabolic syndrome. These studies demonstrated that individuals with the lowest birth weight were around six times more likely to have T2DM or impaired glucose tolerance at age 64 compared with those individuals with the highest birth weight. These findings have now been reproduced in over 50 studies worldwide. The relationship between birth weight and T2DM holds true in monozygotic (identical) twins (51, 417), suggesting that the fetal environment plays a critical role in mediating the relationship between birth weight and long-term metabolic health. While nutrient supply is one important determinant of fetal growth, assessing the importance of fetal nutrition in mediating these relationships is difficult in humans. However, evidence from studies of individuals who were in utero during periods of famine have provided direct evidence that alterations in maternal nutrition during pregnancy can influence long-term risk of T2DM. Prior to the "Dutch Hunger Winter," the western part of the Netherlands was a well-nourished population. The abrupt onset of the famine and its short duration (5 mo) provided a unique opportunity to retrospectively study the effects of maternal nutrient restriction on offspring glucose tolerance. At age 50, those individuals who were in utero during the famine had worse glucose tolerance compared with those individuals born either the year before or the year after the famine (427). Those exposed during late gestation were most affected, suggesting that the third trimester represents a particularly vulnerable developmental period in terms of long-term regulation of glucose homeostasis. In contrast, risk of cardiovascular disease and obesity was more pronounced in those individuals exposed to famine during early gestation (428). This highlights the different critical periods of development for different organ systems. A subsequent, larger, study of a population exposed to the Chinese Famine (1959–1961) showed a similar association between exposure to suboptimal nutrition in utero and increased risk of T2DM in later life (309). In both studies, it was demonstrated that exposure to a nutritionally rich environment in later life exacerbated the detrimental effects of undernutrition in utero. The causative relationship between poor nutrition in utero and long-term health has been further substantiated by studies in animal models (see below).

II. CENTRAL REGULATION OF ENERGY AND GLUCOSE HOMEOSTASIS

A. The Central-Peripheral Conversation in the Control of Energy and Glucose Homeostasis

Energy homeostasis is defined as the balance between energy intake on the one hand and output as thermogenesis (heat production) on the other. When intake exceeds output, energy is stored primarily as fat in adipose depots. When food supplies are limited and intake is restricted, those adipose stores are called upon as the major energy source over long periods of time. While it is generally agreed that the brain is the controller of energy and glucose homeostasis, it is able to carry out this function only because it receives vital information about the metabolic and physiological status of the body from enteroceptive inputs from the various organs via metabolic signals and neural afferents. Afferents from the majority of viscera are carried primarily within the vagus (X^{th}) cranial nerve that has its cell bodies in the nodose ganglion. Their central axons terminate within the caudal part of the nucleus of the solitary tract (NTS) in the medulla (96, 442, 443, 466). Other small unmyelinated nerves from the viscera, which travel with somatic efferents, have their cell bodies in the dorsal root ganglia of the spinal cord. Their central processes also terminate in the caudal NTS. Thus the NTS represents the first important neural link between the viscera and the brain. These neural inputs carry sensations of stretch, pain in the viscera, as well as from chemical sensors within the portal vein, carotid body, and small intestines (96, 442, 443, 466). Importantly, the brain also monitors the metabolic status of the body by the transport of hormones such as leptin, insulin, and ghrelin and substrates such as glucose, free fatty acids, lactate, ketone bodies, and cytokines across the blood-brain barrier (BBB) (28, 29, 31, 362). The BBB excludes many toxins and molecules that do not have dedicated transporters from entering the brain by virtue of tight junctions between the vascular endothelial cells and apposition of astrocyte foot processes on cerebral microvessels. However, tight junctions in some vessels in areas such as the ARC may vary in permeability depending on the nutritional state of the individual (273). Finally, these neural, hormonal, and substrate signals from the body are integrated within a distributed network of brain sites that contain specialized metabolic sensing neurons (see below) which gather these signals from the body, together with indirect neural inputs from the primary senses of taste, smell, sight, hearing, and sensation, to alter their membrane potential, neural activity, neuro-transmitter and -peptide release, as well as gene transcription (303).

B. Metabolic Sensing Neurons: the Basic Integrators and Regulators of Glucose and Energy Homeostasis

In the 1950s Jean Mayer (322) first postulated that there were neurons in the hypothalamus that sensed changes in glucose oxidation as a means of regulating feeding. It was not until 1964 that Oomura et al. (372) and Anand et al. (16) identified such glucosensing neurons. The majority of neurons utilize glucose as their primary fuel to produce ATP when their activity increases. When neuronal activity increases, neuronal glucose transporters 3 (Glut3) increase the uptake of glucose proportionally (530). Most neurons can also utilize lactate, long-chain fatty acids, and ketone bodies as alternate fuels in some instances (47, 131, 312, 445). However, whereas metabolic sensing neurons also utilize glucose as a primary fuel, ambient extracellular levels of glucose and other metabolic substrates are "sensed" by these neurons using a variety of signaling and metabolic pathways as a means of regulating their activity. Thus, while most neurons utilize such substrates to fuel their ongoing activity, metabolic sensing neurons do as well, but also use these same substrates to regulate their activity (50, 280, 301, 303, 338).

These neurons either increase (glucose excited) or decrease (glucose inhibited) their activity as ambient glucose levels rise and are conversely inhibited and excited as glucose levels fall (16, 20, 304, 373). Thus, after a meal, glucose-excited neurons are generally activated, while glucose inhibited neurons are inactivated. During fasting or insulin-induced hypoglycemia, glucose inhibited neurons are powerfully activated (450, 452, 484). Within the ventromedial portion of the hypothalamus (VMH), which is composed of the ARC and VMN, ~10–15% of neurons are either glucose excited or inhibited (305). Of those, 40–65% utilize the pancreatic form of glucokinase as a gatekeeper for the regulation of glucose-induced changes in their activity (236). Formation of ATP within glucose-excited neurons leads to inactivation of an ATP-sensitive K^+ (K_{ATP}) channel leading to membrane depolarization, entry of calcium via a voltage-dependent calcium channel, increases in activity, propagation of an action potential, and release of neurotransmitters and -peptides from their axon terminals (20, 305). Glucose-inhibited neurons form nitric oxide and, via activation of AMP-activated kinase and soluble guanylyl cyclase, increase neuronal firing when glucose levels fall by an action on the cystic fibrosis transmembrane receptor (148). Catabolic ARC POMC neurons are predominantly glucose excited (221), while anabolic ARC NPY/AgRP (351) and LHA orexin/hypocretin neurons (350) are mostly glucose inhibited in type. However, other glucosensing neurons have been identified which utilize several other ion channels and transporter mechanisms to regulate their activity (239, 365, 375, 390).

There remains a controversy as to whether physiological changes in blood and/or brain glucose are actually involved in the regulation of feeding as Mayer originally proposed (129, 172, 305). To summarize this controversy, studies using very high or low levels of glucose or glucose availability, especially in the brain, can inhibit or stimulate feeding, respectively (186, 474, 479, 529). Some investigators have shown a relationship between spontaneous, small dips in blood glucose preceding meals in rats and humans (72, 74, 313). However, others have failed to confirm such a relationship between blood or VMH glucose levels and meal onset (129). Also, manipulation of VMH neuronal glucosensing by altering glucokinase activity fails to affect either short- or long-term feeding (129), while it does markedly alter the counterregulatory responses to insulin-induced hypoglycemia (290). Such results suggest that hypothalamic glucosensing neurons are not critical regulators of normal feeding but are important for the defense against hypoglycemia.

Many of these same VMH glucosensing neurons are also fatty acid sensors which respond to long-chain fatty acids by altering their activity (230, 278, 280, 281, 337, 374). While early work suggested that this fatty acid sensing was mediated by intracellular metabolism of long-chain fatty acids (230), it now appears that much of this sensing is mediated by fatty acid translocator/CD36 (which appears to act as a receptor and may also be a transporter of fatty acids) in many VMH neurons and that this regulatory step is independent of neuronal fatty acid oxidation (278, 280, 281). Furthermore, although impairment of VMH glucosensing has no effect on energy homeostasis, altering fatty acid sensing by depletion of VMH neuronal CD36 inhibits linear growth as well as causes redistribution of fat stores from visceral to subcutaneous adipose depots and marked insulin resistance (278). Thus, while the glucosensing properties of VMH metabolic sensing neurons do not appear to be critical for the regulation of energy homeostasis, their ability to sense and respond to long-chain fatty acids is critical for some aspects of both energy and glucose homeostasis. Importantly for this review, the interaction among an obesity-prone genotype, diet, and the presence of maternal obesity has a major effect on both the glucose- and fatty acid-sensing properties of these VMH metabolic sensing neurons (281).

In addition to their responses to glucose and long-chain fatty acids, the activity of many of these same neurons is also altered by ambient levels of lactate (485) and ketone bodies (279, 510), both of which are produced locally by astrocytes (48, 49, 131). They also respond to hormones produced in the periphery such as leptin (225, 486), insulin (487, 541), and ghrelin (99) which are transported across the BBB. Thus the term metabolic (or nutrient) sensor is an apt term for these neurons. Importantly, while a great deal of the research on such neurons has focused on ARC and

VMN neurons, glucosensing neurons have been identified in the lateral hypothalamus (16, 350), hypothalamic paraventricular nucleus (PVN) (128), amygdala (578), basal ganglia (285), NTS (343), and several other brain areas known to be involved in the regulation of both energy and glucose homeostasis (289, 305). Most of these neurons make critical connections with brain areas that provide efferent output to a variety of neuroendocrine, autonomic, and behavioral centers required for such homeostatic processes. The network of brain areas containing these metabolic sensors forms a distributed network that functions as an integrated system. Thus the early observations that destruction of the VMH or LHA leads to marked disturbances in energy and glucose homeostasis (209, 210, 240, 241, 341, 534) do not mean that these are satiety and feeding centers; it simply means that destroying one node of this distributed network can lead to dysfunction of its integrated function. While there is a great deal of redundancy in this distributed network, many of its component parts can undergo plasticity, particularly during early pre- and postnatal development through alterations in neural connections and expression of neuro-transmitters and -peptides (58, 59, 62, 98, 391–393, 490).

C. Homeostatic and Reward-Based Systems

To ensure adequate nutrition, it is necessary for the brain to have intrinsic neural circuits that sense and regulate the levels of various nutrients in the blood and body stores. As mentioned above, a primary importance has been given to the hypothalamus, in part because this brain region can integrate hormonal, autonomic, and somatomotor control mechanisms and, in turn, induce a variety of neuroendocrine homeostatic responses **(FIGURE 1)**. However, we now know that the central systems regulating energy homeostasis involve a distributed and interconnected neural network (181, 182, 301). For example, the ARC, that was originally thought to be exclusively "anorexigenic," contains two chemically identified neuronal types that play opposite roles in energy balance regulation: the POMC neurons that are anorexigenic but also the NPY/AgRP neurons that are orexigenic (94, 483). Moreover, POMC neuronal activity can be modulated indirectly via transsynaptic GABAergic inputs arising from NPY neurons, showing the anatomical intricacy of these neural networks (17, 100, 516). Arcuate POMC and NPY neurons project to multiple hypothalamic and extrahypothalamic sites to regulate feeding (65, 94). Of particular importance are projections to the PVN because it is the most thoroughly characterized pathway involved in feeding and energy balance regulation, and the PVN is anatomically connected to endocrine, autonomic, and somatomotor systems (461, 506, 544). For example, the parvocellular part of the PVN contains corticotropin-releasing hormone and vasopressin neurons that regulate adrenocorticotropic hormone secretion and thyroid-stimulating hormone neurons that influence thyroid-stimulating hormone production in the pituitary. In addition to neuroendocrine neurons, the PVN also contains neurons that send direct projections to preautonomic sites, such as the brain stem and spinal cord (458, 506). In addition to forebrain structures, the caudal brain stem, and particularly the dorsal vagal complex, plays an essential role in the regulation of energy homeostasis. The dorsal vagal complex comprises the dorsal motor nucleus of the vagus nerve, NTS, and area postrema. Although the hypothalamus predominantly integrates long-term adiposity signals, dorsal vagal complex neurons appear to be more involved in the short-term control of feeding control in response to satiety signals (see Refs. 46, 182 for reviews).

If feeding were controlled solely by homeostatic systems, most individuals would likely maintain a stable, relatively lean body weight. However, virtually any mammal will eat beyond its homeostatic needs when exposed to highly palatable foods such as a high-fat/high-sucrose diet. Such observations support the contention that the hedonic ("reward") system plays an important role in regulating feeding behavior **(FIGURE 1)**. The hedonic system deals with the rewarding value of stimuli (e.g., food) and has neural circuits which encode wanting (incentive motivation) and liking (experienced pleasure) of those stimuli. A key neurobiological substrate involved in incentive motivation to eat is the mesolimbic dopaminergic pathway. This pathway is composed of dopamine neurons in the ventral tegmental area (VTA) of the midbrain that connects to limbic centers such as the nucleus accumbens, the amygdala, hippocampus, and medial prefrontal cortex (45). The observation that rodents with defective dopamine signaling in this mesolimbic system become aphagic and adipsic and can even die of starvation supports the idea that the mesolimbic dopaminergic system plays an incentive role in feeding regulation (507, 526). In addition to being activated by a variety of addictive substances, including cocaine and alcohol, VTA dopamine neurons are also directly modulated by metabolic hormones such as leptin and ghrelin. Leptin exerts a direct inhibitory influence on VTA dopamine neurons, and hyperphagia of leptin-deficient mice is blunted in the absence of dopamine (146, 163, 217, 507). In contrast, ghrelin increases the activity of VTA dopaminergic neurons and direct injection of ghrelin into the VTA promotes feeding (3, 354). These studies show that metabolic hormones are not only involved in the short- and long-term control of energy homeostasis, but also modulate motivated behaviors and both our need and desire to eat.

D. Central Roles for Leptin, Insulin, and Ghrelin

1. Leptin

The discovery of leptin reinforced the concepts originally proposed by Woods and Porte for insulin (561) that our

penditure and glucose homeostasis with a more moderate effect on body weight regulation (27, 44).

Prior to 2005, a widely held view was that most, if not all, of leptin's effects are mediated by neurons located in the ARC. However, peripheral leptin administration also acts on neurons in other brains regions such as the VMN, LHA, VTA, and NTS (76, 134, 194, 195, 468). Such observations slowly moved the attention of the field away from the arcuate-centric notion of leptin action. Thus mice lacking LepRb in SF1-expressing neurons of the VMN develop mild obesity when fed a chow diet and are markedly sensitive to high-fat diet-induced obesity, supporting a role for VMN neurons in leptin's regulatory actions (121). In addition, targeted deletion of LepRb in LHA neurotensin neurons causes early-onset obesity due to hyperphagia and locomotor inactivity (284). Notably, neurotensin neurons appear anatomically well-poised to relay leptin's actions on the mesolimbic dopaminergic system, suggesting that neurotensin neurons may be a crucial point of convergence for homeostatic and hedonic interactions that regulate ingestive behavior. Supporting a role for leptin on brain reward circuits, leptin receptors are expressed and functional on dopaminergic neurons in the midbrain and direct manipulation of LepRb in VTA dopamine neurons influences feeding behavior (146, 163, 217). Another site of particular interest outside the hypothalamus is the NTS, a hindbrain nucleus involved in the processing of meal-related satiety signals where LepRb mRNA was shown to be expressed (335). But it was another 12 yr before the functional relevance of these NTS LepRbs was demonstrated. Downregulation of LepRb in the medial NTS led to increased body weight and adiposity and caused chronic hyperphagia, likely due to a reduction in leptin's potentiation of gastrointestinal satiation signaling such as cholecystokinin (CCK) (204). The NTS also receives neural inputs from the hypothalamus, and recent studies have demonstrated that leptin's modulation of energy expenditure and brown adipose thermogenesis is via a GABAergic ARC-PVN-hindbrain pathway (258). In summary, the effects of leptin on the central control of energy homeostasis are anatomically distributed and appear to involve a complex, distributed, and interconnected neuronal network involving neurons located in throughout the brain.

2. Insulin

Despite its sole production by the β-cells in the pancreas, plasma insulin, like leptin levels, generally parallel overall levels of carcass adiposity (23, 416). In addition, plasma insulin levels also vary over a wide range during ingestion and absorption of nutrients. While peripheral insulin's main actions are on glucose homeostasis, several lines of evidence suggest that insulin can act centrally to affect many brain functions. First, there are abundant levels of insulin receptors in several brain areas including the olfactory bulb, hippocampus, and hypothalamus (147, 226, 238, 573). There is still a debate about whether insulin is actually produced within the brain (376, 463), but it does appear that, despite its large size, it is transported across the BBB (30). During brain development, insulin acts on its brain receptors (sometimes in association with insulin-like growth factor I) as a trophic factor for facets of neural development (206, 423, 432) including neurite outgrowth (206, 464) and neuronal differentiation (355) and survival (359). However, when injected into the hypothalamus of rat neonates, insulin alters neuronal density in the VMN in association with increased body weight gain as adults (410). While controversial (159), some studies suggest that insulin might cross the placenta to enter the fetal circulation in humans (332). For example, in rats, insulin injections in third trimester dams predispose to adult obesity in offspring (232). However, maternal hyperinsulinemia might increase transplacental glucose transport to the fetus (378). Maternal hyperinsulinemia and hyperglycemia could thus cause fetal hyperglycemia with attendant hyperinsulinemia (235) and later increases in fetal weight in offspring of mothers with gestational diabetes (511). On the other hand, insulin clearly does cross the gut wall in the early postnatal development in rodents (213, 349) such that elevations in maternal milk insulin levels can be absorbed by the offspring as potential mediators of obesity development in later life (176).

In addition to these developmental effects, insulin has important glucose-dependent actions on the activity of hypothalamic metabolic sensing neurons (451, 487) as one way in which a signal relating to adiposity can be "sensed" by the brain. There is a large amount of literature on the effects of centrally injected insulin on food intake, energy, and glucose homeostasis. Both chronic and acute intracerebroventricular infusions of insulin reduce food intake (9, 560, 562) and reducing periventricular insulin receptors causes increased food intake, adiposity, and peripheral insulin resistance (367). However, reducing insulin receptors focally in the VMH causes glucose intolerance without altering body weight (388). In mice with selective neuronal knockout of insulin receptors, females have increased food intake, and both males and females develop diet-induced obesity, mild insulin resistance, and hypertriglyceridemia (68). However, such mice reportedly had no abnormalities of brain development or neuronal survival. Direct injections of insulin into the hypothalamus (415) or via the carotid arteries (426) alter hepatic glucose production (415), although the physiological significance of these studies has been questioned because of the large doses or nonphysiological conditions used to assess these central actions of insulin (306). Thus there is a great deal of conflicting information about the physiological role of insulin on brain development and the regulation of energy and glucose homeostasis. On balance, it seems likely that insulin is transported across the BBB and does have effects on all of these parameters.

3. Ghrelin

Ghrelin was originally discovered as an endogenous ligand for the growth hormone secretagogue receptor (GHSR) (254). In adults, ghrelin is mainly synthesized within oxyntic mucosa cells of the stomach, whereas the primary source of ghrelin production during neonatal life appears to be the pancreas (254, 454). In part because of its discovery from its linkage to GHSR, ghrelin was originally reported to stimulate growth hormone (GH) secretion (254). But it rapidly became evident that it also exerts an important role on feeding behavior. When injected peripherally or centrally, ghrelin promotes feeding, suppresses energy expenditure, and causes weight gain (276, 352, 563). Remarkably, ghrelin-induced hyperphagia occurs within 5 min and persists for 24 h after injection. The observations in both human and other animals of a preprandial rise and a postprandial decline in plasma ghrelin levels suggested that ghrelin plays a specific role in hunger and meal initiation (105, 106, 515). Based on these physiological effects, it is not surprising that GHSRs are abundantly expressed in various brain regions involved in somatic growth, food intake, and body weight regulation such as the hypothalamus, hindbrain, and midbrain (342, 580). Empirical studies employing direct intra-ARC injections of ghrelin and selective lesions of the ARC demonstrated the primary importance of ARC neurons, specifically in mediating ghrelin's action on feeding (509, 563). Within the ARC, the highest proportion of neurons activated by systemic ghrelin injection coexpress NPY and AgRP (100, 540, 554). Consistent with these findings, pharmacological blockade of NPY or its receptors blunts the effects of ghrelin on food intake (276, 352). Ghrelin can also regulate the activity of POMC neurons in the ARC, but this effect appears indirect and likely involves trans-synaptic GABAergic inputs arising from NPY neurons (17, 100, 516).

Leptin and ghrelin therefore appear as two complementary, yet antagonistic, regulators of energy balance. Notably, the distribution pattern of GHSR resembles that of LepRb (401), suggesting that leptin and ghrelin might reciprocally regulate many of the same neurons. However, whether there is a direct interaction between leptin and ghrelin signaling at the cellular level remains unclear. For example, although ARC neurons coexpress GHSR and LepRb, GHSR knockout mice display unaltered leptin sensitivity (401). Nevertheless, similar to leptin, the regulatory actions of ghrelin on feeding likely involve a complex and distributed neural network. In addition to its actions on hypothalamic neurons, ghrelin also regulates mesolimbic dopaminergic neurons in the midbrain to modulate more complex aspects of feeding such as food-reward behavior (3, 85, 354, 400, 478). More recent genetic evidence demonstrated that reactivation of GHSR signaling selectively in hindbrain neurons does not ameliorate ghrelin-induced food intake but rescues hypoglycemia of GHSR null mice, suggesting that hindbrain neurons relay ghrelin's effects on glucose homeostasis (471).

E. Neuronal Plasticity

The mammalian brain ensures adaptive behavior through its large capacity for cellular and circuit plasticity. One unique property of the hypothalamus, compared with other brain structures such as the cortex and hippocampus, is that its regulation is to a large degree activity-independent, but instead is controlled by physiological signals that reflect environmental conditions. The biological processes involved in neuronal plasticity fall into two major categories: the birth of new neurons (neurogenesis) and the reshaping of existing neural circuits (synaptic remodeling). Low rates of neurogenesis are observed in the mature hypothalamus under basal conditions (255, 256), and median eminence tanycytes appear to be a possible source of these newborn neurons (282). This constitutive hypothalamic neurogenesis can be enhanced by hormonal factors. For example, central injections of ciliary neurotrophic factor (CNTF) induced marked neurogenesis in the hypothalamus that appears to participate in the weight loss effects of CNTF in *ob*/*ob* and DIO mice (256). Moreover, microimplantation of neural progenitors that express leptin receptors into the hypothalamus of newborn *db*/*db* mice allows differentiation of the donor cells into neurons that integrate into functional neural circuits that lead to reduced hyperphagia and obesity (107). Nonneurotropic factors, such as aging and neurodegeneration, can also promote hypothalamic neurogenesis (405). Hypothalamic neurogenesis can also be downregulated. For example, high-fat feeding alters cellular remodeling as demonstrated by a reduction in the number of newly generated cells and the maintenance of old neurons in the mature hypothalamus (327). Together, these findings demonstrate that neurogenesis might represent an important adaptive cellular mechanisms in response to environmental insults.

Neuronal plasticity of hypothalamic feeding circuits also occurs through rearrangement of synapses. The excitatory and inhibitory synaptic inputs to the POMC and NPY neurons are markedly altered in adult *ob*/*ob* mice; leptin deficiency increases excitatory inputs on NPY/AgRP neurons while it decreases excitatory synaptic inputs to POMC neurons (406). Acute leptin injection in adult *ob*/*ob* mice rapidly (within hours) reverses these effects, both at the electrophysiological and ultrastructural levels. Other hormones, such as ghrelin and corticosterone, also have organizational effects on hypothalamic neural circuits by modulating the synaptic inputs of ARC POMC and NPY neurons in adult mice (193, 406). Moreover, a significant remodeling of synapses has been reported in obesity-prone (DIO) rats, with an increase in inhibitory inputs to POMC neurons in the ARC of DIO rats compared with diet-resistant (DR) rats (218). The capacity of nutritional challenges

to cause structural changes also appears to differ between DIO and DR rats. High-fat feeding causes a loss of synapses onto POMC neurons in DIO rats, but a gain in synaptic coverage in obesity-resistant DR rats (218). Together, these observations indicate that remodeling of brain circuits involved in energy balance regulation occurs throughout the entire lifespan and is influenced by both metabolic and physiological cues and pathological insults. This neuronal plasticity allows the elaboration of adaptive behavioral and physiological responses that are essential for optimal regulation of energy balance.

F. Gut-Brain Interactions

1. Neurohumoral inputs

The brain receives a wide variety of signals from the gastrointestinal (GI) tract, via either sensory afferents or hormonal signals. The vagus nerve is indisputably the most important neural link between the gut and the brain. It is the longest of the cranial nerves and innervates the entire alimentary tract. It comprises fibers carrying afferent sensory information from the periphery to the brain, but also fibers carrying efferent motor information from the brain to the viscera (420). Afferent signals carried by the vagus nerve include information about gastric stretch, enteroendocrine signals from hormones released within the GI tract, and blood glucose and fatty acid levels. The caudal brain stem, and particularly the NTS via its vagal afferents and efferents, acts as a nodal point in the gut-brain axis. Vagal afferents from the GI tract synapse within subregions of the NTS, and the activation of these afferents regulates postprandial function by inhibiting food intake (465). In turn, the NTS sends reciprocal projections to other regions of the brain involved in feeding regulation such as the hypothalamus, amygdala, and nucleus accumbens. The NTS therefore represents a major portal through which visceral afferent information for homeostatic reflexes enters the brain.

Vagal afferent fibers are also sensitive to a variety of peripheral factors, including CCK, an endogenous peptide released by duodenal enteroendocrine cells (310). CCK is released after a meal and inhibits food intake [i.e., reduces meal size and induces meal termination (480)] in part by increasing the firing rate of vagal afferents projecting to the NTS (170, 347). The regulatory action of CCK on vagal-NTS projections appears to be mediated via the CCK-A receptor subtype (64, 259, 277, 395).

In addition to CCK, the gut secretes a number of other hormones that signal to the brain to regulate feeding. These hormonal effectors include ghrelin, peptide YY (PYY), and glucagon-like peptide-1 (GLP-1). Ghrelin is produced mainly by the gastric mucosa and is the only known peripheral hormone that promotes feeding. That secretion of ghrelin is increased in response to starvation, increased before a meal, and suppressed by meals, supports the hypothesis that ghrelin is primarily involved in meal initiation (105, 106, 515). The hypothalamus is a primary site of ghrelin's orexigenic effects. The highest density of ghrelin receptors and ghrelin-responsive neurons is found in the hypothalamus, particularly in the ARC, VMN, and PVN (211, 352, 342, 580). The observations that blockade of the gastric vagal afferent abolishes the feeding response to intravenous ghrelin and that GHSRs are expressed in vagal terminal suggest that ghrelin also induces some of its regulatory effects through the vagus nerve (115). For example, ghrelin does not stimulate feeding in human patients with surgical procedures involving vagotomy (115). However, data to the contrary exist regarding an essential role for the vagus in transmitting peripheral ghrelin's effects on feeding (19).

PYY is produced by L-type enteroendocrine cells, mainly in the ileum and colon, in response to the caloric content of the meal (5). The bioactive peptide, PYY3–36, is stimulated in proportion to the energy content of food and peaks 1–2 h postprandially. Peripheral administration of PYY3–36 inhibits food intake in rodents and humans (34, 35). PYY3–36 has a high affinity for the NPY Y2 receptors, which are widely distributed throughout the periphery and CNS, including in vagal endings (253). Consistent with these findings, gastric vagotomy blocks the anorectic effects of PYY3–36 (1, 253). In addition, PYY3–36 acts on hypothalamic neurons to reduce feeding and ARC injection of PYY3–36 inhibits food intake and inhibits the electrical activity of NPY nerve terminals causing a reduction of the inhibition of POMC neurons (35).

GLP-1, GLP-2, and oxyntomodulin are produced by the posttranslational processing of the preproglucagon gene in the gut and the brain stem (24). The GLPs are produced by intestinal L-cells in response to fatty acids or carbohydrates. GLP-1 is released into the circulation after a meal to inhibit gastric secretion and emptying and induce postprandial secretion of insulin (24, 268). Direct oxyntomodulin injection into the ARC causes a sustained reduction in refeeding after a fast, indicating the importance of the hypothalamus and particularly the ARC in mediating oxyntomodulin's anorectic action (113). However, intra-ARC administration of the GLP-1 receptor antagonist exendin9–39 does not block the anorectic action of GLP-1, indicating that oxyntomodulin and GLP-1 use different neural pathways to mediate their feeding effects (113). Sites of action of GLP-1 include neurons in autonomic control sites such as brain stem catecholamine neurons (565, 566).

2. Gut microbiota

Gut microflora and their interactions with obesity have become a subject of great interest in recent years. Leptin-deficient *ob/ob* mice have significant reductions in Bacteroides and increases in Firmicutes, two major gut bacterial phyla (307). Similarly, some obese humans demonstrate an

increase in Firmicutes in their stools (308), and prolonged ingestion of a high-fat diet is associated with decreased bacterial abundance and increased Firmicutes content (520). Importantly, bacterial transplants from lean and obese mice into otherwise high-fat obesity-resistant, germ-free mice cause them to develop the weight gain phenotype of the donors, suggesting a causal role of gut microbiota in the development of obesity (521, 522). Also, increased body and fat mass in human twin pairs discordant for obesity could be transmitted to germ-free mice by transplantation of the fecal microbiota of those humans (438). The mechanism by which alterations in microbial gut flora might determine the propensity of an individual to become obese has not been established. However, one hypothesis is that these microflora might alter nutrient absorption by changing the absorptive surface of the gut in association with inflammatory changes induced by some diets (429, 520, 521). Such changes in gut permeability might become more important as the individual matures since large molecules such as antibodies, leptin, and insulin cross the neonatal intestinal barrier and enter the circulation (287, 349). Regardless of the specific mechanism, early postnatal nutrition and milk content might alter gut microbiota as an explanation for the increased obesity of diet-resistant pups cross-fostered to obese DIO dams (75, 176, 272, 315).

G. Peripheral Organs and Glucose Homeostasis

1. Pancreas

The pancreatic β-cells within the islets of Langerhans are the only cells that have the capability to secrete insulin. They are therefore central to the appropriate regulation of glucose homeostasis. The islets of Langerhans were first identified in 1869 by the German anatomist Paul Langerhans and, despite the fact that they constitute <5% of pancreatic mass, they are critical for maintenance of glucose homeostasis. They contain five major cell types: α-cells (that produce glucagon), δ-cells (that produce somatostatin), PP cells (that produce pancreatic polypeptide), ε-cells (that produce ghrelin), and β-cells (that produce insulin and amylin). Pancreatic β-cells produce insulin primarily in response to elevated levels of glucose. However, production can also be increased in response to other factors such as certain amino acids, free fatty acids, and the sulfonylurea class of antidiabetic drug. The stimulation of insulin secretion involves changes in β-cell electrical activity and ultimately exocytosis of insulin (reviewed in Rorsman and Braun, 447). T2DM is thought to arise in general when pancreatic β-cells malfunction such that they cannot further increase insulin secretion to compensate for progressive peripheral tissue insulin resistance. This may arise because of an inherent or progressive reduction in β-cells mass (reviewed in Weir and Bonner-Weir, 545), genetic defects that reduce β-cell function (reviewed in Bonnefond et al., 54), programming events that occurred in early life resulting in a permanent reduction in β-cell mass and/or function (reviewed in Reusens et al., 435), or postnatal triggers that could involve epigenetic mechanisms (171).

2. Liver

The liver is the major site of glucose production under fasting conditions, and thus resistance to the action of insulin to inhibit hepatic glucose production can contribute to hyperglycemia (66). There are a number of mechanisms by which hepatic insulin resistance can occur. Nonalcoholic fatty liver disease (NAFLD), which is thought to affect up to 30% of the population in the Western world, is thought to be a major contributing factor (571). Under physiological conditions fatty acids enter hepatocytes and are either oxidized by mitochondria or stored in the form of triglycerides. However, under conditions where there is an imbalance between influx and oxidation excessive storage occurs. This can occur, for example, when lipid storage capacity of adipose tissue becomes exceeded, leading to increased flux of fatty acids into the liver and consequently increased deposition of triglycerides and other lipid intermediates such as phosphatidic acid and diacylglycerol (21). These can result in activation of various kinases (e.g., inhibitor of kappa B kinase and Jun NH_2-terminal kinase) that inhibit insulin signaling through serine phosphorylation of IRS-1 and consequently cause hepatic insulin resistance. In addition, there is evidence to suggest that under conditions of hyperinsulinemia, as a consequence of resistance to the action of insulin in relation to inhibition of hepatic glucose production, insulin's ability to promote de novo lipogenesis can remain intact. This will further promote hepatic triglyceride accumulation (66). There is good evidence to suggest that fatty liver and hepatic insulin resistance can develop as a result of both early environmental (86) and genetic factors (168).

3. Skeletal muscle

Skeletal muscle is the major site of glucose disposal postprandially and thus insulin resistance at this site is a substantial contributor to the development of T2DM. Skeletal muscle takes up glucose in an insulin-dependent manner as a result of the stimulation of translocation of the glucose transporter GLUT4 to the plasma membrane via stimulation of the phosphoinositol 3-kinase-protein kinase B (Akt) pathway. In addition to this insulin-stimulated pathway, there is an alternative pathway that potentiates glucose uptake into skeletal muscle that is activated by exercise and caloric restriction (453). This is mediated by AMP kinase, which has therefore become a focus of potential therapeutic strategies for insulin resistance and associated syndromes. As with liver, skeletal muscle is a major site of triglyceride accumulation in situations where the adipocyte lipid storage capacity has been exceeded. There is a strong positive

correlation between muscle triglyceride content and insulin resistance (385). The mechanism(s) by which increased lipid accumulation induces insulin resistance in skeletal muscle remains a subject of debate (reviewed in 55). However, it has been suggested that such lipotoxicity results in increased levels of bioactive lipid metabolites such as ceramides that are known to inhibit activation of protein kinase B. Paradoxically intramyocellular triglycerides are also increased in highly insulin-sensitive trained athletes (reviewed in 89). This suggests that it is not the presence of the triglycerides per se that is causing the insulin resistance and that perhaps if their turnover is increased, for example, by regular exercise, generation of lipotoxic intermediates is reduced.

4. White adipose tissue

In recent years, the contribution of adipose tissue to whole body glucose homeostasis and regulation of energy balance has been increasingly recognized, and it is therefore no longer considered merely a site of lipid storage. It can both directly and indirectly influence glucose homeostasis. Adipose tissue takes up glucose in an insulin-dependent manner. Although it was initially considered to account for only ~5% of postprandial glucose uptake, studies with transgenic animals have suggested that loss of insulin-dependent glucose uptake to adipose tissue leads to substantial loss of glucose tolerance (2). In addition to directly taking up glucose, adipose tissue can indirectly affect whole body glucose homeostasis through release of factors including free fatty acids, adipokines (e.g., resistin and adiponectin), and inflammatory mediators (e.g., TNF-α) that influence glucose uptake and/or insulin action in other tissues, especially skeletal muscle (reviewed in 165). It is well established that obesity-associated insulin resistance is associated with inflammation of adipose tissue and consequently increased production of inflammatory markers and cytokines (including TNF-α, IL-6, and IL-1β) that inhibit insulin signaling (reviewed in 144). Adipose tissue is also the major site of leptin production, a major regulator of energy balance across the life course (discussed in detail elsewhere in this review).

III. PERINATAL BRAIN DEVELOPMENT

The hypothalamus develops from the rostral diencephalon after induction by the underlying prechordal plate. Classical birth dating studies using [^{3}H]thymidine or the thymidine analog BrdU revealed that the majority of neurons composing the hypothalamus are born between embryonic day (E) 11 and E14 in mice and E12 and E17 in rats (14, 101, 227, 317, 383). Hypothalamic neurons acquire their terminal peptidergic phenotype soon after they are generated. For example, melanin concentrating hormone neurons in the LHA are born between E12 and E13 in rats, and its mRNA is detected in the LHA as early as E13 (63). More recent genetic cell lineage experiments also indicated that hypothalamic progenitor cells can give rise to neurons that express antagonistic neuropeptides in adult life. For example, embryonic *Pomc*-expressing precursors can subsequently adopt either a POMC or an NPY phenotype (383).

Although hypothalamic neuronal proliferation and differentiation occurs primarily during the second half of gestation in rodents, the rodent hypothalamus remains relatively immature at birth and continues to grow during the first 2–3 wk of postnatal life. Axonal tract tracing experiments in mice showed that hypothalamic axonal connections are not formed at birth. For example, ARC axons reach their target nuclei between postnatal day (P) 6 and P16 (60). Axon terminals containing NPY/AgRP are found in a pattern that coincides with the innervation of axons from the ARC (25, 187, 361). Efferent projections from the VMN and dorsomedial nucleus (DMN) appear to develop prior to those from the ARC and are fully established by P6 and P10, respectively (60). Synapses are another key component of neuronal connectivity. We still know relatively little about the exact time point (if any) at which synapse assembly is fully established in the hypothalamus, but a few reports indicate that synapses mature gradually in the hypothalamus from birth to adulthood (319, 328).

Brain stem projections develop relatively early in rodents. Brain stem catecholaminergic inputs to the PVN are present as early as P1 in rats (440). However, different neurotransmitter systems show different developmental patterns. For example, the density of noradrenergic projections to the PVN is relatively low at birth and gradually increases to reach adult levels at weaning. In contrast, adrenergic projections are relatively high in the PVN of newborn rats but gradually decrease until weaning (440). Reciprocal descending projections from the hypothalamus to the caudal brain stem also develop early in life. Retrograde tracing experiments showed that hypothalamic neurons, such as those in the DMN, PVN, and LHA, send axonal projection to dorsal vagal complex neurons at birth and continue to develop to achieve adult-like patterns at weaning (439, 441). In summary, projections to and from the hypothalamus and brain stem develop primarily after birth and appear chemically and structurally immature until weaning.

The considerable importance of postnatal hypothalamic development in rodents differs from that in humans and nonhuman primates where the hypothalamus develops almost entirely during fetal life. For example, in Japanese macaques NPY/AgRP fibers innervate the PVN as early as gestational day 100 (i.e., late second trimester) and a mature pattern of NPY/AgRP projections is not apparent until gestational day 170 (180). These findings emphasize the importance of recognizing species differences in terms of timeline of developmental events. Although the regional development of the rodent hypothalamus proceeds on a

timeline of days, the same developmental process takes weeks to months in human and non-human primates. Similar to non-human primates, the human hypothalamus also develops primarily prenatally with NPY-containing axons detected in the ARC and PVN as early as at 21 weeks of gestation (262).

IV. GENETIC BASIS OF OBESITY

A. Single Gene Mutations

Although single gene mutations that cause obesity are rare, their identification has helped greatly in our understanding of energy homeostasis regulation. One very successful approach to identify monogenic forms of obesity has been to focus on children who were extremely obese from an early age and to use a combination of biochemical and genetic approaches to identify the affected locus (reviewed in 366). O'Rahilly and colleagues (345) used this approach to identify a pair of cousins who were severely obese as a result of having undetectable levels of leptin. They were established as having a homozygous frame shift mutation in the leptin gene (345). Treatment of these and other leptin-deficient individuals with daily injections of recombinant leptin normalized their body weight, thus proving causality between the single gene mutation and the obese phenotype (143). To date, there are still only 24 confirmed instances of individuals with this mutation (S. Farooqi, personal communication). Furthermore, these studies demonstrated that human food intake regulation, as in the leptin-deficient *ob/ob* mouse, was dependent on a functional leptin-signaling pathway. Since these initial studies, it has been demonstrated that human obesity can result from defects in various components of the leptin signaling pathway including the leptin receptor (88), POMC (270), and the melanocortin-4 receptor (MC4R) (569). The latter is now thought to be the most common monogenic form of obesity, with some studies demonstrating that ~1 in 200 obese people have disease-causing mutations in the MC4R (12, 274). There are now over 20 single gene disorders that have been shown to cause severe obesity. In addition to direct components of the leptin signaling pathway, they include genes such as prohormone convertase 1 (which is required for the processing of pro-peptides into active peptides such as POMC) (228), SIM 1 (a transcription factor required for hypothalamic development) (425) and SH2B1 (an adaptor protein that modulates signaling through tyrosine kinase and JAK-associated cytokine receptors) (123). It is notable that these single gene mutations generally influence central sensing and control of energy homeostasis rather than through peripheral systems. Further analyses of these individuals demonstrate that the defects influence appetite and satiety resulting in increased food intake. In contrast, little or no effect is observed on energy expenditure, with MC4R mutation patients being the exception and showing a small but significant reduction in metabolic rate (264).

B. Obesity as a Polygenic Disorder

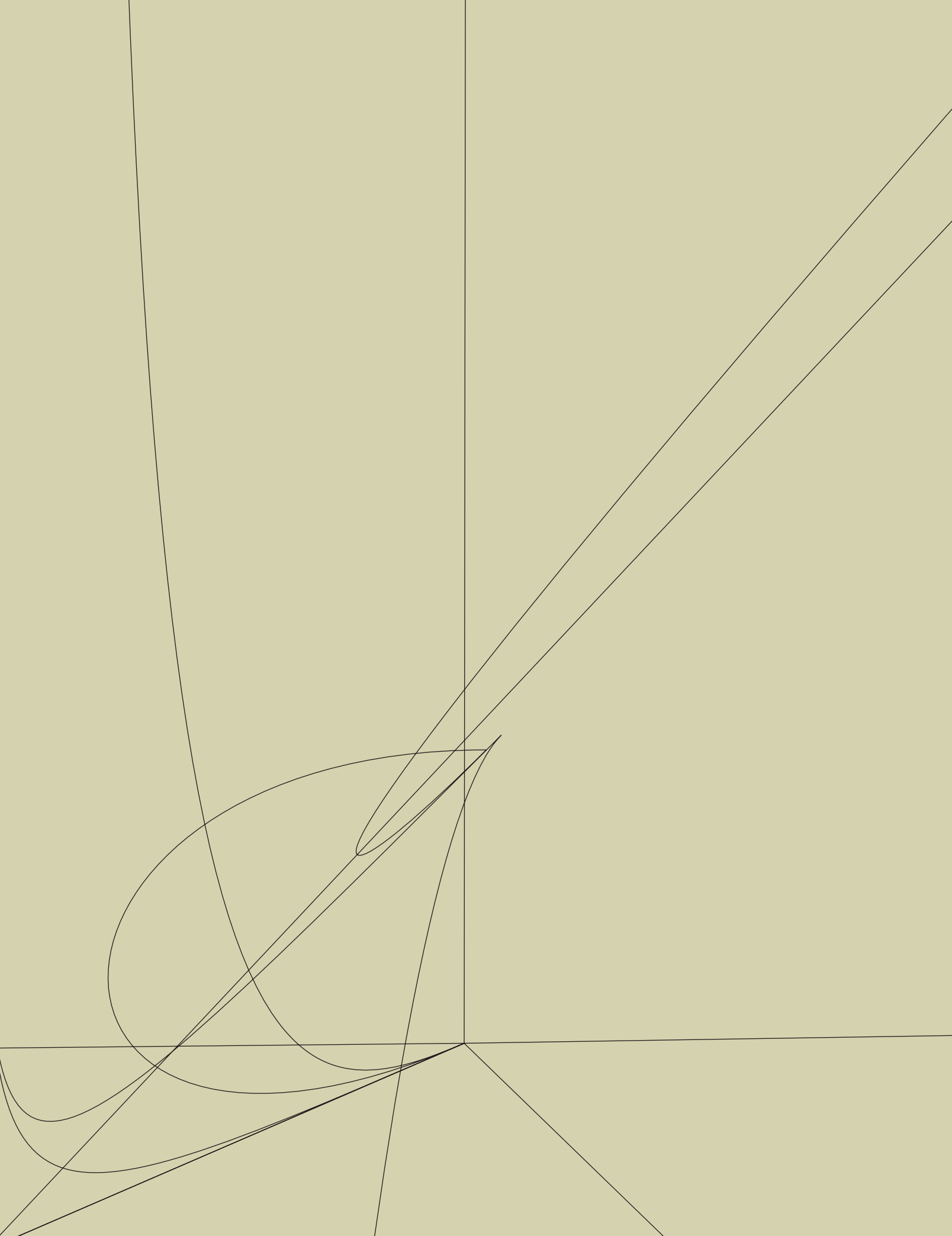
As above, although there are several single gene mutations that have been identified which cause obesity and diabetes in humans (142), approximately two-thirds of obesity is inherited in what is probably a polygenic fashion (57, 502). Genome-wide association studies (GWAS) were greatly facilitated by the International HapMap (www.hapmap.org) defining common single-nucleotide polymorphisms (SNPs) and existing linkage disequilibrium that provided near-genomic coverage of common genetic variations. We are now in the fourth wave of GWAS studies of obesity that has used a variety of variables such as BMI as a continuous trait or extremes of obesity in large populations of children or adults. FTO was one of the first genes identified, originally as having a high association with T2DM but later showing that this was through its association with obesity (158). Similarly, although homozygous inheritance of mutations of the MC4R leads to severe obesity (142), variants near the MC4R gene have a relatively strong association with obesity (269, 581). Other variants with obesity associations are BDNF, TMEM18, SH2B1, NEGR1, MTCH2, FAIM2, and GNPDA2 (36, 203, 216, 219, 434). It is important to point out that, as opposed to being causal for obesity, the way that direct mutations of the MC4R gene are (142), these GWAS genes are merely associations. Many are in noncoding areas of the genome and might be markers rather than playing any contributory role in obesity causation (456). However, several of the genes such as BDNF, MC4R, SH2B1, NRXN3, TMEM18, and NEGR1 are known to be involved in the regulation of energy homeostasis, reward, and/or neural development (142, 158, 179, 205, 321). Importantly, FTO has been shown to play a critical role in leptin receptor trafficking (500). There are also likely to be many other genes that singly or in combination contribute to the genetic propensity to become obese which have yet to be identified by such studies. In addition, epigenetic modifications of some of these known or as yet to be identified genes are likely to play a critical role in determining their expression under conditions of varying environmental conditions.

V. PERINATAL ENVIRONMENT AND THE DEVELOPMENT OF OBESITY AND T2DM

A. Prenatal Influences

1. Parental undernutrition

Addressing the consequences of parental undernutrition is technically challenging in a human context. The best evidence for a direct effect of undernutrition during pregnancy on long-term metabolic health of the offspring has come from the study of individuals who were in utero during



A number of studies in animal models have also investigated

two generations, at least in mice (162). This is accompanied by changes in gene expression in testes and sperm and global DNA methylation in the sperm.

3. Prenatal stress and offspring obesity and diabetes

Psychosocial stress is a common factor in human existence. Such stress increases the likelihood of becoming obese and diabetic in humans (316, 449) and rodents (140, 431, 503). Not surprisingly, severe stress during pregnancy can have major adverse effects on offspring. Many of these effects are likely due to the fact that cortisol, which is released in stressful situations, can cross the placenta and alter the development of the brain and other organs (137, 237, 364). In addition to a range of abnormalities in behavior and cognitive function (364), there is evidence that severe maternal psychosocial stress is associated with higher BMI, percent body fat, insulin resistance, and abnormal lipid profiles (137, 139) and hypothalamo-pituitary-adrenal dysregulation in young adult offspring (138). Much of our knowledge of the mechanisms underlying these abnormalities comes from rodent studies in which dams are subjected to different types of stress and/or corticosteroids during various stages of gestation. As a broad generalization, depending on the stage of pregnancy, prenatal stress or exogenous glucocorticoids can have a major adverse impact on the development of the brain, including neurotransmitter systems and brain areas involved in the regulation of energy and glucose homeostasis (161, 237, 437) and pathways regulating motivated and reward behaviors (208, 323). Depending on the timing of stress and the sex of the offspring, adverse offspring outcomes of prenatal stress include permanent dysfunction of the neuroendocrine axis (237) and stress responsiveness (160, 208), delayed learning (160) and abnormal glucose tolerance, hyperphagia, as well as increased body weight and adiposity (111, 363, 387, 508, 546). Importantly, prenatal stress results in less maternal grooming and attention in offspring (81, 418), which can have important effects on offspring behavior and metabolic phenotype (80, 81, 95). In keeping with these fetal/neonate-maternal interactions, at least some of the abnormalities in offspring stress responsivity can be reversed by blocking the mother's stress-induced corticosterone response (32), by fostering their offspring to nonstressed dams (32) or by postnatal handling (482). Intriguingly, in addition to an effect of maternal stress on developing offspring, paternal stress prior to mating significantly reduced the stress responsivity of resultant offspring with global changes in transcriptional regulation suggestive of epigenetic programming (444). Unfortunately, no data were presented with regard to either alteration in adiposity or glucose tolerance in this study. Nevertheless, such studies, if they can be translated to the human condition, suggest that much of the damage done by prenatal stress can be undone by either ameliorating the mother's stress response or by postnatal manipulations that control the offspring-mother interactions.

4. Gestational diabetes

Initial epidemiological studies highlighted the association between low birth weight and increased metabolic disease risk in later life, observations that have been reproduced in over 40 populations worldwide (356). However, in some of these studies, such as those of native North American population, increased risk of T2DM and metabolic syndrome was also observed at the high birth weight end of the spectrum (324). These populations have a high prevalence of T2DM, obesity, and consequently gestational diabetes (>10% of all pregnancies) (157). Therefore, the increased risk of metabolic disease in individuals with high birth weight was proposed to reflect an increased risk of diabetes in the macrosomic offspring of women with gestational diabetes (108, 318, 403, 536). This hypothesis is supported by sib pair studies that have demonstrated a greater prevalence of T2DM and high BMI in siblings born after the mother was diagnosed with T2DM compared with those born prior to the development of T2DM (109). Further evidence for the association between maternal gestational diabetes and increased offspring weight being causative has come from a retrospective study that demonstrated that intensive treatment by diet and/or insulin of gestational diabetic mothers attenuated this association (212).

Studies in animal models have also provided strong evidence that gestational diabetes can cause increased risk of diabetes in the offspring **(FIGURE 2)**. In most rodent studies, the effects of maternal diabetes have generally been assessed using models where diabetes is induced in the mother by chemical destruction of the maternal β-cells using streptozotocin (reviewed by Van Assche et al., 528). The phenotype of the offspring is determined by the severity of the glucose intolerance induced in the mother. The offspring of mildly diabetic mothers are large at birth and in neonatal life demonstrate an apparent enhanced development of their endocrine pancreas. However, in adulthood they have a deficit in their insulin secreting capacity (199) and develop impaired glucose tolerance (6, 472). The offspring are also hyperphagic, leptin resistant, and obese (491). This is associated with hypothalamic defects (409) including a reduction in neuronal connections between the ARC and the PVN (491). If the maternal diabetes is severe, the offspring are born small for gestational age. As a result of overstimulation by the high glucose levels, the offspring β-cells are almost completely degranulated with lower insulin content and the offspring become insulin resistant as adults (6). In light of the growing epidemic of obesity, a growing number of animal models of maternal diet-induced obesity are being established (see above and below). In some of these it has been demonstrated (unsurprisingly) that the dams develop impaired glucose tolerance during pregnancy. Although gestational diabetes is not the only altered metabolic parameter in these models, it is conceivable that at least some of the detrimental consequences of maternal obesity in the offspring are caused by accompanying gestational diabetes.

B. Postnatal Influences on Offspring Metabolic Outcomes

1. Maternal-infant interactions

Early infancy exposure to a variety of experiences and metabolic milieus can have an important impact on the ways in which the infant learns to cope with their environment. The content of breast milk is influenced by the physiological and metabolic state of the mother and can have important effects on the metabolic state and feeding preferences of their infants. Hormones such as leptin and insulin are secreted into the milk and, during early infancy, can be absorbed directly into the bloodstream of suckling infants (78, 176, 213, 234, 349). In addition, the milk content of nutrients such as essential fatty acids which are required for neural development (524) are heavily influenced by the genetic and metabolic status of the mother (176). While many studies support a protective effect of breast versus formula feeding during infancy against later obesity and glucose intolerance (104, 154, 266, 379), some suggest that factors such as maternal diabetes might have an adverse effect on the metabolic development of their offspring (408). In rodents, cross-fostering of genetically obesity-resistant (DR) pups to obese dams with a genetic propensity to become obese on high-fat diets (DIO) causes them to become obese and insulin resistant when subsequently exposed to a high-fat diet as adults (176). Much of this effect may be attributed to abnormalities in milk content of nutrients such as poly- and monounsaturated fatty acids and hormones such as insulin and leptin which are essential for normal brain development (176). Similarly, dietary choices of the breast-feeding mother or early exposure to specific tastes and orders in infant formulas can have marked effects on dietary and taste preferences of the developing infant (154, 329–331, 518). In both humans and experimental animals, the major issue left unanswered is what basic mechanisms underlie these persistent changes in behavior as well as metabolic and physiological function. Some are associated with changes in the anatomical development of pathways critical to these functions (62), while others may be due to epigenetic changes in gene expression, or both.

2. Catch-up growth in intrauterine growth retardation and accelerated postnatal growth

Accelerated early neonatal growth and/or obesity has been shown to amplify the detrimental consequences of being born small for gestational age on metabolic health outcomes. The original Hertfordshire studies by Hales et al. (198) demonstrated that the men with the worst glucose tolerance at age 64 were those that were in the lowest quartile of birth weight but who were obese as adults. Likewise, in the Dutch Hunger Winter studies, the worst glucose tolerance was observed in individuals who were exposed to famine in utero but became obese as adults (427). The particular detrimental effects of rapid growth during childhood following fetal growth restriction emerged from a study of primary school children in South Africa. Those with a low birth weight who gained weight rapidly during early childhood had the worst glucose tolerance at age 7 (102). Studies in Finland also demonstrated that men and women who develop T2DM are those born small for gestational age and then cross BMI centiles between the ages of 2 and 11 (141). These detrimental effects of catch-up growth may be related to the observation that during periods of such accelerated growth there is preferential accumulation of fat mass rather than lean tissue (344). Studies in animal models reinforce this concept that rapid postnatal growth following in utero growth restriction is detrimental to long-term metabolic health, including increased risk of obesity. Rodent models of maternal protein restriction, caloric restriction, and intrauterine artery ligation, which all demonstrate low birth weight, develop increased adiposity when suckled by normally fed dams during the lactation period and therefore undergo postnatal catch up growth (381, 475, 532).

There is now also growing evidence to suggest that accelerated postnatal growth not only exaggerates the effects of suboptimal growth in utero but can also have detrimental effects on later health regardless of an individual's birth weight. This is particularly prominent in relation to risk of increased adiposity and obesity. At least three systematic reviews demonstrate in humans that accelerated postnatal growth increases risk of subsequent obesity (26, 346, 371). These studies show associations, but do not provide information regarding the causes of the accelerated growth. However, in humans, both observational and randomized feeding trials suggest that nutritionally induced rapid weight gain in the first half of infancy predicts later obesity and cardiovascular risk factors such as higher blood pressure (173, 523, 547). Studies comparing breast-fed infants to formula-fed infants revealed that the former were at reduced risk of obesity (18, 200). These observational studies do not provide causal evidence that nutrition per se mediates these relationships. However, it is well known that formula-fed infants gain more weight over the first year of life than breast-fed infants (120). Causal relationships between nutrition during infancy and subsequent metabolic health have emerged from randomized intervention studies and control trials. In these studies low levels of nutrient intake during the neonatal period are protective against risk of obesity and cardiovascular disease (257, 476, 477). The precise duration of this early neonatal critical time window for determination of obesity risk is not clear. However, it has been suggested that it could be as little as the first postnatal week of life (495). Animal models have again confirmed these studies in humans. Use of a range of animal models has repeatedly confirmed the fact that early overnutrition in the neonatal period predisposes to later obesity **(FIGURE 2)**. Raising rodent pups in small litters increases their intake and markedly increases their propensity to be-

come obese as adults (231, 246). Similarly, overfeeding neonatal rats for the first 18 days of life by intragastric tubes markedly increases their body weight gain (549). On the other hand, raising rodent pups in large litters restricts their access to food and can protect even genetically obesity-prone animals from becoming obese (231, 392).

VI. GENE-ENVIRONMENT INTERACTIONS

A. Epigenetics

The term *epigenetics* (literally meaning "above the genetics") was first defined by the developmental biologist Conrad Waddington as the "interactions of genes with their environment which bring the phenotype into being" (539). The epigenetic changes that mediate this interaction include alterations in DNA methylation, covalent modifications of histone tails (e.g., acetylation, methylation, phosphorylation, and ubiquitination), and expression of noncoding RNAs (e.g., miRNAs). The phenomenon of epigenetics therefore explains how one genotype can give rise to multiple different phenotypes through alterations in the epigenotype. It also provides a molecular framework through which the environment can interact with the genome to alter gene expression and thereby influence phenotype. As gene-environment interactions are key to the concept of developmental programming, much attention has been directed towards the potential role of epigenetic mechanisms in mediating the effects of a suboptimal exposure of a fetus in utero to permanent changes in its long-term metabolic health including risk of T2DM and obesity. Epigenetics provides an attractive mechanism to underlie the cellular memory by which a suboptimally exposed cell during a critical period of development stably affects gene expression following multiple rounds of cell division.

The potential for diet during pregnancy to permanently alter the epigenotype and therefore adult phenotype and disease susceptibility was first demonstrated 15 years ago using the Agouti viable yellow (A^{vy}) mouse (559). The A^{vy} allele is epigenetically sensitive as a result of a retrotransposon insertion upstream of the Agouti gene. When the

Data from humans in relation to evidence for epigenetic modifications contributing to the developmental origins of T2DM and obesity are much more limited and are often hindered by the lack of availability of metabolically relevant tissues from living humans. The majority of studies have therefore focused on clinically accessible tissues such as white blood cells or umbilical cord. However, a major goal has been to identify epigenetic changes in these tissues that are reflective of epigenetic changes in tissues such as adipose tissue, the brain, and the endocrine pancreas. Genome-wide methylation analysis of cord blood cells demonstrated that intrauterine growth restriction in humans was associated with altered methylation of the HNF-α locus, again highlighting the potential importance of programming of transcription factors (132). Human studies have also demonstrated association between patterns of early postnatal growth and epigenetic modifications. Groom et al. (185) reported a link between rapid postnatal growth and differential methylation of the TACSTD2 locus, a gene associated with childhood adiposity. Evidence for the effects of diet during pregnancy and epigenetic changes in the offspring in humans is sparse, and most has come from studies of individuals who were in utero during the Dutch Hunger Winter. Initial studies of this cohort identified differential methylation of the Igf2 locus six decades after exposure to the famine in utero (207), and a further five vulnerable loci were identified in a subsequent study (514). Other human studies have demonstrated the potential use of epigenetic modifications as markers of future risk of metabolic disease. In two separate cohorts, Godfrey et al. (175) demonstrated that methylation of the retinoid X receptor in umbilical cord tissue correlated strongly with percent fat mass later on in childhood and explained ~25% of the variation in adiposity.

In addition to studies showing associations between changes in early patterns of growth and nutrition, there are also a limited number of studies showing epigenetic variation in candidate genes associated with T2DM and obesity. Small but significant differences in methylation of FTO (39), insulin (568), and KCNQ1 (517) loci have all been shown to correlate with disease risk. Furthermore, there is evidence that lifestyle factors associated with changes in obesity risk can alter promoter methylation of key genes in skeletal muscle including PGC-1α, PDK4, and PPAR-δ (33).

B. Hormonal Influences

As discussed above, a plethora of data from rodent and human studies have suggested that changes in nutrition during perinatal life have a significant impact on the development of obesity and related diseases in later life. Hormones, such as leptin, insulin, and ghrelin, are dynamically regulated by nutritional and metabolic status and are therefore major signals to the developing fetus and neonate of nutrient availability **(FIGURE 2)**. In addition, hormones produce a multitude of effects on functions in the developing fetus and neonate that are well outside the functions they serve in later life. Thus the biological actions of several metabolic hormones are different during neonatal versus adult epochs. For example, in sharp contrast to the potent effects of leptin and ghrelin on feeding in adults, peripheral leptin or ghrelin injections have no significant effects on milk intake or body weight during the first 2–3 wk of postnatal life in rats and mice (340, 404, 490). These observations suggest that leptin and ghrelin might exert different functions during neonatal life such as altering neural development. Early observations by Bereiter and Jeanrenaud (40, 41) reported structural defects in the obese *ob*/*ob* mice, including a reduction in soma size of cells in the VMN and dorsal motor vagal nucleus neurons, as well as alterations in the dendritic orientation of VMN and LHA neurons. Twenty years later, Ahima and Flier (8) showed that the same mutant mice display an immature pattern of expression of synaptic and glial proteins. This pioneer work paved the way for subsequent research on leptin in brain development and plasticity.

The availability of *ob*/*ob* mice and more modern neuroanatomical tools to study neural circuits allowed more detailed studies on the role of leptin on hypothalamic development. Axonal tracing of ARC neurons demonstrated that the leptin deficiency permanently disrupts the development of projections from the ARC to each of its major targets, including the PVN (61). Remarkably, peripheral leptin injection in *ob*/*ob* neonates restores the density of ARC axons to a density that was comparable to that of wild-type littermates, but the treatment of adult *ob*/*ob* mice with leptin is largely ineffective (61). Also, leptin restores normal brain weight in *ob*/*ob* mice but only when the hormone is injected during early life (494). These observations suggest that leptin acts primarily during a restricted critical neonatal period to exert its neurotrophic effects. Notably, obesogenic environments, such as maternal obesity, diabetes, and postnatal overnutrition, can cause hyperleptinemia throughout postnatal life and impair central leptin sensitivity during critical periods of hypothalamic development (62, 174, 250, 491). Notably, this early leptin resistance is associated with a disrupted development of ARC neural projections to the PVN (62, 174, 250, 491). In contrast, maternal undernutrition during pregnancy and lactation or the postnatal period blunts the naturally occurring postnatal leptin surge and also causes abnormal development of ARC projections (97, 118, 572), and daily leptin treatment during early postnatal life in pups born to undernourished dams normalizes their metabolic abnormalities (533). These findings show the importance of neonatal leptin in life-long metabolic regulation and raise the importance of early endocrine intervention in metabolic (mal)programming.

More recent studies have also implicated ghrelin in the development of metabolic systems. Ghrelin is one of the first

major metabolic hormones to appear during development. It is expressed in embryos as early as the morula stage and continues to be expressed in the developing fetus and neonate. During perinatal development, ghrelin is transiently expressed in the pancreatic α-cells where it colocalizes with glucagon (116). But ghrelin is also produced by the pancreatic β-cells (419). This transient expression of ghrelin appears to play a role in pancreas development. Newborn rats exposed to ghrelin for 7 or 14 days had reduced pancreatic weights, attenuated pancreatic DNA synthesis, and reduced DNA content (119). The morphological effects of neonatal ghrelin appear widespread because chronic neonatal ghrelin injections also reduce growth of the stomach, as evidenced by a decrease in gastric weight, DNA synthesis, and DNA content. On the other hand, ghrelin injections in adult animals increase pancreatic and gastric weight, DNA synthesis, and DNA content (119, 542), indicating that ghrelin can induce biphasic effects on gastric growth depending on the age of exposure.

Ghrelin also exerts developmental effects on the brain. In vitro incubation of hypothalamic and brain stem cells with ghrelin induces proliferation with many of the resultant newborn cells acquiring a neuronal and/or glial phenotype (224, 575, 576). Insulin has also long been associated with brain development. Consistent with a trophic role of insulin in the developing hypothalamus, offspring of insulin-deficient mothers display a reduced number of ARC neurons, and this reduction of neuronal cell number is preventable by the normalization of glycemia using pancreatic islet transplantation (156). Moreover, hypoinsulinemic pups born to protein-restricted dams display a reduction in the number of astrocytes (411), while the offspring of gestationally diabetic mothers, which have increased insulin levels, have increased numbers of astrocytes (409, 412). In addition to influencing hypothalamic cell numbers, insulin can also influence hypothalamic neuronal connectivity. Pups born to insulin-deficient dams display abnormally organized POMC and NPY/AgRP neural projections that could result from the attenuated responsiveness of hypothalamic neurons to the neurotrophic actions of leptin during neonatal development (491). Notably, intrahypothalamic insulin injections during early postnatal life cause life-long metabolic dysregulation, raising the importance of neonatal insulin in the developing brain on life-long metabolic regulation (410, 412).

C. Rodent Models of Gene-Environment Interactions

1. Mouse models

Although transgenic and knockout experiments are typically conducted in mice, a significant variability in adiposity, DIO, and obesity-related diabetes exists among the mouse strains commonly used in laboratory research (see 548 for a review). The inbred C57BL/6J (B6) strain is probably the most widely used strain to conduct transgenic and knockout experiments, in part because of its susceptibility to develop obesity on high-fat diets. C57BL/6J mice are not obese on a standard chow, but when fed a high-fat diet they develop hyperglycemia, hyperinsulinemia, and hyperleptinemia (133, 505, 548). In contrast, some strains, such as 129/Sv and A/J mice, are almost totally resistant to obesity and diabetes when fed a high-fat diet (503). Remarkably, both 129/Sv and C57BL/6J mice eat an equal number of calories when fed a high-fat diet (13), suggesting that C57BL/6J have a higher feeding efficiency and gain greater weight per calorie consumed. Even within the C57 mouse strain there are significant differences among sub-strains in response to the high-fat diet. Thus C57BL/6J mice fed a high-fat diet exhibit a marked metabolic phenotype, whereas C57BL/6KsJ mice only display a weak phenotype (93). Furthermore, in some laboratories it has been noted that C57BL/6J mice within the same colony exhibit a bimodal response to high-fat diet; half develop DIO, and half are obesity-resistant (136). Given the fact that they all share the identical genotype, this marked difference in metabolic phenotypes when offered a high-fat diet suggests the presence of an as yet to be determined epigenetic influence. Background genes also appear to play an important role in determining the metabolic phenotype of mice with naturally occurring mutations or mice that have been genetically altered by introduction of transgenes. For example, *ob*/*ob* and *db*/*db* mice on the C57BL/Ks background are obese and develop severe diabetes and a marked hyperglycemia, whereas *ob*/*ob* mice on the C57BL/6J background are obese but only exhibit mild diabetes and hyperglycemia (92). Similarly, mice with a double-heterozygous deletion of the insulin receptor and insulin receptor substrate-1 become insulin resistant and severely hyperinsulinemic on the C57BL/6J background, but on the 129/Sv background these double mutant mice only exhibit a mild hyperinsulinemia (271). Together, these observations indicate that background genes in mice greatly influence the development of obesity and obesity-related diseases, such as T2DM, in response to either an obesogenic environment or genetic defects.

2. Rat models

The selectively bred DIO and DR strains of rats have proven to be a valuable model for studying the interactions of genes with environment. These strains were derived from the outbred Charles River Sprague-Dawley rat. Sprague-Dawley rats from this breeder have the fairly unique characteristic of showing a wide variation in body weight and adipose gain when placed on a relatively high-fat (31%), high-sucrose (25%) diet, designated as a "high energy" (HE) diet (296). Approximately half the rats placed on such a diet overeat for 4–6 wk and become obese (296). The remaining rats overeat for only a few days and gain no more weight than controls fed a low-fat chow diet (299). Importantly, these outbred rats have been selectively bred to produce

DIO and DR strains which have maintained their distinctive phenotypes for more than 50 generations. The obesity of the DIO rat appears to have a genetic origin since breeding DIO males with another obesity-resistant strain of rats passes on this phenotype to the offspring of these crosses in an apparently polygenic manner of transmission similar to most human obesity (57, 298, 502). This model is an excellent one for the study of human obesity since, like most obese humans, it maintains its higher body weight and adipose set-points even when switched to a low-fat diet or after being calorically restricted for many weeks (291, 302). This defense of a higher body weight set-point is what occurs in obese humans and is likely the reason for the high recidivism rate in the medical treatment of obesity and the extreme measures many previously obese individuals must undertake to keep off lost weight (326, 448, 538, 557).

The DIO/DR model is extremely useful for the study of gene-environment interactions associated with maternal obesity and insulin resistance since dams can be fed the same high-fat diet but only the DIO dams become obese and insulin resistant during gestation and lactation (176, 177, 294, 300). This obesity of DIO dams is not accompanied by an increase in offspring body weight unless such offspring are also fed HE diet from weaning. As opposed to DIO offspring, offspring of DR dams, whether the dams were made obese with a highly palatable diet or stayed lean on HE diet during gestation and lactation, gained no more weight or adiposity than controls regardless of their postweaning diets. However, maternal obesity, regardless of genotype, was associated with enlargement of the VMN and DMN and differentially affected the density of norepinephrine and serotonin transporters in the PVN (294). On the other hand, offspring of DIO dams, regardless of whether their dams were lean or obese during gestation and lactation, showed defective development of the α-melanocyte stimulating hormone (α-MSH, a catabolic peptide derived from POMC) and AgRP pathways projections from the ARC POMC and NPY/AgRP neurons to the PVN. These defective projections appeared to be due to the inherent leptin resistance of the DIO rat (176, 178, 295, 297, 299, 392), since leptin is required for normal development of this pathway (62).

Although it is uncertain whether DIO pups are born with inherent leptin resistance, it does appear in the first few days of life (62), making this early postnatal period an important focus of potential interventions that might alter later life development of obesity. In fact, cross-fostering DR pups from lean DR dams to obese, but not lean, DIO dams fed HE diet causes them to become obese and insulin resistant when they are fed HE diet as adults (176). This is associated

the predisposing factors, it remains challenging to identify those individuals who are most at risk and the predisposing factors that push them into a vicious cycle of obesity and insulin resistance from which few can recover. Because organs, particularly the brain, undergo the majority of their development during the perinatal period, there is a premium on identifying at risk individuals and risk factors during this critical period. Importantly, while most organs undergo continuing change of structure and function throughout life, the brain is much less plastic with regard to changing the connections of critical neuronal pathways established during critical periods of early development. The problem is that, even if we could reliably identify such individuals and risk factors, we are a long way from knowing how to alter the perinatal environment to prevent offspring from being set on the path to near-permanent predisposition to obesity and diabetes.

Also, we understand even less about the factors that make obesity, once it develops, a near-permanent condition in so many individuals. Given our current state of knowledge, there are some possible guidelines, although some of these are based on animal research that might not apply to humans. First, several factors increase the probability of offspring obesity and/or diabetes. These include obesity in one or both parents, gestational diabetes, intake of a high-fat, calorically dense diet during pregnancy and lactation, gestational undernutrition with postnatal overfeeding ("catch up growth"), genetic mutations known to cause obesity in affected individuals, and possibly some gene variants which have a high association with obesity such as FTO. However, it is important to recognize that these latter gene variants are only associations, and we are a long way from understanding the combinations of genes and the epigenetic modifications of these and other genes that promote obesity. Similarly, while research in animal models has identified several factors that appear to adversely alter the development of neural pathways involved in the regulation of energy and glucose homeostasis, it is unclear if these same factors apply to humans and, if they do, the stage of gestational and postnatal development which is most at risk. Finally, even if we could identify at risk individuals and obesogenic factors, changing the perinatal environment is a socioeconomic and cultural challenge for which we have so far failed to find a practical solution in the vast majority of at risk individuals. The hope would be that continued research into the factors that predispose individuals to become obese might identify those that lend themselves to relatively simple, straightforward interventions.

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GRANTS

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