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REVIEW

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Trapped fat: Obesity pathogenesis as an intrinsic disorder in metabolic fuel partitioning

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Summary

Our understanding of the pathophysiology of obesity remains at best incomplete despite a century of research. During this time, two alternative perspectives have helped shape thinking about the etiology of the disorder. The currently prevailing view holds that excessive fat accumulation results because energy intake exceeds energy expenditure, with excessive food consumption being the primary cause of the imbalance. The other perspective attributes the initiating cause of obesity to intrinsic metabolic defects that shift fuel partitioning from pathways for mobilization and oxidation to those for synthesis and storage. The resulting reduction in fuel oxidation and trapping of energy in adipose tissue drives a compensatory increase in energy intake and, under some conditions, a decrease in expenditure. This theory of obesity pathogenesis has historically garnered relatively less attention despite its pedigree. Here, we present an updated comprehensive formulation of the fuel partitioning theory, focused on evidence gathered over the last 80 years from major animal models of obesity showing a redirection of fuel fluxes from oxidation to storage and accumulation of excess body fat with energy intake equal to or even less than that of lean animals. The aim is to inform current discussions about the etiology of obesity and by so doing, help lay new foundations for the design of more efficacious approaches to obesity research, treatment and prevention.

KEYWORDS
adipose tissue, energy homeostasis, energy intake, fuel partitioning, obesity

1 | INTRODUCTION

After more than a century of research and debate on the etiology of obesity, our understanding of its pathophysiology remains at best incomplete, even as rates of obesity continue to rise to unprecedented levels. During this time, two alternative perspectives have helped shape thinking about the etiology of the disorder. One focused on the observation that obesity is often associated with excessive appetite and food intake. This currently prevailing view holds that excessive fat accumulation results because energy intake exceeds energy expenditure.[1,2] Excessive food consumption is now considered the primary cause of the imbalance.[3,4] The other perspective was prompted by the common

observation that many individuals appear to accumulate and sustain excessive adiposity even with restricted food intake. This view attributes the fundamental cause of obesity to intrinsic metabolic defects that shift fuel partitioning from pathways for mobilization and oxidation to those for synthesis and storage. In this scenario, the failure to limit energy intake to energy expenditure is not a primary or initiating cause of excessive fat accumulation, but rather a manifestation and consequence of primary disturbances in fuel partitioning and the sequestration of fat in adipose tissue. The resulting reduction in fuel oxidation, trapping of energy in adipose tissue, and greater energy requirements of a larger metabolically active body mass in turn drives a compensatory increase in food consumption.

Historically, this fuel partitioning theory of obesity pathogenesis has garnered relatively less attention from the scientific community despite its pedigree and, as this paper will discuss, observations since the 1940s that animal models of obesity accumulate excess body fat with energy intakes equivalent to, or even less than, that of lean controls. While a specific application of this theory to dietary drivers of the obesity epidemic, the carbohydrate-insulin model, has recently generated considerable discussion and debate in relation to the energy balance view,[4–8] this paper does not engage in this debate nor explore diet-related factors in the obesity epidemic. Rather, we present a comprehensive update of the theory, focusing on evidence accumulated since its last full exposition in 1941.[9] Our aim is to inform current discussions of the etiology of obesity and by so doing, help lay new foundations for the design of more efficacious approaches to obesity research, treatment and prevention.

After a brief historical overview, we describe the fuel partitioning theory at a conceptual level and present general methodological and interpretive issues in testing this theory. Next, we apply these broad considerations to a detailed analysis of the evidence for the partitioning theory at a mechanistic level from studies of the seminal animal models of obesity. Then, we explore genetic, neural and hormonal controls of fuel partitioning that may contribute to disordered fuel fluxes leading to increased fat accumulation and apply the fuel partitioning perspective to interpretation of results from studies of human obesity. Finally, we consider future directions for research on obesity pathogenesis based on disordered fuel partitioning that may inform prevention and treatment.

2 | THE FUEL PARTITIONING THEORY OF OBESITY

2.1 | History

Through the 1930s, medical textbooks explicitly considered the possibility that obesity could be a primary metabolic disorder "not always due to excessive intake of food," as stated earlier in Osler's 1914 *Principles and Practice of Medicine*.[10] By then, von Bergmann had departed "from the purely energetic viewpoint"[11] and proposed instead that adipose tissue in individuals predisposed to obesity has an exaggerated tendency to take up and sequester fat, and that this predisposition constitutes the primary cause of obesity.[12] Bauer later referred to this characteristic of fat tissue as "lipophilia," and described how the accumulation of excessive fat in lipophilic adipose tissue would deprive other tissues of energy leading to increased hunger and/or lethargy.[9,13] In his 1942 monograph, *Functional Pathology*, Lichtwitz described this process as "the fat tissue dominat[ing] over the active tissues in the competition for food stuffs."[14] The Bauer/von Bergmann hypothesis persisted as a viable explanation of obesity pathogenesis through the mid-20th century, described variously as endogenous, constitutional or metabolic obesity.[15–19]

Laboratory research, beginning in the 1930s, that elucidated the functions of adipose tissue in the synthesis, uptake, storage, and mobilization of fat fuels bolstered this perspective. This work refuted earlier thinking that regarded adipose tissue "an inert site for fat storage,"[20] and later led to the incorporation of the dynamics of adipose tissue function into formulations of obesity pathophysiology based on chronic disturbances in metabolic fuel trafficking that cause and sustain excess fat storage and, in turn, increase food intake.[5,21–28]

2.2 | The theory

The fuel partitioning theory takes as its starting point the basic biological requirement for a continuous supply of energy-yielding substrates and production of biological energy. The theory explains obesity as resulting from a primary intrinsic disorder in this homeostatic system that (i) biases fuel partitioning from oxidation to storage; (ii) reducing circulating fuel availability and oxidation while increasing body mass and energy needs; (iii) resulting in a relative reduction in cellular energy production and signaling that; (iv) consequently stimulates energy intake and/or reduces energy expenditure as compensatory responses to restore homeostasis (Figure 1).

2.2.1 | Energy homeostasis as foundational

Endocrine, neural and cellular processes maintain energy homeostasis by providing a continuous supply of metabolic fuels and production of cellular energy. As a result, energy-yielding substrates are partitioned among different tissues and utilized as necessary to satisfy maintenance requirements and special needs generated by physiological (e.g., reproduction, lactation), pathophysiological (e.g., illness) and environmental (e.g., ambient temperature, famine, predation) factors. Such trafficking also allocates fuels in conjunction with meal-to-meal, diurnal and seasonal feeding and fasting cycles associated with, respectively, anabolic (fuel synthesis and storage) and catabolic (mobilization and oxidation) processes. Adipose tissue plays a critical role in energy homeostasis by buffering the fuel supply across feeding and fasting cycles and in response to changing conditions. In this context, excessive adiposity arises from imbalances in fuel fluxes across adipocytes,[26] increased adipogenesis/hyperplasia,[29] or related processes operating outside of adipose tissue involving other peripheral organs, hormones and the nervous system that shift substrate partitioning toward excessive storage (Figure 2). Such a potential multifactorial etiology is consistent with the polygenic nature of obesity.[30,31]

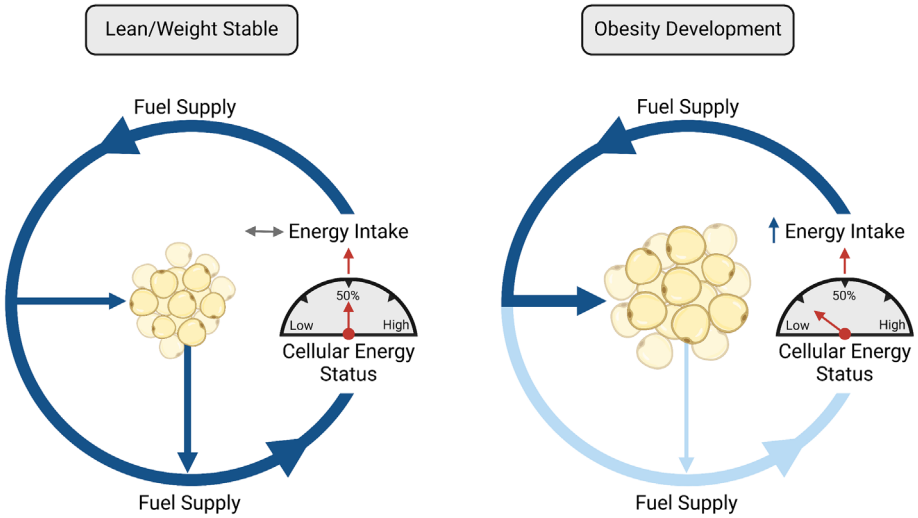

FIGURE 1 Basic features of the fuel partitioning theory. In lean individuals with a stable body weight, fuel partitioning between pathways of fat synthesis and storage versus mobilization and oxidation are in equilibrium, resulting in a relatively constant fat mass, metabolic fuel supply, and cellular energy production, which is monitored to control energy intake. Individuals with developing obesity, have an intrinsic disorder in fuel partitioning that shifts the equilibrium of fuel fluxes toward lipid synthesis and deposition, which in turn decreases the supply of metabolic fuels and cellular energy production, resulting in a compensatory increase in energy intake that can foster additional increases in fat mass in a feed-forward fashion.

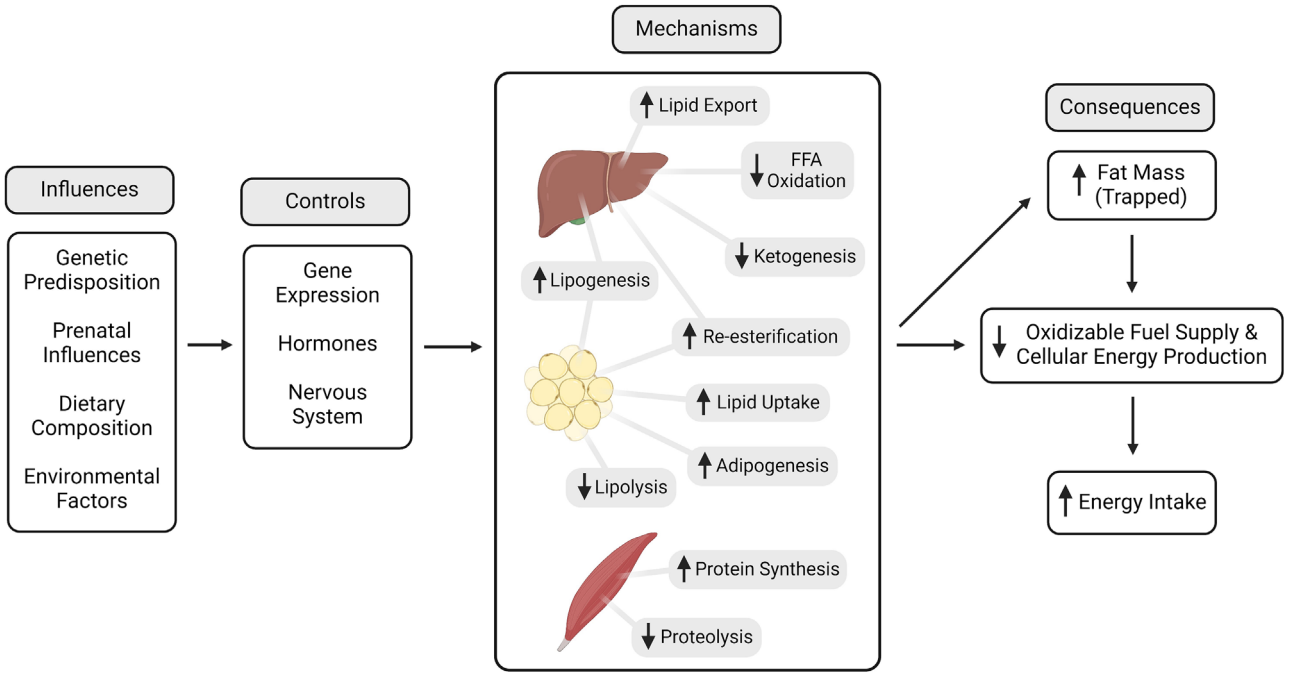

FIGURE 2 Potential mechanisms and controls of fuel partitioning leading to fat sequestration. An intrinsic shift in fat fuel partitioning toward storage is mediated by upregulation of cellular mechanisms of lipid synthesis, uptake and adipogenesis and downregulation of lipid mobilization and oxidation, which traps fat in adipose tissue and reduces energy production leading to increased energy intake. Increased protein synthesis and decreased proteolysis drive the growth of lean mass and contribute to weight gain with ad libitum access to food. Under the influence of genetic, environmental, and dietary factors, changes in gene expression, secretion and action of hormones, and neural activity control these cellular mechanisms of partitioning.

2.2.2 | Compensatory effects on energy intake and expenditure

While mobilization of internal bodily energy reserves increases fuel availability to organs and cells, continuing resting and physical activity-related energy expenditures require eventual replenishment from external sources through food intake. In turn, changes in the availability, uptake and oxidation of fuels provide feedback control of food intake,[21,32–34] possibly through the operation of energy sensors in liver and brain[35–37] that stimulate or inhibit eating behavior in response to, respectively, a reduction or increase in the production of cellular energy. In this way, a shift in fuel partitioning toward synthesis, storage and sequestration of fat results in the increase in food intake usually associated with the development of obesity.[38]

In addition to increasing energy intake, a shift in fuel partitioning favoring fat deposition over oxidation may also reduce energy expenditure, especially if intake is restricted, by limiting the supply and/or oxidation of fuels in metabolically active tissue or through neuroendocrine responses to a detected energy deficiency. Such an effect in muscle could inhibit physical activity, especially considering the relatively high energetic cost of carrying greater body weight in obesity.[39,40] Similarly, storage and sequestration of body fat in white adipose tissue could blunt energy expenditure from brown adipose tissue (BAT) thermogenesis, which is fueled by oxidation of fatty acids and their acylcarnitine metabolites, among other metabolites.[41–44]

2.2.3 | Body composition

Common obesity in humans is typically associated with an increase in absolute lean mass,[45] arising in part from the increased muscular work and metabolic demands of moving and maintaining a greater body mass[39,40] and from the operation of metabolic and hormonal processes driving the anabolic state of increasing body mass. This increase in metabolically active lean mass may exacerbate the deficit in available fuels caused by the shift in fuel trafficking from oxidation to storage because additional energy is required for lean tissue synthesis and maintenance; the associated energy demand would contribute to an increased drive to eat.[27,46] However, when food intake does not increase, or is experimentally restricted as in experiments with many animal models of obesity, lean mass may decrease while fat mass continues to enlarge. In this situation, the persistent shift in substrate partitioning toward energy deposition requires that the body catabolize lean tissue to release amino acids as a substrate for gluconeogenesis as occurs with fasting. This coexistence of increased adipose mass with decreased lean mass and other signs of starvation (e.g., increased hunger, decreased voluntary physical activity, lower resting energy expenditure) observed in controlled animal experiments discussed below provides prima facie evidence for the state of "internal starvation," as hypothesized by Astwood,[19] Hetherington & Ranson[47] and others[5] and postulated by the fuel partitioning theory.

3 | TESTING THE THEORY – GENERAL CONSIDERATIONS

If obesity results from an intrinsic shift in fuel partitioning away from energy production to storage with secondary (compensatory) effects on energy intake and/or expenditure, then it should be possible to dissociate excess fat accumulation from increases in energy intake or decreases in expenditure. In this section, we discuss necessary features of experimental designs that provide such appropriate tests of the theory, and highlight issues of data interpretation. This discussion provides the foundation for the subsequent detailed review of findings from rodent models of obesity.

3.1 | Design consideration

3.1.1 | Excess fat deposition and food intake

A wide variety of evidence suggests that excessive fat accumulation can occur without increases in energy intake above that of lean animals under controlled conditions. As detailed below, in animal models of obesity, increases in fat storage or alterations in the metabolic underpinnings of fat deposition (e.g., increased lipogenesis, decreased lipolysis) have often been observed when energy intake is equivalent to or less than that of lean controls, or before the onset of increases in intake. In some experiments in which an increase in energy intake occurs simultaneously with weight gain, the reported increases in feed efficiency (defined by the gain in body weight or fat mass per calorie or gram of food consumed) also provides evidence consistent with a primary shift in partitioning toward fat storage, although increased absorption of dietary energy may also play a role. For obesity-inducing treatments, experiments designed to test the independence of excess fat accumulation from increased food consumption may involve restriction of food intake to baseline (pre-treatment) levels. To compare lean and obese animals, intakes may be restricted to the level of lean controls by pair-feeding or further restriction below that of lean controls. Limiting energy intakes to control levels in animals otherwise inclined to increase consumption may induce a gorging pattern of eating that in itself can foster fat accumulation.[48] Consequently, many such experiments as cited below minimize this confound by spacing food delivery over the day, yoking food availability via mechanical dispensers to the intake of the control group, or restricting the amount of or access time to food for both ad libitum and food-restricted groups.

3.1.2 | Excess fat deposition and energy expenditure

Historically, a relative inhibition of energy expenditure has been seen as a potentially important contributing cause of excess fat accumulation. In humans eating ad libitum, however, obesity is usually associated with increased energy expenditure due to the typically

concomitant increase in lean mass and the energy required to carry and move the excess weight.[39,40,49] Accordingly, the role of reduced energy expenditure in the development of human obesity has been minimized.[3,4] Studies in laboratory rodents sometimes, but not always, find markedly reduced energy expenditure especially during the development of obesity.[50,51] Some of these discrepant findings may be artifactual, resulting from normalizing whole-animal energy expenditure to body weight when adipose tissue, which is relatively inactive metabolically, comprises a large proportion of body mass.[50,51] When metabolic rate is expressed per animal, such differences may be reduced or eliminated.

Measurement of whole-body energy expenditure can help to distinguish between obesity models focused on increased intake versus altered fuel partitioning on an organismic level, but it has little relevance for understanding physiological energy homeostasis, which, like all homeostatic systems, depend on feedback from sensors sensitive to changes in a regulated variable.[52] Because such sensors are invariably specialized cells (with respect to function and/or connections) in specific tissues, it is unclear how energy expenditure at an organismic (whole-body) level could be sensed. The fuel partitioning theory proposes that variations in the supply and production of energy caused by shifts in fuel fluxes are detected by energy sensors in the brain and liver[34–37] that control energy intake and expenditure.

A reduced capacity for thermoregulatory thermogenesis in BAT has been interpreted as a cause of excessive fat deposition in animal models,[53] but, as detailed below, eliminating the need for thermogenesis by maintaining animals at thermoneutral temperatures does not necessarily prevent excess fat deposition, challenging this interpretation. Furthermore, in some experiments as discussed below, excess body fat accumulates even when food is restricted *and* animals are kept at thermoneutral temperatures. Similarly, as covered below, excess fat deposition has been reported under conditions of food restriction with apparently no concomitant decrease in energy expenditure. In these instances, considering the first law of thermodynamics, measures of expenditure are presumably insufficient to detect this change or counter-balancing changes may occur (e.g., catabolism of lean mass, an increase in dietary energy absorption, or, perhaps, a decrease in excretion of energy-containing substances in urine or feces).[54]

3.2 | Interpretive considerations

3.2.1 | Energy intake as causal driver versus contributor

Although excess adiposity may occur with food restriction, such as by pair-feeding or even underfeeding relative to controls, the magnitude of fat accumulation will be reduced relative to ad libitum feeding conditions. This observation demonstrates that increased food intake in response to a shift in fuel flux toward storage may facilitate the full manifestation of an obese phenotype, but not that increased intake constitutes the initiating event. Indeed, whereas increasing intake by forced overfeeding may cause excess fat deposition,[55,56] retention of this extra fat after termination of overfeeding would only be expected in the case of an obesity-susceptible phenotype with a propensity to partition fuels into fat storage. Furthermore, depending on the composition of the diet (see below), initial increases in intake might exacerbate the shift in fuel flux away from oxidation, contributing to a vicious cycle of increased fat deposition and food consumption.

From a fuel partitioning perspective, obesity results from dysfunction of mechanisms and controls directing fuel fluxes. The machinery controlling food intake is not defective, but rather works well, detecting changes in the supply and production of energy resulting from these disturbances in fuel partitioning.[34] However, malfunction in the physiological and neural mechanisms directly controlling eating behavior could also cause obesity independently of a primary shift in peripheral fuel fluxes toward storage, without necessarily conflicting with the fuel partitioning theory, if these controls lie downstream of fuel partitioning. In this scenario, preventing the increase in intake would prevent excess fat accumulation. Our review of the literature on rodent models of obesity indicates that this latter scenario is, at best, rare; thus, the fuel partitioning theory offers substantial explanatory power to account for otherwise anomalous pathophysiological features in these animals.

3.2.2 | Challenges and insights from a complex system

Because living organisms require a continuous supply and production of energy, including amid changing nutritional and pathophysiological conditions, fuel partitioning can be understood as part of a resilient homeostatic system with a myriad of compensatory and counter-regulatory responses that evolved to resist perturbation in the supply of metabolic fuel and the generation of biological energy. The reciprocal utilization of carbohydrate and fat fuels, as described by Randle and colleagues in the mid-1960s,[57] is one notable example. The capacity for compensation and counter-regulation can also present a challenge for the experimental evaluation of obesity pathogenesis. For instance, experimentally-induced reduction in the capacity for lipolysis in adipose tissue that might be expected to increase lipid stores may be counter-balanced by a reduction in adipocyte lipid synthesis and storage, thereby preventing excess fat accumulation.[58] From a practical standpoint, studies testing the fuel partitioning theory need to include measures of or control for these redundant and compensating mechanisms in the energy homeostasis system.

This complexity, however, can also provide mechanistic insights: A shift in fuel partitioning away from storage, associated with diminishing insulin sensitivity in enlarging adipocytes,[59–61] may explain the commonly-observed transition from a dynamic stage of weight gain to a body weight plateau as an equilibrium is reached in adipocytes between fat deposition and mobilization.[21] Similarly, restoration of body weight and fat stores to baseline or control levels after food restriction can be understood in terms of fuel partitioning. Consumption of a meal during prolonged caloric restriction results in rapid

(within 1–2 h) and exaggerated increases in lipogenesis and the capacity for lipid uptake in adipose tissue.[62,63] Longer term recovery of body weight and fat during refeeding after restriction is similarly associated with increased lipogenesis, adipose tissue fat uptake, and feed efficiency independent of the increase in food intake during refeeding.[64,65]

4 | ANIMAL MODELS: EVIDENCE FOR INTRINSICALLY DISORDERED FUEL PARTITIONING

The development of human obesity typically involves net average increments of as little as 1–2 g (<20 kcal) per day of excess fat deposition over years or decades.[66,67] Such a small increment in fat storage, representing 1% or less of total daily energy intake, can be difficult to quantify in the short-term (days to weeks) given the normal variability of these parameters and the inadequate sensitivity of existing techniques to measure them. Shifts in fat deposition can be assessed in longer-term (months) residential studies that allow for rigorous control over food intake, but these are difficult and expensive to carry out. Consequently, there is little conclusive evidence to assess the role of disordered fuel partitioning in the pathogenesis in human obesity.

In contrast to humans, obesity in laboratory rodents (most commonly, mice and rats) develops quickly, within weeks, often with increments in fat deposition proportionally much greater than that seen in humans. This developmental course, together with the ability to precisely manipulate and measure food intake, offers an opportunity to rigorously test the fuel partitioning theory. Experiments using rodent models of obesity have shown that excessive fat deposition or, in the absence of quantifiable changes in body composition, upregulation of the metabolic processes associated with fat deposition, typically occur independently of an increase in energy intake.

4.1 | Hypothalamic models

4.1.1 | Ventromedial hypothalamic lesions

Experimentally induced lesions of the ventromedial hypothalamus (VMH) in rats, as pioneered by Hetherington and Ranson,[47,68] was the first widely used animal model of obesity. Early on, these investigators noted that some animals become obese without increasing food intake post-surgery.[47] Brobeck and colleagues soon reported a similar observation, although they emphasized that hyperphagia – i.e., voracious eating – occurs in this form of obesity.[69] Subsequent pair-feeding experiments, however, using various methods to lesion the VMH or adjacent hypothalamic regions, confirmed the original observation that obesity can develop in these animals in the absence of hyperphagia or any increase in intake, consistent with a fuel partitioning disorder.[70–75] Weanling rats, which do not become hyperphagic for at least six weeks after hypothalamic lesions,[76] deposit more body fat than control animals, even when eating half the amount of food as ad libitum fed animals.[77] In VMH-lesioned rats food-deprived after surgery to avoid confounding effects of food intake, an incipient shift in fuel partitioning towards fat deposition, evidenced by increased lipogenesis and fatty acid esterification as well as decreased lipolysis, can occur within 1 h after hypothalamic damage.[78–82]

Using lesioned rats pair-fed to intact controls, low physical activity levels in VMH animals were estimated to account for only 9 g of the approximately 180 g of body fat accumulated during an 8-week experiment with ad libitum feeding.[83] Although pair-fed lesioned rats had lower resting metabolic rates, this effect was attributed to reduced lean mass in the pair-fed animals; lean body mass is normal in ad libitum fed VMH-lesioned rats. The loss of lean mass in the pair-fed lesioned animals is reminiscent of weanling rats with VMH damage that do not become hyperphagic for several months after surgery.[84] Pair-feeding (and even some degree of underfeeding) of lesioned rats relative to control levels during maintenance at a thermoneutral ambient temperature does not prevent excess fat deposition,[85] suggesting that reduced BAT thermogenesis is not essential to development of VMH obesity.

4.1.2 | Hypothalamic peptidergic circuits

Impairment of signaling in the hypothalamic melanocortin system causes increased food intake and obesity in laboratory rodents[86] and has been implicated in human obesity.[87] Inactivation of melanocortin-4 (MC4R) receptors in the paraventricular nucleus (PVN) of the hypothalamus by deletion of the *Mc4r* gene or chronic intra-cerebroventricular (i.c.v.) administration of a melanocortin receptor antagonist increases food intake and body fat mass in mice.[88–90] Genetic deletion of the gene encoding the MC4R accessory protein (MRAP2) also results in increased energy intake and obesity.[91] Pair-feeding experiments and time course analysis show that the increase in fat deposition in *Mc4r* and *Mrap2* null mice is independent of, and precedes, the increase in food intake.[88–91] Similar effects are seen with genetic deletion of the MC3R receptor. In these animals, knockout mice fed ad libitum gain fat mass despite eating the same amount or less than do wildtype controls depending on sex.[92]

Neurons in the hypothalamic arcuate nucleus that project to the PVN release agouti-related protein (AGRP), an antagonist of melanocortin receptors (MC3R and MC4R). Chronic infusion of ARGP[93] or chronic activation of AGRP-producing neurons[94] increase both food intake and body fat mass in mice. Neuropeptide Y (NPY) is co-expressed in AGRP neurons. Repeated injection of NPY into the PVN[95] or chronic i.c.v. infusion of the peptide[96] induces an increase in food intake and obesity. As with genetic or pharmacological suppression of melanocortin receptors, excess fat deposition in response to AGRP or NPY treatments is also observed when food intake is restricted to that of control animals, albeit to a lesser extent than under ad libitum feeding conditions.[93,94,96] Consistent with the

inhibitory effect of AGRP on melanocortin receptors, targeted destruction of AGRP neurons in adult animals results in reduced intake and body fat.[97] However, using the same method for targeted ablation of AGRP-containing neurons in neonates results in obesity in adulthood with no effect on food intake compared with control mice.[98]

As predicted by the fuel partitioning theory, manipulation of these neuro-peptidergic circuits produces profound changes in fuel partitioning.[99,100] The excess fat deposition seen independently of changes in food intake is associated with a shift from fat oxidation toward synthesis, as evidenced by increased gene expression of lipogenic enzymes, whole body respiratory quotient (RQ), and hepatic triglyceride secretion.[88–92,94,96,101] Increased RQ is seen minutes after acute stimulation of AGRP neurons and is blunted by pharmacological inhibition of fatty acid synthase.[94] Along similar lines, i.c.v. injection of NPY in food restricted rats increases hepatic VLDL secretion within 2 h.[102] The reported shift in fuel partitioning in experiments with pair-fed or normo- and hypophagic *Mc3r* null mice occurs without any measurable changes in energy expenditure, locomotor activity or brown fat thermogenesis.[88–92,94] Neonatal ablation of AGRP neurons results in an unusual pattern of fuel partitioning in which RQ is reduced, apparently the result of increased fatty acid oxidation in muscle, but with increased hepatic triglyceride synthesis and secretion.[98] These observations highlight the limitation of whole-body measurements of metabolism and fuel utilization for mechanistic explanations of obesity pathogenesis.

4.2 | Genetic leptin deficiency models

4.2.1 | Obese (ob/ob) mouse

A loss-of-function mutation in the ob gene causes deficiency in the production of the peptide hormone, leptin, which results in the hyperphagic obese phenotype of *ob/ob*.[103] The *ob/ob* mouse, first described in 1950,[104] is one of the most studied genetic animal models of obesity. Excess fat accumulation in these animals was soon shown to occur in the absence of hyperphagia. *ob/ob* mice fed 25% less than lean controls still deposit about three time as much body fat over a 7-month period.[105] Early work also suggests that fat accumulation is associated with an increased rate of lipogenesis even in mice that are food restricted and losing weight over several days[106] or food deprived for 24 h.[107]

Numerous studies subsequently confirmed these early observations in pair-fed or food restricted *ob/ob* mice.[108–111] Coleman reported that *ob/ob* mice fed half the calories consumed by lean controls nevertheless developed excessive adiposity.[111] When allowed to eat ad libitum, fattening precedes the increase in food intake during ontogeny. Suckling *ob/ob* mice have greater body fat content than normal mice as early as 7 days of age[112,113] despite no measurable difference in milk intake.[114] Lipogenesis in *ob/ob* animals increases between 10–15 days of age in suckling mice,[115] prior to any increase in food intake in newly weaned mice.[116]

Excess fat deposition in *ob/ob* mice is also commonly attributed to reduced energy expenditure, although in some cases this has been interpreted as an artefact of normalizing oxygen consumption in terms of body weight[50] as considered above. Expressing O_2 consumption on a per animal basis can eliminate the difference between lean and ob/ob mice.[113,117,118] A deficit in BAT thermogenesis is thought to contribute to fat deposition in *ob/ob* mice that are maintained at relatively cool temperatures (i.e., room temperature of ~22°C or lower). However, these animals still gain excess fat when pair-fed and maintained at thermoneutral ambient temperatures, largely obviating a role for thermogenesis.[108–111] Indeed, *ob/ob* mice appear to have no deficit in BAT thermogenesis, but rather a disorder in thermoregulation involving alterations in heat loss that affect their ability to defend body temperature in the cold.[50,118]

4.2.2 | Diabetic (db/db) mouse

The *db/db* mouse lacks the long isoform of the leptin receptor, required for leptin's cellular effects. As in *ob/ob* mice, *db/db* mice are hyperphagic, and accumulate excessive fat independent of increased energy intake. Suckling *db/db* mice as young as 12 days of age have a greater percentage of body fat than do non-diabetic littermates.[119] At weaning (21 days), epididymal fat pads weighs four times as much in *db/db* mice as they do in normal animals.[120] These effects in *db/db* suckling and weanling mice are associated with, respectively, increased adipose tissue uptake of milk lipids and increased adipose and hepatic lipogenesis. Energy expenditure per animal is similar in *db/db* and normal mice housed at a thermoneutral temperature, although, unlike *ob/ob* mice, is lower in *db/db* mice housed at room temperatures.[121] Pair-feeding and even some degree of underfeeding relative to intakes of lean mice do not prevent excess fat deposition in *db/db* mice maintained at either room temperature or thermoneutral conditions.[110,111,121–123]

4.2.3 | Zucker (fa/fa) rat

The *fa/fa* rat has a leptin receptor missense mutation that prevents leptin signaling. The *fa/fa* rat was first described in 1961 by Zucker & Zucker[124] who recognized that hyperphagic *fa/fa* rats, like *ob/ob* mice, "have a more basic metabolic disturbance than simply an increased appetite. When restricted to a normal food intake, they are still obviously fat in appearance. Therefore, in these two cases, it is indicated that there is an abnormality in intermediary fat metabolism." Subsequent experiments by Lois Zucker[125] and others[126,127] confirmed this initial observation by demonstrating that *fa/fa* rats deposit more body fat when pair-fed or under-fed relative to lean Zucker rats. Suckling *fa/fa* rats as young as 7–10 days old consume no more milk from their mothers than do normal littermates,[128,129] but have heavier fat pads.[128,130–132]

The early, pre-weaning increase in adiposity in *fa/fa* rat pups is associated with increased adipose tissue lipoprotein lipase (LPL)

activity,[128,132,133] lipogenesis,[131] lipogenic enzyme activity[130,134] and expression of glucose transporter 4 expression,[134,135] all of which would favor substrate shunting toward storage. Adipocyte LPL activity and lipogenesis is also greater in pair-fed post-weanling and adult *fa/fa* rats[126,127] Studies of the disposal of administered radiolabeled triglycerides, fatty acids and glucose also demonstrate increased fuel shunting into adipose tissue in weanling and adult *fa/fa* rats compared with lean Zucker rats as well as in chronically food-restricted *fa/fa* rats.[136–139] Suckling *fa/fa* rats have a reduced capacity for thermoregulatory thermogenesis,[140] which, while contributory, does not account entirely for their excess fat deposition relative to nonobese littermates.[141,142]

4.3 | Other genetic models

4.3.1 | *Yellow* (A^Y or A^{vy}) *mouse*

Obesity in the yellow mouse is caused by a dominant mutation in the *agouti* gene, normally expressed only in skin, that results in ectopic expression of the agouti protein in other tissues.[143] Overexpression of the *agouti* gene results in increased production of AGRP and chronic inhibition of MC4R signaling in the brain.[144] Obesity in the yellow mouse was first documented in 1927[145] and this model has been used extensively in obesity research since. The development of obesity in yellow mice is associated with increased food intake and develops relatively slowly, with the appearance of increased body weight, fat content and lipogenesis at about 8–10 weeks of age.[146–148] Young and adult yellow and non-yellow mice have similar resting metabolic rates (per animal) at cold, room and thermoneutral temperatures.[149] However, yellow mice gain more body weight and fat per calorie of food consumed than do non-yellow agouti control animals[146,150] and require 18% less food than lean littermates to maintain the same weight from 4–8 weeks of age.[151] Consistent with these observations, obesity in yellow mice has been attributed to an increased "efficiency of food utilization more than the total caloric intake,"[150] indicative of a shift in fuel flux toward fat storage.[152]

Transgenic aP2-agouti mice overexpressing the agouti protein specifically in adipose tissue show greater body weight and body fat deposition even though food intake is identical to wild-type littermates.[153] This effect on body fat is consistent with the observation that agouti protein increases fatty acid synthase activity and triglyceride content of cultured adipocytes.[154]

4.3.2 | Otsuka Long-Evans Tokushima Fatty (OLETF) rat

The OLETF rat, originally developed as a model for type 2 diabetes mellitus,[155] lacks cholecystokinin-A receptors in pancreas and brain.[156] Whereas diabetes develops relatively late in adulthood, obesity begins to develop at 5–7 weeks of age,[155,157–159] following the onset of increased food intake.[159] In two experiments, OLETF rats pair-fed with lean control Long-Evans Tokushima Otsuka (LETO) rats from 3 or 6 weeks of age did not gain excess body weight and fat by 12 weeks of age.[158,159] In contrast, another study[160] found that OLETF rats pair-fed with LETO controls from 5 weeks of age had more body fat at 21 weeks. As compared with sedentary conditions, voluntary exercise starting at around weaning (3–5 weeks) in OLETF rats prevents weight gain and fat accumulation without reducing intake from increased levels.[161–163] These effects of exercise are associated with a shift in fuel partitioning reflected in a decrease in hepatic lipogenesis and increase in fatty acid oxidation.[163] Although the results of these pair-feeding experiments in OLETF rats are inconsistent, this model, among the major ones reviewed here, may be a relatively rare example of obesity arising from primary hyperphagia, with no underlying defect in substrate partitioning.

4.4 | Diet-induced obesity

Interest in creating animal models of obesity through changes in dietary composition, in view of the importance of diet in human obesity, followed discoveries of hypothalamic and genetic obesity in laboratory rodents.[164] However, translation of data from these models to humans should be restricted to shared, conserved mechanisms for control of fundamental aspects of intermediary metabolism. Because of species-specific differences in nutritional requirements and diet, inferences from animal studies regarding optimal human dietary composition to prevent obesity should be made cautiously.

Fats. Early work on "dietary" or "nutritional" obesity focused on the effects of fat content, finding that increasing the proportion of fat in rodent food resulted in increased body weight, body fat, or percentage body fat.[164–166] Obesity in these studies was accompanied by an increase in not only energy intake, but also feed efficiency.[164,166] While such a change in feed efficiency is consistent with the fuel partitioning theory, other findings provide more direct evidence. Body fat increases more in animals fed diets with a relatively high versus low fat content even when voluntary calorie intakes are similar.[167–170] More critically, excessive fat accumulation also occurs when animals are fed isocaloric amounts of diets with higher fat content[171–176] and does so even when fat digestibility is similar among isocaloric diets differing in fat content.[172]

The fatty acid composition of high-fat diets may influence fat deposition independent of changes in total energy intake. High-fat diets comprised of long-chain saturated fats have been found in some,[177,178] but not all,[179,180] experiments to induce greater body fat deposition in laboratory rodents than those containing unsaturated fats, an effect that has been attributed to hypothalamic inflammation.[181] Fatty acid saturation per se does not appear to be the critical factor because diets high in saturated fats with medium-chain lengths cause neither obesity[182] nor hypothalamic inflammation.[183] The fuel partitioning theory offers an explanation for these effects on fat accumulation in that long-chain saturated fatty acids are oxidized less readily than are unsaturated long-chain fatty acids,[184–186] and

medium-chain fatty acids are more readily and rapidly oxidized in comparison with long-chain fatty acids.[182,187]

4.4.1 | Fat-carbohydrate interaction

Manipulation of dietary fat content necessitates changes in other macronutrients, most commonly carbohydrates as was noted in one of the earliest such studies.[171] This issue is more than just methodological, because the excessive fat deposition induced by feeding diets high in fat content appears to depend on the carbohydrate content of such diets. Indeed, dietary carbohydrates (i.e., starch or sucrose), not fats, may drive both the increased fat accumulation and hypothalamic inflammation associated with consumption of long-chain saturated fat diets in mice[188] discussed above. Diets fed ad libitum that provide most calories as fat, but lack carbohydrate, typically do not induce obesity in laboratory rodents.[189–192] However, adding a small amount of carbohydrate (as low as 3–4% by weight) will make such high-fat diets obesogenic.[165,166,189,193]

So-called "high-fat" diets that cause excess fat accumulation, including those marketed commercially to induce obesity, typically contain 20–50% (by weight) of refined carbohydrates, including cornstarch, maltodextrin, sucrose or some combination thereof.[164,167–169,171–176] Such diets with equicaloric proportions of carbohydrates and fats (approximately 40% each) appear most effective in causing excess fat deposition[194,195] compared with diets matched for caloric density but differing in the proportion of carbohydrates and fats.[195] Fat accumulation and feed efficiency decline as this ratio diverges from parity in favor of either macronutrient,[195] consistent with a primary metabolic effect of dietary composition that shifts the flux of fuels toward storage.

4.4.2 | Carbohydrates

Typical commercial laboratory rodent chow is low in fat and high in carbohydrates comprised mainly of minimally processed, low-glycemic index grains. These "stock" or "standard" diets are often used as control diets in studies of diet-induced obesity because normal or genetic wild-type animals fed such food remain relatively lean during their laboratory life span. Purified diets containing refined carbohydrates and sugar induce body weight and fat gain compared with stock diets despite similar or lesser energy content,[196,197] although other differences in diet composition could be contributory.[198] Laboratory rodents consuming diets with high-glycemic index starch gain more body fat than do those eating diets with more slowly digestible starch, even when food-restricted to a level that prevents excess weight gain.[199–202]

In general, laboratory rats consuming low-fat diets formulated to contain sucrose as the carbohydrate source deposit more body fat than do those eating diets made with low-glycemic index starch or some other sugars when energy intakes are similar or matched by pair-feeding[196,203–206] consistent with the lipogenic effects of sucrose.[207] Feeding granulated sucrose to rats as a supplement to their standard chow increases body fat relative to feeding chow alone without a significant change in total energy intake.[208,209] However, providing sucrose as a concentrated solution in addition to chow results in a much more substantial increase in fat deposition or body weight,[198,209–212] in some cases without an increase in total calorie intake.[210,211] When offered along with chow, consumption of sucrose, glucose or polysaccharides in solution, but not in powdered form, increases both total calorie intake and body fat.[198,209] Although we can find no reports of pair-feeding studies conducted with carbohydrate solutions, the increase in fat deposition is associated with a greater feed efficiency.[198,211]

4.4.3 | Susceptibility to diet-induced obesity

An etiologic model of obesity pathogenesis should explain heterogeneity in individual predisposition to excess fat accumulation.[67] Susceptibility to diet-induced obesity varies among different strains of laboratory rodents[166,213] and also within strains. Distinct populations of animals prone and resistant to diet-induced obesity (OP and OR, respectively) have been identified in several outbred strains of rats[214,215] and inbred strains of mice.[216–218] Selective breeding of outbred OP and OR rats[219] has generated sub-strains of animals prone and resistant to diet-induced obesity (Levin DIO and DR rats, respectively). The non-Mendelian bimodal distribution of OP and OR subtypes within a strain suggests a polygenic pattern of inheritance, resembling the genetics of common obesity in humans.[219] Recent work[220,221] has found that induced deficiencies in the *Trim28* and *Nnat* genes in inbred mice also result in stable, bimodal distributions of obese and lean animals. Consistent with the fuel partitioning theory, obese *Nnat* deficient animals show increases in body fat weeks before any increase in food intake relative to controls.[221]

Typically, body weight, body fat content, and food intake do not differ between OP and OR outbred rats or inbred rodents eating standard chow, nor do chow-fed OP and OR rats differ with respect to energy expenditure[222,223] or physical activity.[223,224] Chow-fed selectively bred OP (DIO) rats are often,[219] but not always,[225–227] fatter than their OR (DR) counterparts. However, OP animals regardless of strain become clearly obese relative to OR animals when switched to an obesogenic (typically high-fat, high refined carbohydrate/sugar) diet. This greater fat deposition in OP animals is associated with increased feed efficiency[214–216,219,225] and, although often accompanied by increased food intake, has been observed with intakes equivalent to that of OR animals.[218,227,228]

Animals susceptible to diet-induced obesity appear predisposed to excessive fat storage before being switched from chow to an obesogenic diet. Compared with their OR counterparts, chow-fed OP rats have (i) lower rates of adipose tissue lipolysis in vitro,[229] (ii) a reduced capacity for whole body[226,227,230] and hepatocyte[231] fatty acid oxidation, (iii) reduced liver[226] and adipose[227] expression of genes involved in oxidation of fatty acids, and (iv) increased expression of genes involved in adipose tissue lipogenesis[227] and hyperplasia.[216]

Pharmacological stimulation of fatty acid oxidation with fenofibrate reduces food intake, feed efficiency and body fat in obese OP rats, but not lean OR rats.[232] The decrease in food intake of fenofibrate-treated OP rats appears secondary to their loss of body fat because untreated OP rats pair-fed to treated OP animals do not lose body fat. These results suggest that susceptibility to diet-induced obesity reflects a preexisting disorder in fuel partitioning favoring fat storage over oxidation.

5 | CONTROLS OF FUEL PARTITIONING

The mechanisms that direct fuel partitioning within cells and among tissues discussed above are under interconnected genetic, neural, and hormonal controls, which direct fuel fluxes in response to perturbations in energy homeostasis resulting from internal and environmental factors (Figure 2). Dysfunctions in these controls can modify intracellular and inter-organ mechanisms of fuel partitioning resulting in a shift in metabolic fuel fluxes toward excess fat accumulation. Indeed, genetic, neural, and hormonal disorders have been implicated in the etiology of obesity for many years, albeit largely in terms of their observed (and presumed direct) influence on energy intake and expenditure. The fuel partitioning perspective offers a different lens through which to view the role of these controls in the development of obesity.

5.1 | Genetic control

Variations in gene sequences, structure, and regulation modify expression or function of proteins (e.g., enzymes, transporters, receptors) that mediate metabolic fuel fluxes. Dysfunction of such genetic control is reflected in the excessive fat deposition independent of increased food intake seen in animal models of genetic obesity associated with spontaneous mutations such as the *ob/ob* or yellow mouse. Susceptibility to diet-induced obesity is associated with pre-existing changes in the expression of proteins involved in, for example, lipogenesis and fatty acid oxidation. Illustrating the interconnection of genetic and neural controls of fuel partitioning, similar changes in gene expression in peripheral tissues are observed after obesity-inducing manipulations of hypothalamic neuronal function that are independent of changes in intake.

Genetic variants associated with adipose tissue function have long been implicated in the development of obesity.[233] Large-scale genome wide association studies (GWAS) have identified a number of genetic variants correlated with increased risk of obesity, such as polymorphisms in the fat mass and obesity related (*FTO*) and melanocortin 4 receptor (*MC4R*) genes.[234] *FTO* and *MC4R* risk variants have been thought to engender obesity through increased energy intake because these genes are robustly expressed in the central nervous system.[30,234] However, as reviewed above, deletion of the *Mc4r* gene or suppression of MC4 receptors in mouse hypothalamus, which cause obesity and increase food intake, shift the partitioning of fuels into storage even when intake is restricted. *FTO* variants can act locally in adipose tissue to direct fat metabolism from oxidation to storage[235] and the obesity-related effects of *Fto* variants appear to be mediated by changes in the expression of *Irx3* and *Irx5* in brain as well as adipose tissue.[236] Thus, from a fuel partitioning perspective, *FTO* and *MC4R* gene associated variants, and others considered directly involved in hunger or satiety,[6] may, at least in part, drive intake and obesity through changes in fuel fluxes favoring fat storage.

5.2 | Neural control

Claude Bernard's work in the 1850s first established the existence of a central nervous system control of peripheral fuel metabolism.[237] This control is now known to be mediated by autonomic efferent nerves that innervate tissues important in maintaining energy homeostasis (e.g., adipose tissue, liver, gastrointestinal tract, pancreas, adrenal medulla) and afferent autonomic neurons that carry information (e.g., regarding nutrients, hormones, intracellular metabolic processes) from peripheral tissues signaling metabolic fuel status and energy production.[238–242] The hypothalamus integrates inputs from autonomic sensory nerves and central neuronal sensors of circulating nutrients, energy production, and hormones, and modulates sympathetic and parasympathetic (vagal) outputs to control, respectively, catabolic and anabolic metabolic processes. Accordingly, reduced sympathetic activity and/or increased parasympathetic activity would be expected to foster fat storage over oxidation.

Obesity caused by experimental disruption of hypothalamic function has long been thought to involve changes in peripheral autonomic nervous system function.[243] Highlighting the interconnection of neural and hormonal controls, hyperinsulinemia after VMH lesions, which is in part due to vagal activation,[244] contributes to the development of obesity.[245] As discussed above, chronic activation of hypothalamic AGRP neurons induces fat deposition independent of food intake, acutely decreases fat oxidation, and increases lipogenesis.[94] Pharmacological stimulation of the sympathetic nervous system prevents these acute metabolic effects of AGRP neuron activation,[94] although the precise mechanism of this reversal is unknown. Interruption of efferent, but not afferent, nerve fibers in the hepatic branch of the vagus nerve prevents fat accumulation induced by reduction of brain Mc4r signaling in pair-fed mice.[88]

Changes in fuel partitioning associated with autonomic control of adipose tissue function are mediated by its sympathetic innervation. Activation of adipose sympathetic nerves stimulates lipolysis and suppresses adipogenesis, whereas sympathetic denervation has the opposite effects.[240,246] Reduced adipose tissue sympathetic innervation or function would therefore be expected to shift fuel partitioning toward excessive fat deposition. This appears to be the case in leptin deficient *ob/ob* mice that show markedly reduced adipose tissue sympathetic innervation, which is normalized by long-term (7–14 days) peripheral or i.c.v. leptin treatment independently of the decrease in food intake induced by the hormone.[247] Deletion of hypothalamic neurons mediating this effect of leptin blunts restoration of the neural innervation

as well as the associated reduction of body weight and food intake.[247] Reduced sympathetic tone has long been hypothesized as an important factor in obesity pathogenesis,[248] however to what extent excessive fat deposition in other forms of obesity besides the *ob/ob* mouse can be traced directly to such autonomic dysfunction remains to be determined.[249]

5.3 | Hormonal control

Multiple hormones affect fuel partitioning with consequences for fat deposition. For example, estrogen modulates fat deposition in female rats by altering free fatty acid partitioning independent of its effect on food intake.[250] In rats, prolactin directs circulating triglycerides away from storage in adipose tissue into mammary glands for high-fat milk production by decreasing LPL activity in adipose tissue and increasing it in mammary glands.[251] Glucocorticoids foster fat accumulation and alter the distribution of body fat stores,[252] and may do so under some conditions without alterations in food intake.[253] Two hormones, insulin and leptin, warrant special consideration because of their pronounced, opposite effects on fuel partitioning.

5.3.1 | Insulin

Insulin exerts major effects on fuel partitioning by directly stimulating lipogenesis, facilitating fatty acid uptake in adipose tissue, and inhibiting lipolysis and fatty acid oxidation. Given these anabolic effects of the hormone, chronic hyperinsulinemia can be considered a potential mechanism for obesity development. Indeed, long-term insulin administration results in obesity in rats, even with restriction of food intake to or below that of control animals.[254] Similarly, intensive insulin treatment in patients with type 1 diabetes increases body fat content with no apparent change in caloric intake.[255,256] In addition to chronically elevated plasma insulin concentration, more subtle changes in insulin secretion and action might contribute to a shift in fuel fluxes that facilitate fat accumulation, such as (i) enhanced secretion in response to glucose or other secretagogues in the postprandial state; (ii) modification of receptor signaling affecting insulin sensitivity/resistance in different tissues or metabolic pathways; (iii) temporal patterning of secretion with regard to prandial, circadian or seasonal rhythms; and (iv) interactions with the actions of other hormones, especially glucagon.

Hyperinsulinemia, whether basal or in response to a glucose stimulus, appears to be at least a contributing cause of excess fat accumulation in many, but not all, animal models of obesity. Lesions of the VMH increase plasma insulin concentrations[70,257] and potentiate the effect of glucose on insulin release,[258] both independently of hyperphagia. In this case, hyperinsulinemia appears contributory to weight gain because rats with chemically-induced diabetes that are then given VMH lesions still gain more body weight and fat[245,259] and show increased adipose tissue lipogenesis and decreased fatty acid oxidation[259] compared with diabetic rats without lesions.

ob/ob and *db/db* mice are hyperinsulinemic during the early suckling period[260,261] before the onset of hyperphagia and coincident with the appearance of excess fat deposition,[112,113] suggesting a role for elevated insulin in these forms of genetic obesity. Accordingly, suppression of hyperinsulinemia in *ob/ob* mice by genetic reduction of insulin secretion prevents obesity.[262] Prenatal Zucker rats carrying at least one *fa* allele are hyperinsulinemic.[263] However, obesity in Zucker *fa/fa* rats may not be dependent on chronic hyperinsulinemia because LPL activity and fat mass increase in *fa/fa* rats early during the suckling period[128,130,132] well before an observable increase in basal circulating insulin concentration.[264,265] In addition, pair-feeding into adulthood prevents observable hyperinsulinemia, but not excess fat deposition.[126] *Nnat* deficient mice are hyperinsulinemic during their early weight gain period, which precedes the onset of hyperphagic.[221]

Insulin also plays a role in diet-induced obesity. Insulin secretion following oral glucose administration strongly predicts weight gain and fat accumulation in animals fed a high-glycemic index diet.[200] Mice fed a high- versus low-glycemic index diet also oxidize less intravenously-infused fatty acid (palmitate) prior to developing excess body fat,[202] suggesting a causal role for insulin on fuel partitioning. Preexisting hyperinsulinemia or increased insulin sensitivity as assessed by glucose tolerance may not underlie susceptibility of outbred[230] or selectively-bred[225,266] rats to diet-induced obesity. Conversely, hyperinsulinemia may facilitate the development of obesity once an obesogenic diet is consumed because genetically-induced inhibition of insulin secretion prevents and reverses such diet-induced obesity in mice.[267,268]

Sensitivity to insulin may differ with respect to tissue and metabolic pathway, limiting inferences drawn from whole body measurements. Regarding the former, mice with tissue-specific knockout of adipose insulin receptors are resistant to diet-induced obesity,[269] whereas those with muscle-specific knockout develop obesity,[270] consistent with a redirection of substrate toward or away from oxidation, respectively, as postulated by the fuel partitioning theory. Insulin sensitivity may also differ with respect to glucose and fatty acid metabolism, with consequences for fuel partitioning and fat deposition. In dogs, intravenous insulin infusion reduces the circulating concentration of free fatty acids at much lower doses than it does glucose.[271] Similarly, insulin inhibits lipolysis in isolated rodent adipocytes at concentrations at least one order of magnitude lower than those that stimulate glucose metabolism.[272–274]

Obesity is common in type 2 diabetes, characterized by insulin resistance and hyperinsulinemia. Obesity in this case may seem paradoxical given insulin's predominant anabolic effect on fat storage; one might expect less fat accretion with reduced insulin sensitivity. However, as consistent with the foregoing, control of glucose uptake by insulin is impaired in adipose tissue explants from insulin resistant obese *ob/ob* mice or mice with dietary obesity, whereas the antilipolytic effect of the hormone remains unimpaired.[275] Furthermore, insulin resistance restricted to liver by insulin receptor knockout or hepatocytes by receptor inhibition results in similar divergent effects, such that insulin fails to inhibit hepatic glucose production but still stimulates lipogenesis.[276,277] The selective effects of insulin resistance

on adipose tissue and liver glucose metabolism appear conducive to fat synthesis and storage, which might underlie, contribute to, or maintain obesity in type 2 diabetes.[275,278]

5.3.2 | Leptin

When first discovered, leptin was considered the long-hypothesized negative feedback "satiety signal," secreted by adipose tissue in response to fat accumulation with actions in the brain to restrain eating behavior and maintain body weight, as proposed initially in Kennedy's lipostatic hypothesis.[103,279,280] Subsequent findings from studies in obese and lean rodents and in humans led to a reinterpretation of this initial view, suggesting that the relative absence of the hormone may in fact signal starvation.[281,282]

Both perspectives are commonly interpreted as consistent with a role for leptin as an adipose signal to the brain, controlling energy intake in the regulation of body fat mass. However, leptin's involvement in obesity development and treatment may derive in part from direct effects on fuel partitioning with secondary (downstream) consequences for energy intake and expenditure, a possibility supported by pair-feeding and time-course studies: Administration of leptin by peripheral or i.c.v. injection or by overexpression of the hormone produces a loss of body fat in *ob/ob* and lean rodents substantially greater than that in pair-fed controls.[283–286] Metabolic effects of leptin treatment (i.e., loss of body fat and weight and increases in energy expenditure) precede its suppressive effect on food intake in developing[287–291] and adult rodents,[292] and result in a shift in metabolic fuel utilization away from lipogenesis and fat storage and toward fat mobilization and oxidation.[286,293–296]

This view of leptin's actions is consistent not only with the pathogenesis of obesity in the *ob/ob* mouse considered above, but also with the observations that (i) leptin is less effective in reducing food intake in lean mice and in mouse models of obesity with less severe obesity than seen in *ob/ob* mice;[284,297] (ii) acute injection of leptin increases whole-body fat oxidation, measured by decreased RQ, before decreasing food intake;[298] and (iii) the acute increase in food intake elicited in rats by injection of the fatty acid oxidation inhibitor, mercaptoacetate, is greater early during long-term leptin treatment when fat mobilization is maximal than it is later after body fat is depleted.[299] Studies in which the metabolic effects of leptin treatment are specifically manipulated should help to determine to what degree leptin affects food intake directly by signaling central pathways for appetite control or indirectly through its peripheral metabolic effects that in turn signal these pathways.

6 | HUMAN OBESITY

Research to understand the pathogenesis of human obesity is limited by practical and ethical considerations involving, among other factors, long-term studies under conditions allowing for precise manipulation and measurement of intake, environmental variables, physical activity, and biological parameters of interest. Consequently, investigations into the etiology of obesity in humans depend largely on indirect evidence from observational or correlational studies of biological or environmental variables and body weight, comparison of individuals with and without obesity, and inferences drawn from the efficacy of dietary, behavioral or pharmacological treatments for weight loss and, less often, weight gain. Until resources and methods are available to overcome these limitations, the value of models and theories of human obesity pathogenesis lay in their explanatory power and benefit to clinical practice and public health. With this in mind, we briefly review evidence that goes some distance to address the above limitations, illustrating how a fuel partitioning perspective can be usefully applied to advance a cohesive understanding of obesity pathogenesis in humans.

6.1 | Relationship between fat fuel partitioning and obesity

In studies tracking the metabolic fate of fixed oral fat loads containing long-chain triglycerides, individuals with obesity oxidize less fat and sequester more fatty acid in adipose tissue than do lean controls, and have a rate of fat oxidation that is inversely related with their degree of obesity.[300–303] Consistent with this latter finding, adipose tissue lipid turnover and lipolysis are reduced in obesity, and lipolysis is inversely correlated with future long-term weight gain.[304–306] Whole-body fat oxidation after overfeeding is also inversely correlated with long-term weight gain up to 1 and 5 years later.[307,308]

6.2 | Fuel partitioning associated with genetic, familial and post-obesity risk

Studies that attempt to address limitations of correlational studies or comparisons between subjects with and without obesity employ participants who, though without obesity at the time of the study, are considered at risk or obesity-prone because they carry genetic variants associated with obesity, have a family history of obesity, or have achieved substantial diet-induced weight loss. Compared with women homozygous for the wild-type *FTO* gene, carriers of a *FTO* risk allele with normal body mass index (BMI), waist circumference, and percent body fat have reduced in vivo lipolytic activity measured by circulating glycerol and lower rates of basal in vitro adipocyte lipolysis.[309] Similarly, whole-body fat oxidation is lower in carriers of the risk allele despite similar BMI, fat mass, and estimated energy intakes.[310,311] People with Prader-Willi syndrome (PWS), a well-studied syndrome,[312] develop severe hyperphagia and obesity during childhood. Studies indicate that an increase in adiposity[313,314] and in circulating insulin[315] precede hyperphagia. Ghrelin is increased in this initial phase of weight gain, despite the absence of hyperphagia, leading to the suggestion[316] that this "hunger hormone" may drive fat deposition through direct stimulation of lipogenesis.[317–319]

Whole-body fat oxidation is negatively correlated with fat mass gain 1 and 2 years later in lean women with a family history of

overweight or obesity who had lost weight to a BMI of < 25.[320] Similarly, during overfeeding, individuals self-identified as obesity-prone based on personal and familial histories have, compared with those identifying as obesity resistant, lower nocturnal concentrations of circulating fatty acids and rates of fat oxidation, and greater future long-term body weight and fat mass gains independent of baseline body composition and BMI.[321] Fat oxidation is lower after a meal containing carbohydrates and fat in lean men with a family history of overweight or obesity (BMI > 25.0) than it is in lean men with lean parents.[322]

Fat oxidation is reduced in patients who, through dieting, no longer have obesity compared with controls who never had obesity, despite similar BMI, body fat mass, or total and resting energy expenditures.[323,324] Basal and stimulated lipolysis in adipocytes in vitro is lower in people with prior obesity following weight loss than it is in lean controls with similar BMI and body fat mass.[325] Compared with controls who never had obesity and matched for BMI and body fat mass, people with prior obesity oxidize less dietary fatty acids,[326] clear dietary lipids from the circulation more rapidly, and have lower whole-body fat oxidation after a high-fat test meal.[327,328] The above findings suggest that low fat oxidation and adipose lipolysis could enhance storage of dietary fat in adipose tissue and thus help drive the weight re-gain that is often observed when dieting is discontinued.

6.3 | Insulin sensitivity

Consistent with animal studies reviewed above: (i) insulin inhibits lipolysis in human adipocytes at lower concentrations than it stimulates glucose uptake and metabolism[329]; (ii) insulin administration in humans stimulates plasma fatty acid uptake and suppresses lipolysis in adipose tissue, and inhibits hepatic fatty acid oxidation and ketogenesis at concentrations with little to no effect on glucose tissue uptake or plasma levels[330–332]; and (iii) patients with obesity and type 2 diabetes are insulin resistant with respect to glucose disposal, but show normal suppression of lipolysis and ketogenesis in response to insulin infusion.[332,333] As discussed above, these effects of insulin on fat metabolism could serve to promote or maintain obesity in type 2 diabetes.[275,278,333]

Insulin sensitivity is reportedly increased and fat oxidation is reduced after a high-fat meal in normal-weight healthy men with familial predisposition to obesity versus normal-weight men without such a predispotion.[322] Similarly, compared with controls who never had obesity, women with prior obesity following weight loss show normal insulin sensitivity involving glucose metabolism, but increased sensitivity to antilipolytic action, which would favor fat storage.[334] Consistent with this observation, weight-reduced participants in a feeding study eating a high-carbohydrate diet, compared with those eating a low-carbohydrate diet, have lower level of circulating energy availability in the late postprandial period, primarily because of reduced fatty acid concentrations.[335] Recent genetic analyses[221] suggest that children and adults can be stratified into obesity sub-types, including one with elevated circulating insulin concentrations associated with decreased *NNAT* expression, analogous to that found in *Nnat*-deficient mice (although, in this case, differential insulin sensitivity by tissue or metabolic pathway has not been studied). Finally, acute insulin secretion in response to intravenous glucose infusion and insulin sensitivity are positively correlated with prospective long-term weight gain.[336]

7 | CONCLUSIONS AND IMPLICATIONS

The fuel partitioning theory of obesity pathogenesis presented here derives from well-documented mechanisms of intermediary metabolism and energy homeostasis. Results from studies using a wide variety of animal models throughout the last 80 years are, with few exceptions, broadly consistent with the theory that obesity arises, at least in part, from intrinsic disorders in fuel partitioning that lead to the trapping of fat in adipose tissue, resulting, in turn, in compensatory effects on energy intake and/or expenditure.

Rigorous mechanistic studies and well-powered clinical trials of adequate duration will be needed to further establish whether and to what extent such is the case in common forms of human obesity. As discussed above, studies of individuals not currently with, but at risk for, obesity seem especially promising. Within the limits of ethical considerations and with adequate resources, these investigations could be modeled after animal studies in which fat accretion and metabolic processes in critical tissues associated with fat deposition are measured under conditions of fixed or restricted energy intake. Prospective studies of normal and at-risk individuals involving measurements of dynamic changes in tissue and organ metabolism and of circulating fuel fluxes could provide insights into factors that are predictive of future weight gain and excess fat deposition. Such studies could involve, for example, manipulation of diet composition, responses to over- and under-feeding, drug and hormone treatment, and the use of subjects post weight loss. These investigations may uncover parameters of fuel partitioning that could identify additional at-risk subpopulations for future studies.

The fuel partitioning theory has major implications for strategies to prevent and treat obesity. Instead of a focus on reducing energy intake and increasing energy expenditure, interventions that directly target fuel partitioning would be expected to have greater efficacy over the long term. Lifestyle interventions might emphasize diets that lower the anabolic drive toward fat storage. Dietary treatment strategies could also be used in conjunction with drugs that modify endocrine, neural, or cellular molecular mechanisms to augment this effect. In this regard, it is worth considering that drugs currently in use (e.g., glucagon-like-1 receptor agonists) to treat obesity may have effects on fuel partitioning, independent of those on food intake, that would contribute to their efficacy for weight loss.[337–339]

A fuel partitioning theory may also inform an obesity research agenda by broadening the focus from how body fat mass is maintained to encompass how changes in fat synthesis, storage, mobilization, and oxidation affect the supply and use of metabolic fuels for energy production. Critical questions in this regard include (i) to what

extent various genetic, endocrine, and neural factors affect food intake directly by signaling satiety and hunger versus indirectly through their effects on peripheral fuel metabolism, and (ii) how alterations in metabolic fuel supply and cellular energy production resulting from shifts in fuel partitioning are sensed and drive changes in energy intake and expenditure. Investigation into the multitude of potential causes of obesity – e.g., the microbiome, circadian patterns, obesogens, food insecurity and diet – might also benefit by consideration of what these factors do to fuel partitioning. More broadly, it remains to be elucidated whether the rapid development of obesity during the recent decades among populations with essentially unchanged genetic risk can be better explained by direct neuropsychological effects of recent changes in the food supply (e.g., on the palatability or reward associated with modern industrial foods) or by their effects on the metabolic mechanisms of fuel partitioning.

A vast amount of data has accumulated since the development of the first reproducible animal models of obesity; however, there is still no validated comprehensive pathophysiological explanation for obesity, and the efficacy of conventional approaches to prevention and treatment remains limited. As discussed by Popper in his essay, "*The bucket and the searchlight: Two theories of knowledge*,"[340] a collection of observations itself does not generate understanding – a theory, a "searchlight," is required to provide meaning and significance to the observations. Here, we described a perspective of obesity pathogenesis with potentially broad explanatory power, in the hope that it will illuminate a path to inform, quoting Popper, "… what kind of observations to make: whereto we ought to direct our attention; wherein to take interest" in the continuing effort to end the obesity pandemic.

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CONFLICT OF INTEREST STATEMENT

D.S.L. reported receiving royalties for books on obesity that recommend a carbohydrate-modified diet. G.T. receives royalties for books that discuss the history and science of obesity, and therapeutic applications of carbohydrate-restricted eating. M.I.F., J.L. and T.I.A.S. report no conflict of interests or financial ties.

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