# Chapter 18
# Animal Models of Obesity

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## Introduction

Animal models have provided and still provide major contribution to our understanding of the physiological and genetic bases of obesity. Notwithstanding the usefulness of specific models such as dogs, pigs, and nonhuman primates, I will focus this chapter on laboratory rodents, mostly mice and rats. Indeed, these species represent the bulk of animals used for research due to their rapid and high reproduction rate, well-established breeding and caging conditions, and large availability of molecular tools for the genome cartography and various types of transgenic modification. Most rodent models of obesity have been investigated since the early 1950s, but it is only after an extending period of time that the mechanisms underlying their phenotype started to be identified. Despite the tremendous progress brought by the development of molecular biology, not all the components of obesity phenotypes have been deciphered and new animal models are still needed to unravel the complexity of energy balance regulation. Here, I will review various types of rodent models for obesity (Table 18.1), which each provides information related to specific aspects of human obesity.

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**Table 18.1** Different types of rodent models of obesity

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|---|
| Diet-induced obesity (High-fat diet) |
| Hypothalamic obesity (stereotaxic lesions) |
| Genetic obesity |
| Polygenic obesity (QTL) |
| Monogenic obesity (mutations *agouti, fat, tubby, Lep, and LepR*) |
| Obesity induced by mutagenesis or genetic manipulation (transgenic and knockout models) |

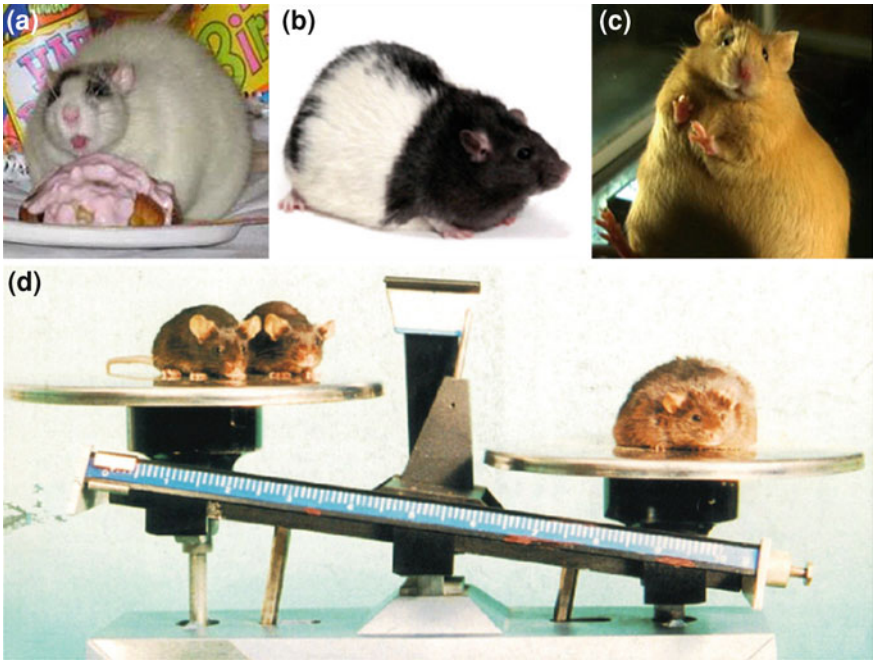


**Fig. 18.1** Examples of rodents' models. **a** Nutritional obesity in rat; **b** Obese Zucker *fa/fa* rat; **c** Agouti mouse, obese and yellow; **d** Obese *Lep/Lep* mouse (*right*) and two non mutated control mice (*left*)

## Rodent Models of Diet-Induced Obesity

Exploring the effects of the diet on the regulation of body weight was the driving force for the development of early rodent models of obesity. In this paradigm, mice or rats are fed calorically dense high-fat, high-fat/high-sugar, or cafeteria-type diets. Current commercial diets include 30, 45, or 60 % of calories from fat, while the control isocaloric diet contains around 10 % of calories from fat. Although rodents tend to reduce their food intake when fed a high-fat diet, they ingest more calories from fat, leading to increased adiposity and eventually obesity (Fig. 18.1). Not only the amount, but also the type of dietary fats can be changed to investigate responses to specific diets (Burcelin et al. 2002; Hariri and Thibault

2010). As in humans, genetic resistance or predisposition to obesity exists in rodents, with some strains gaining little weight on high fat compared to normal chow, whereas others rapidly progress to obesity. Studies comparing obesity-prone and obesity-resistant strains have been instrumental to identify the mechanisms and metabolic consequences of high-fat feeding (Surwit et al. 1995; Levin et al. 2004; Fearnside et al. 2008; Madsen et al. 2010).

Nowadays, rodent models are still frequently used in kinetic studies investigating systemic and organ-specific alterations associated with diet-induced obesity. One pathogenic component is leptin resistance, which develops gradually as evidenced by a progressive rise of circulating concentrations, but it is still debated whether it is secondary or causal to the diet-induced obesity (Scarpace and Zhang 2009). Insulin resistance is initially an adaptive response to high-fat diet that reduces hepatic glucose production and switches substrate utilization toward lipids, but becomes deleterious in the long run leading to type 2 diabetes. Diet-induced obese rodents represent valuable models for this life-threatening complication of human obesity. Importantly, these models have been crucial for the discovery of immune cells accumulation in the adipose tissue and its link to metabolic co-morbidities (see Chap. 20). The reversibility of high-fat diet-induced obesity has been addressed in obese rodents submitted to food restriction (Levin and Dunn-Meynell 2000; Kosteli et al. 2010) or to gastric bypass (Troy et al. 2008) after a period of high-fat feeding. In genetically modified mice, variations in the nature and amplitude of diet-induced responses are routinely checked to detect whether a specific gene is implicated or not in the regulation of body weight and obesity co-morbidities. Another area of research developed, to explore the still elusive mechanisms of early programming and epigenetic events, relies on diet-induced obese rodents (Ainge et al. 2011). Indeed, high-fat diet consumption during pregnancy and/or lactation, prepubertal high-fat feeding, as well as manipulation of milk intake by varying litter size, influence body weight, body fat content, and adipose tissue inflammation in adult offsprings (Guo and Jen 1995; Leibowitz et al. 2007; Boullu-Ciocca et al. 2008; Patterson et al. 2010). Finally, it is now established that gut bacteria interact with high-fat diet to promote obesity and insulin resistance (Cani et al. 2008; Ding et al. 2010), extending the use of diet in rodents to explore the complex relationship between energy balance and microbiota.

## Rodent Models of Hypothalamic Obesity

A second model of obesity developed in the 1950s is the rat "VMH" (King 2006) that was produced by stereotaxic lesions of the ventro-medial hypothalamus (VMH). Rats with VMH lesions eat two to three times more food than normal, overeating starting almost immediately after the lesion. The weight gain that follows is rapid and quite dramatic as it is not uncommon to observe weight gains averaging 10 g per day, resulting in a doubling of body weight within 1 month. Eventually, daily food intake decreases and body weight usually stabilizes.

A similar morbid obese phenotype can be obtained by goldthioglucose injection in mice or rats (Marshall et al. 1955). Gold being toxic to neurons, it is linked to glucose by sulpfur (thio) to destroy the cells that take up glucose. When goldthioglucose is injected, there is an extensive damage in the VMH, which is enriched in glucose-responsive neurons. It is noteworthy that VMH lesion-induced hyperphagia and obesity have been reported in nonrodent species, including rabbits, cats, dogs, and monkeys [see Refs. in (King 2006)]. In humans, obesity is a severe sequel to tumors in the hypothalamic region or their surgical treatment (Pinkney et al. 2002).

## Rodent Models of Genetic Obesity

### *Models of Polygenic Obesity*

There are numerous evidences for a genetic influence on human obesity (see Chap. 24). In this field, both mice and rats provide highly relevant models for deciphering the genetic basis of obesity. Numerous genome-wide searches for obesity genes have been performed in rodents characterized by distinct body fat content or proneness to high-fat feeding. The experimental approach consists in correlation analyses between phenotypic traits related to obesity and the genotype using chromosomal markers that differ between groups of rodents under study. The chromosomal loci that statistically associate with the variation in the phenotypic character of interest have been named quantitative trait loci (QTL). Studies in two-strain backcrosses, F2 intercrosses, and recombinant inbred lines have led to the identification of hundreds of QTL influencing body weight, illustrating the polygenic nature of energy balance regulation (Brockmann and Bevova 2002; Rankinen et al. 2006). Unfortunately, identification of QTL at the gene level has proved mostly elusive. The dramatic improvement in genomic and bioinformatic resources holds promise to accelerate obesity gene discovery. Alternative rodent models, including heterogenous stocks of mice created from a limited number of founders (Churchill et al. 2004; Valdar et al. 2006) and new ways to exploit data, such as in silico mapping (Liu et al. 2007), the creation of genetic maps for gene expression (eQTL) (Schadt et al. 2005), or the application of systems biology to obesity genetics (Pomp et al. 2008) are expected to improved the identification of genes influencing energy balance and fat deposition.

### *Models of Monogenic Obesity*

Genetic analysis of rodent models of monogenic obesity has been more successful, leading to the identification of five genes that, when mutated, result in obesity (Table 18.2). This significant progress has been achieved by applying the method

**Table 18.2** Rodent models of monogenic obesity

| Mutation | Chromosome | Type | Mutated gene, function | Phenotype |
|---|---|---|---|---|
| Mouse | | | | |
| $A^y$, $A^{vy}$ | 2 | Gain of function, dominant | Agouti, inhibition of α-MSH food intake reducing effect via MC4-R | Late-onset obesity, yellow fur |
| Fat | 8 | Loss of function, recessive | Carboxypeptidase E, hormones, and neuropeptides maturation | Late-onset obesity, diabetes, infertility |
| Tubby | 7 | Loss of function, recessive | Tub, unknown function | Late-onset obesity, blindness, deafness |
| Lep | 6 | Loss of function, recessive | Leptin, control of food intake | Early-onset obesity diabetes[a], infertility |
| LepR | 4 | Loss of function, recessive | Leptin receptor | Early-onset obesity, diabetes, infertility |
| Rat | | | | |
| fa | 5 | Loss of function, recessive | Leptin receptor | Early-onset obesity infertility (females) |
| $fa^k$ | 5 | Loss of function, recessive | Leptin receptor | Early-onset obesity diabetes, infertility |

[a] Depends on the genetic background

of positional cloning in spontaneously obese mice detected in large breeding colonies. Most of the naturally occurring mutations being recessive, selective crosses were crucial to keep them in the progeny, thereby allowing identification of the mutated gene often decades after the discovery of the affected mice. Mutations in the same genes or members of their molecular pathways have been found (expect for the tubby mutation) in a very limited number of obese humans, but with remarkably similar phenotypes in humans and rodents (Clement 2006). In the case of leptin, identification of the mouse gene in 1994 was followed by the successful treatment of a leptin-deficient child only 5 years later (Farooqi et al. 1999). Leptin treatment was then successfully applied to 13 identified patients with leptin deficiency, reflecting a major therapeutic breakthrough based on experimental researches in obese mice started 50 years earlier (Table 18.3). Additionally, the study of the five mouse obesity genes has markedly increased our understanding of the mechanisms involved in energy regulation.

## The *Agouti* Mutations

Several mutant alleles have been identified at the mouse "agouti" locus, given their easily detectable effect on coat color. Two of them, *lethal yellow* ($A^y$) and

**Table 18.3** Leptin: from gene to therapeutic

| | |
|---|---|
| 1950 | Description of monogenic obesity phenotypes in rodents (*ob/ob* and *db/db* mice) |
| 1960 | Hypothesis of a circulating satiety factor (parabiosis experiments) |
| 1994 (December) | Cloning the leptin gene |
| 1995 (July) | Successful treatment of *ob/ob* mice by recombinant leptin |
| 1995 (December) | Cloning the leptin receptor gene |
| 1997–1998 | Discovery of rare mutations in the genes of leptin and its receptor in humans |
| 1999–present | Successful treatment of 13 leptin deficient patients |

*viable yellow* ($A^{vy}$), induce a phenotype of late-onset obesity and yellow fur in heterozygote mutants (Fig. 18.1). The mouse *agouti* gene was cloned independently by two groups in 1992 (Bultman et al. 1992; Miller et al. 1993). This breakthrough allowed showing that *agouti* transcripts, normally expressed exclusively in the skin of neonatal mice, were actually detectable in virtually all tissues in the obese yellow mutants. The structure of the $A^y$ allele, where a 170-kb deletion brings the coding region of the *agouti* gene under the control of a ubiquitous promoter, accounts for this ectopic expression (Michaud et al. 1994). The double phenotype of the obese yellow mice has been attributed to a competitive antagonism between the agouti protein and the α-melanocyte stimulating hormone (α-MSH) on two melanocortin receptors, MC1-R, expressed in the skin, and MC4-R, in the hypothalamus [see Refs. in (Barsh et al. 1999; Moussa and Claycombe 1999)]. In the skin, agouti binding on MC1-R switches the production of black eumelanin pigment to yellow pheomelanin. In the hypothalamus, the protein inhibits the negative control of food intake exerted by MC4-R, leading to hyperphagia and obesity. An endogenous agouti-related protein (AGRP) was cloned subsequently and showed to act similarly to agouti as a potent antagonist for MC4-R. Deciphering the central mechanism of action of the agouti protein has led to the identification of a previously unknown pathway in the control of food intake, which comprises anorexigenic (α-MSH) and orexigenic (AGRP) components acting through MC4-R. The yellow obese mouse model is at the basis of the discovery of MC4-R mutations in humans (see Chap. 24), opening a whole area of pharmacological research targeting this receptor.

### The *Fat* Mutation

In 1995, a single base mutation was found in the gene coding for the enzyme carboxypeptidase E (CPE) in the obese *fat/fat* mouse (Naggert et al. 1995). This was associated with loss of CPE activity, leading to hyperproinsulinemia, which is one of the earliest phenotypic characteristics caused by the fat mutation. Multiple defects in other peptide hormones or neuropeptides processing have been reported in CPE deleted mice (Cawley et al. 2010), but a causal relationship with the late-

onset obesity observed in this model still remains unclear. Mice genetic manipulation yielding to an increased CPE expression specifically in proopiomelanocortin (POMC) neurons, shed light to this question (Plum et al. 2009). Indeed, this manipulation induces a reduction in food intake associated with alterations in the neuropeptide profile in the mediobasal hypothalamus, including increased amount of α-MSH, a product of CPE-dependent processing of POMC. These observations suggest that the obese phenotype of *fat/fat* mice relies, at least in part, on defect in POMC processing in hypothalamic neurons that alleviates the negative control of food intake by the α-MSH/MC4-R signaling pathway discovered in the agouti mouse model.

### The *Tubby* Mutation

The mutated gene responsible for the *tubby* obesity was identified in 1996 (Kleyn et al. 1996; Noben-Trauth et al. 1996). The naturally occurring single base mutation in the *tub* gene abolishes a splice donor site, resulting in the replacement of 44-carboxy-terminal amino acids of the tub protein with 24 intron-encoded amino acids. The unusual phenotype of the *tubby* mouse combines vision and auditory deficits and late-onset obesity. The mutant mice begin to diverge in weight at about 12 weeks of age, and ultimately reach twice the weight of their wild-type littermates. It is now established that Tub is the founding member of the tub-like proteins family, composed of Tub and TULP1-3. These proteins are highly conserved among various vertebrate genomes and expressed primarily in nervous tissues. Unfortunately, little is known about their biochemical functions. Structure–function analyses and cell-based experiments have raised the possibility that Tub might function as heterotrimeric-G-protein-responsive intracellular signaling factor (Carroll et al. 2004). Although widespread *tub* gene expression in the hypothalamus suggests a potential control of food intake, the way Tub influences energy balance is far from being understood.

### The *Lep* and *LepR* Mutations

As previously mentioned, the leptin gene was cloned in 1994 and two distinct mutations were identified in *Lep/Lep* mice, previously referred as *ob/ob* mice (Zhang et al. 1994). In the original strain, a single base mutation creates a premature stop codon, while the second is the result of the insertion of a retroviral-like transposon in the first intron of the gene leading to the absence of transcripts (Moon and Friedman 1997). Given the same phenotype in both strains, it was concluded that the single base mutation in the leptin gene was a loss-of-function mutation. *Lep/Lep* mice are visually obese at weaning demonstrating early onset obesity, and they can end up weighing more than 100 g, which is four times the weight of their littermate controls (Fig. 18.1). In this model, uncontrollable hyperphagia and reduced energy expenditure are constant characteristics, whereas

the presence of type 2 diabetes is strain dependent. The absence of functional leptin is responsible for this extreme phenotype, as unambiguously demonstrated by the immediate and drastic reduction of food intake following recombinant leptin administration in *Lep/Lep* mice (Pelleymounter et al. 1995; Campfield et al. 1995; Halaas et al. 1995). These striking data helped to establish that leptin was, indeed, the unidentified circulating satiety factor proposed in 1973 on the basis of pioneer parabiotic experiments between wild type and *Lep/Lep* mice (reviewed in (Coleman 2010). Following the cloning of the leptin gene, a wealth of information became available, leading to the concept that leptin is an adipocyte secreted hormone that acts in the hypothalamus to regulate food intake in relation with the energy status. As a cytokine-like protein, leptin also exerts pleiotropic effects in a large variety of tissues and cell types, and is implicated in functions such as reproduction and immunity, besides energy homeostasis.

Cloning of the leptin receptor gene by virtue of leptin binding (Tartaglia et al. 1995) was followed by the demonstration that this gene is mutated in several strains of *db/db* mice, now referred as *LepR/LepR* mice (Lee et al. 1996, 1997; Chen et al. 1996; Li et al. 1998) and in two rats models of obesity, the *fa/fa* Zucker rat (Phillips et al. 1996) (Fig. 18.1) and the $fa^k/fa^k$ Koletsky rat (Takaya et al. 1996). All mutations preclude leptin signaling, although through distinct mechanisms, including by creating truncated receptors that lack both the transmembrane and the intracellular domain required for leptin signaling. In all cases, the absence of functional leptin receptor results in massive early onset obesity as observed in leptin-deficient mice. The primary difference between the two models is that leptin receptor-deficient rodents have dramatic elevations in circulating leptin concentrations, reflecting their resistance to the hormone. Of note, leptin-resistant Zucker rats are able to reduce their food intake in response to a systemic load of calorie from glucose (Gilbert et al. 2003) or when placed in condition of hypobaric hypoxia (Simler et al. 2006), indicating that leptin independent anorexigenic pathways remain functional in this model.

## Artificially Generated Mice Models of Obesity

### *Chemical Mutagenesis in Mice*

To circumvent the arbitrary nature of spontaneous mutational events in critical obesity genes, attempts have been made to accelerate the process by increasing the mutation rate artificially. This can be performed by treating mice with mutagenic chemicals, such as ethylnitrosourea (Justice 2000). So far, a few mutant phenotypes differing in body weight or obesity-related traits have been selected. The confirmation of the mutation and its chromosomal localization requires time-consuming backcrossing to show that there is a single gene involved. Moreover,

the final isolation of the mutated gene remains difficult. Currently, the obese mice issued from chemical mutagenesis are in the process of being crossed, but no gene has been yet identified using this strategy.

### *Transgenic Mouse Models*

The 2005 update of the obesity gene map cited more than 200 genes that, when mutated or expressed as transgenes in mice, result in phenotypes that affect body weight and adiposity (Rankinen et al. 2006). These models support roles for a large array of genes and pathways in the regulation of energy homeostasis. Their phenotypic description is beyond the scope of this chapter, but it is interesting to note that two situations are informative: (1) when a gene targeted for a different purpose is unexpectedly found to influence body weight gain and (2) when a gene hypothesized to play a role in energy balance is targeted to confirm its implication. Examples of the latter case are worth mentioning. Following identification of the *tubby* mutation, it was unclear whether the Tub mutant protein retained any biological activity. A *tub* knockout was generated that recapitulated the full spectrum of the *tubby* mouse phenotype, thereby establishing the loss of function of the spontaneous mutant protein (Stubdal et al. 2000). Similarly, the generation of transgenic mice expressing the *agouti* gene from a ubiquitous promoter confirmed that the yellow and obese phenotype of agouti mice was directly related to ectopic expression of the protein (Klebig et al. 1995; Perry et al. 1995). Most importantly, after the demonstration that agouti antagonized α-MSH binding on MC4-R in reconstituted cell systems, the targeted deletion of this receptor in mice revealed its major role to inhibit food intake (Huszar et al. 1997). This knockout model provided crucial information to establish the molecular basis of the obese phenotype of agouti mice and, as a follow up, to promote the systematic screen for mutation in MC4-R in obese subjects.

## Conclusion

Clearly, there is no perfect animal model of human obesity. Nevertheless, the use of rodent models to study the genetic, physiological, epigenetic, and environmental bases of obesity has provided an enormous amount of scientific knowledge, opening new avenues for urgent need of therapeutic targets in obesity. Although reduction in the use of animal models is ethically desirable, it is unlikely that in silico or cell-based experiments will overtake the use of live animals to explore the complexity and multifactorial nature of energy balance regulation in the near future. Moreover, rodent models of obesity represent necessary tools for testing innovatory interventions, such as treatment with chemical chaperone that reduces reticulum endoplasmic stress and improves leptin sensitivity in high-fat fed mice

(Ozcan et al. 2009) or transplantation of hypothalamic neurons that partly restore leptin signaling in *db/db* mice (Czupryn et al. 2011). Finally, new technical approaches, to obtain genetically engineered rodents more rapidly and at lower cost than before (Dow and Lowe 2012), are likely to provide new models in the field of obesity, increasing the chance of finding effective treatment strategies to curb the expanding progression of the disease worldwide.

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