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*Review Article*

# Biology of Obesity: Lessons from Animal Models of Obesity

**Keizo Kanasaki and Daisuke Koya**

*Division of Diabetes & Endocrinology, Kanazawa Medical University, Uchinada, Ishikawa 920-0293, Japan*

Correspondence should be addressed to Daisuke Koya, koya0516@kanazawa-med.ac.jp

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Obesity is an epidemic problem in the world and is associated with several health problems, including diabetes, cardiovascular disease, respiratory failure, muscle weakness, and cancer. The precise molecular mechanisms by which obesity induces these health problems are not yet clear. To better understand the pathomechanisms of human disease, good animal models are essential. In this paper, we will analyze animal models of obesity and their use in the research of obesity-associated human health conditions and diseases such as diabetes, cancer, and obstructive sleep apnea syndrome.

## 1. Introduction

Obesity, defined as a body mass index (BMI) >30 kg/m$^2$, is a significant health problem [1]. Obesity has reached epidemic proportions globally, and the World Health Organization estimates that there are more than 1 billion overweight adults, of which at least 300 million are obese [2]. Societal changes and the worldwide nutrition transition have driven the obesity epidemic over recent decades. Economic growth as well as modernization, urbanization and globalization of food markets are some of the elements that have contributed to the obesity epidemic. Significant shifts toward less physically demanding work have been observed worldwide. Decreased physical activity has also been associated with increasing opportunities to use automated transport, have technology in the home, and engage in more passive leisure pursuits [2].

Obesity is associated with premature death through increasing the risk of many chronic diseases, including type 2 diabetes, cardiovascular disease, and certain cancers (Figure 1) [3, 4]. In addition, obesity is associated with respiratory difficulties, chronic musculoskeletal problems, lumbago, skin problems, and infertility (Figure 1) [4]. Most of the evidence proposing obesity-associated health problems has been obtained from epidemiological analyses of human subjects; the precise molecular mechanisms of obesity-associated health problems have not yet been determined. In this paper, we will summarize reports associated with obesity-related pathology using animal models and also propose further demand for animal research models to address the worldwide obesity epidemic.

## 2. Animal Models of Obesity

There are many rodent and nonrodent models of obesity. We introduce several widely used important animal models of obesity in this section.

### 2.1. Rodent Models

#### 2.1.1. Monogenic Mouse Obesity

*Lethal Yellow Mutant Mouse* ($A^y$). Among the several commonly existing obese mice currently used in research, the *agouti* mutation mouse was first reported more than century ago. In 1992, the *agouti* protein was cloned by Bultman et al., and *agouti* became the first obesity gene characterized at the molecular level [5]. *Agouti* is a pigment control gene transiently expressed in follicular melanocytes to induce the production of red/yellow pheomelanin pigment and inhibit black/brown pigment [6–8]. The lethal yellow mutant mouse ($A^y$) is one of five dominant *agouti* mutations and has been found to be an excellent mouse model of obesity [5]. The $A^y$ mutation is characterized by the deletion of 120–170 kb genomic DNA, resulting in ubiquitous *agouti* expression due

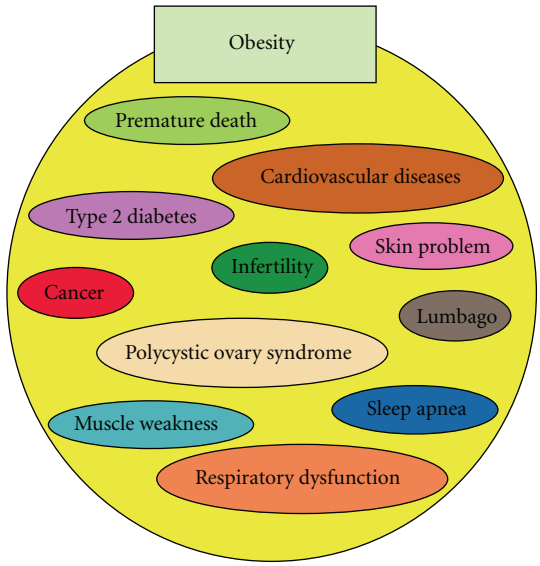


Figure 1: Obesity-associated complications. Obesity is associated with various health conditions in humans.

to loss of the tissue-specific control promoter element [9–11]. $A^y$ mice exhibit several phenotypes such as a yellow coat color, mature-onset obesity, type-II diabetes, hyperleptinemia, increased linear growth, higher tumor susceptibility, and infertility [5]. Transgenic mice expressing ubiquitous *agouti* exhibited yellow coat color, obesity, hyperinsulinemia, and hyperglycemia similar to $A^y$ mouse [12], revealing the molecular mechanism of *agouti* in mouse phenotype. Mice with adipose tissue-specific *agouti* overexpression exhibit an overgrowth of adipose tissue without alteration of food intake, suggesting that increased fat in this model is due to changes in energy metabolism [13]. The adipose tissue *agouti* overexpression model could be relevant to human obesity because *agouti* gene expression is found in human adipose tissue [14, 15] and is increased in the adipose tissue of type 2 diabetic subjects [16]. Likely the ectopic expression of *agouti* in mice pancreas stimulated the release of insulin by pancreatic $\beta$-cells, which may further enhance *agouti*-stimulated lipogenesis [17]. Transgenic *Agouti* expression in skin did not induce obesity, suggesting that the obesogenic role of *agouti* is tissue dependent [18].

*Leptin Signaling Defects in Mice: ob/ob and db/db Mouse Models.* In 1949, researchers from the Jackson Laboratory discovered obese mice by chance [19]. Responsible mutation gene is named as obese (ob) gene. The *ob/ob* mutation is recessive, and neonatal mutant mice are normal when compared to unaffected control littermates. Mutant mice, however, gain weight rapidly throughout their lives, eventually reaching a weight that is three times that of control mice. The phenotype is clear, but identification of the gene responsible for the obese phenotype took nearly 50 years [20]. In 1994, Zhang et al. identified the mutation in the leptin gene as responsible for ob mutation by positional cloning [20]. Leptin is a gene expressed abundantly in the adipose tissue. Characterization of this mutation revealed a single base pair deletion in the leptin coding region that results in a frame shift and a premature stop codon [20]. The leptin protein plays an important role in appetite control. Therefore, *ob/ob* mice exhibit uncontrollable food intake, obesity, type 2 diabetes, and insulin resistance with hyperinsulinemia.

The *db/db* mouse was identified initially in 1966 by researchers in the Jackson Laboratory as an obese mouse [21]. The *db* (stands for "diabetes") mutation is an autosomal recessive trait that encodes for a G-to-T point mutation in the leptin receptor gene, resulting in defective leptin signaling [22, 23]. Impaired leptin signaling in the hypothalamus leads to persistent hyperphagia and obesity, with consequent hyperleptinemia, insulin resistance, and increased insulin levels [22, 23]. At 1 month of age, *db/db* mice are larger/obese when compared to control (heterozygous) littermates, and *db/db* mice present increased fat deposition in the inguinal and axillary regions. *db/db* mice also develop frank hyperglycemia by 8 weeks of age. Consequently, these mice are widely used as a model for the study of type 2 diabetes [22, 23].

*2.1.2. Polygenic Mouse Obesity.* Although monogenic models provide important information on the biology of obesity, human obesity is most likely mediated by multiple genes. Therefore, polygenic models could be much more relevant to human obesity.

*New Zealand Obese (NZO) Mouse.* The NZO strain is a polygenic mouse model of obesity that exhibits type 2 diabetes only in males. NZO mice increase their body weight rapidly during the first 2 months of life because of hyperphagia that may be associated with leptin resistance, although they have genetically normal leptin and leptin receptors. Among polygenic mouse models of obesity, NZO mice exhibit the most severe phenotype, with fat depots accounting for more than 40% of total body weight at 6 months of age [24]. Additionally, NZO mice exhibit decreased exercise activity when compared to control or even *ob/ob* mice [25]. This information suggests that like human obesity, obesity in NZO mice is due to a combination of hyperphagia, reduced energy expenditure, and insufficient physical activity.

*Tsumura Suzuki Obese Diabetes (TSOD) Mouse.* Through the selection of obese and urine sugar positive colonies from the ddY strain of mice, Tsumura and Suzuki established two inbred strains. The TSOD strain develops obesity with diabetes, whereas the Tsumara Suzuki nonobese (TSNO) strain does not become obese [26]. Male TSOD mice exhibit polygenic obesity with hyperglycemia and hyperinsulinemia [26, 27]. Although the mean values of fed blood glucose concentrations in TSOD mice are increased with age (232 mg/dl at 13 weeks, 269 mg/dl at 16 weeks, and 346 mg/dl at 24 weeks), severe diabetes does not develop because TSOD mice display increased $\beta$-cell mass and maintain insulin secretion

to control blood glucose [26]. Older TSOD mice display similar lesion as diabetic nephropathy and neuropathy [28].

*M16 Mouse.* The M16 mouse, an outbred mouse model of early-onset polygenic obesity, was developed through long-term selection for 3- to 6-week weight gain in an ICR background [29]. M16 mice exhibit hyperphagia, hyperinsulinemia, and hyperleptinemia compared to ICR controls. M16 males and females were found to be moderately hyperglycemic compared to ICR controls, with 56% and 22% higher fasted plasma glucose levels, respectively, at 8 weeks of age [29].

*Kuo Kondo (KK) Mouse.* The KK mouse is a polygenic model of obesity that also exhibits type 2 diabetes. The KK mouse was developed in Japan with selective inbreeding for large body size [30]. KK mice display hyperphagia, hyperinsulinemia, and insulin resistance and show moderate obesity by 2 months of age [31, 32]. Insulin resistance in KK mice precedes the onset of obesity [33]. The KK mouse strain was modified to develop the KK$A^y$ mouse by transferring the lethal yellow obese gene ($A^y$); the KK$A^y$ mouse is widely used for obesity and diabetes research in the testing of experimental therapies [34].

### 2.1.3. Rat Models of Obesity

*Zucker Fatty Rat (ZFR).* In 1961, L. M. Zucker and T. F. Zucker reported a seminal finding in obesity research [35]: an autosomal recessive mutation in the *fatty* (*fa*) gene on chromosome 5. These rats are characterized by hyperphagia and early-onset obesity, which appears at 5 weeks of age as an accumulation of subcutaneous fat. Although ZFR also exhibits marked insulin resistance [36], their blood sugar levels remain normal [37]. Later, the *fa* gene was shown to be the leptin receptor gene [38]. A ZFR does not develop diabetes [37]. However, a substrain of the ZFR that exhibits frank diabetes was discovered and was designated the Zucker diabetic fatty (ZDF) rats [39].

*Wistar Fatty Rat.* In 1981, Ikeda et al. reported another obesity rat model, the Wistar fatty rat (WFR) [40]. The WFR strain was derived by transferring the *fa* gene from ZFR (13 M strain) to Wistar Kyoto rats, which exhibit poor glucose tolerance [40]. WFR displays obesity from 3 weeks after birth and develops obesity-related diseases such as type 2 diabetes, hyperinsulinemia, and hyperlipidemia. Metabolic abnormalities are prominent in WFR males, but not in WFR females, which display only mild insulin resistance and some glucose intolerance [40]. The appearance of diabetes in WFR but not in ZFR, despite the presence of the *fa* (leptin receptor) mutation in both strains, could be explained by the presence of other genetic factors in WFR. The WFR strain is widely used for research in type 2 diabetes because aged WFR displays diabetic complications such as nephropathy and neuropathy [41–44].

*Otsuka Long Evans Tokushima Fatty (OLETF) Rat.* OLETF rats, established by Otsuka Pharmaceuticals in Tokushima, Japan, were developed by the selection of spontaneously type 2 diabetic rats from the outbreeding of Long Evans rats in a closed colony of Charles River [45]. OLETF rats are hyperphagic beginning several weeks after birth, with increasing body weight eventually progressing to frank obesity [46]. At approximately 25 weeks after birth, all male OLETF rats display diabetes, as determined by oral glucose tolerance test, whereas only 30% of female OLETF rats develop diabetes even after 60 weeks of age. Hyperinsulinemia is observed beginning at 8 weeks of age, and insulin resistance is observed beginning at 12 weeks of age. At 25 weeks of age, male OLETF rats display hyperplasia of pancreatic islets, but islets become atrophic by 60 weeks of age [46, 47]. In contrast to ZDF rats, hyper-free fatty acidemia has not been observed in OLETF rats. Instead, hypertriglyceridemia is found to precede the onset of hyperglycemia and insulin resistance [47]. OLETF rats are widely used in obesity and diabetes research.

### 2.1.4. Diet-Induced Obesity

*High-Fat Diet.* A high-fat diet (HFD) is often utilized in obesity research as a non-leptin-deficient model. There are mouse strain-specific differences in responses to the HFD (Table 1) [48]. Among the various strains, C57BL/6J mice are the most widely used for HFD-induced obesity because they exhibit abnormalities similar to human metabolic syndrome when fed the HFD [49]. Interestingly, within the C57 mouse strain, there are significant differences among substrains in response to the HFD. For instance, whereas C57BL/6J mice exhibit HFD-induced obesity, hyperinsulinemia, and insulin resistance that closely parallel the progression of human disease, C57BL/KsJ mice display a weak phenotype [49]. Beside C57BL/J6 mice, sand mice and spiny mice are also used in obesity/type 2 diabetes research. Sprague Dawley or Long Evans rats are also used for nonmouse rodent models of HFD-induced obesity [50].

Using such high-fat diet-induced obesity mice models, some clues to fight against human obesity have been reported; manipulation of diet may rescue the obesity phenotype even in high-fat-fed condition.

Watanabe et al. reported seminal finding about the antiobesitogenic role of bile acids (BAs) in mice. BAs have been long recognized as simple lipid solubilizers, however, during the last decades researchers revealed that BAs play pivotal roles in the complex metabolic regulations. Watanabe et al. found that high-fat diet supplemented with 0.5% cholic acid, the BA found in the largest amount, prevented weight gain and adiposity without alteration in the amount of food intake [51]. They found that BAs activate G-protein-coupledTGR5 receptor and induce type 2 deiodinase activity. Such activation of type 2 deiodinase results in the conversion of thyroxine (T4) to triiodothyronine (T3), which enhances energy expenditure [51]. Furthermore, agonistic compound for TGR5, INT-777, mimics such metabolic effect of BAs and inhibited the onset of steatosis in high-fat-fed mice [52]. Furthermore, INT-777 induces incretin effects via the secretion of glucagon-like peptide (GLP)-1 and therefore ameliorated glucose tolerance [52]. These researches revealed

the potential importance of BAs for the prevention of diet-induced obesity and associated health problem. Interestingly postcholecystectomized patients have been shown to have high prevalence of type 2 diabetes [53].

Another nutritional intervention method, which could prevent metabolic abnormality, is the diet with high ketogenic essential amino acid (KAA) such as leucine, isoleucine, valine, lysine, and threonine. Zhang et al. have reported that high-leucine feeding in mice prevented high-fat diet-induced obesity [54]. Such enhanced administration of high-KAA mixture diet modulated lipid synthetic pathway and prevented hepatic steatosis and insulin resistance with the reduction of body weight under the high-fat diet [55]. Interestingly such high-KAA mixture has been shown to improve insulin sensitivity in elderly type 2 diabetic subjects [56]. These reports indicated that the high-fat diet-induced obesity animals could be the good model for the experimental therapy and the translational research to discover a novel therapeutic strategy for obesity epidemic.

### 2.2. Nonrodent Models of Obesity

*Obese Monkeys.* During evolution, primates diverged from rodent lineages about 65–85 million years ago [57]. In comparison, humans and other great apes (Hominoidea) diverged from Old World monkeys (Cercopithecoidea) a relatively recent 25 million years ago [58]. Obesity models in Old World monkeys, such as macaques, rhesus monkey, and baboons, would therefore provide information relevant to human obesity. When raised in indoor cages, Rhesus monkeys exhibit increased rates of obesity, with some of them developing obesity-associated diseases [59–61]. Captive macaques display obesity in an age-dependent manner when given food *ad libitum* [62]. Like humans, these monkeys develop type 2 diabetes and diabetic complications. It is likely that reduced exercise increases the risk of obesity in these monkeys [62–64]. Spontaneous obesity is also found in wild baboons and in a pedigreed colony [65–67] and occurs in free-ranging rhesus monkeys [68]. Furthermore, a species of Japanese monkey, Macaca fuscata, develops obesity without frank diabetes [69].

## 3. Human Disease and Obesity Animal Models

Genetic models provide useful information about the biology of obesity in humans. This does not mean, however, that these models can provide information on how obesity can cause other health problems. In this section, we introduce several animal models for analyzing human obesity-associated disease pathology.

*3.1. Diabetes and Obesity.* Type 2 diabetes is associated with insulin resistance and is one of the most common metabolic diseases. The incidence of type 2 diabetes has dramatically increased in the past two decades, coinciding with the epidemic of obesity. The pathogenesis of insulin resistance and diabetes-associated complications remains unclear. Research on type 2 diabetes using animal models of obesity is therefore quite significant.

Models of obesity with type 2 diabetes are classified into two categories: (1) those containing a mutation in the leptin or leptin receptor gene and (2) polygenic models. Obese rodents, such as Zucker rats, *ob/ob* mice, and *db/db* mice, are used as models for type 2 diabetes. Obesity in these models is due to leptin signaling deficiency. These rodent models exhibit microvascular complications similar to humans, such as diabetic retinopathy and nephropathy, and provide important models for testing experimental therapeutics. However, leptin abnormalities only comprise a minority of obesity/diabetes cases in humans [70–72] and are not the same condition of type 2 diabetes that is a worldwide epidemic.

Polygenic models of obesity with diabetes may provide more insight to the human condition. Certain inbred strains of mice exhibit remarkable obesity when fed on HFD, whereas others remain lean [48, 49, 73], suggesting gene-diet interactions. Furthermore, some of the strains exhibit obesity with severe insulin resistance and glucose intolerance, whereas others are highly sensitive to insulin-mediated glucose uptake and are resistant to the onset of diabetes (Table 1) [50, 74, 75]. In contrast, some strains are very prone to type 2 diabetes but not severely obese. Those polygenic models allow for analysis of diabetic phenotypes alone, or the mice can be fed on HFD or crossed with another obesity mouse model, such as *ob/ob*, *db/db*, or $A^y$ (Table 1) [50, 74, 75].

*3.2. Cancer and Obesity.* Obesity in humans is associated with the incidence of several cancers. Likewise, type 2 diabetes has been associated with an increased risk of cancer. Several mechanisms have been proposed to explain the interaction between obesity and cancer development, including the prevalence of type 2 diabetes, increased insulin resistance, elevated levels of insulin-like growth factor 1 (IGF-1), and increased production of sex steroid hormones and adipocytokines [76–80]. However, clear molecular mechanisms that explain obesity-associated cancer have yet to be determined. Recently, Park et al. reported a breakthrough observation in carcinogenesis in obesity [81]. They found that diethylnitrosamine-induced HCC is significantly higher in both genetically (*ob/ob*) and HFD-induced (59% fat, 15% protein, 26% carbohydrates) obese mice [81]. Furthermore, HFD induced the growth of subcutaneously injected HCC, suggesting that obesity has a systemic effect on tumorigenesis [81]. With regard to the mechanisms of tumorigenesis in obesity, they found that obesity is associated with increased intracellular transcriptional factor STAT signaling and liver inflammation [81]. This inflammation was demonstrated to be essential for the tumor promoting effects of obesity because the depletion of signaling by inflammatory cytokines IL-6 and TNF-$\alpha$ abolished the tumor promoting effects of obesity [81].

Metformin belongs to the biguanide class of antitype 2 diabetic drugs. Since the middle ages, the biguanide *Galega officinalis* (goat's rue or French lilac) has been used to treat diabetic patients. Accumulating evidence suggests that metformin reduces cancer incidence in type 2 diabetic patients. Metformin activates AMPK and inhibits the

Table 1: Different phenotypes of inbred mouse strains with diet- or genetically induced obesity (summary of references [50, 74, 75]).

| Strain | Characteristics | Crossed with obese mice, and so forth |
|---|---|---|
| C57BL/6J | High-fat diet-induced diabetes and obesity [119] | $Lep^{ob/ob}$ mice exhibit obesity but not diabetes [120] |
| C57BLKS/J | High-fat diet-induced diabetes and obesity weaker than C57BL/6J [49] | $Lep^{ob/ob}$ mice exhibit obesity with severe diabetes [120] |
| DBA/2 | More glucose tolerance than C57BL/6 on a high-fat diet [121] | $Lep^{ob/ob}$ mice exhibit obesity with severe diabetes [122] |
| 129sv | Low insulin; more glucose tolerance than other strains on a high-fat diet [123] | Homozygous for db allele $db^{3J}$ mice display mild/transient hyperglycemia with marked hyperinsulinemia and develop hypoglycemia leading to sudden death [124] |
| BTBR | Abdominal obesity with peripheral, but not hepatic insulin resistance [125] | $Lep^{ob/ob}$ mice exhibit obesity with severe diabetes [126] |
| A/J | Low glucose level even on a high-fat diet; obesity and diabetes-resistant [119, 127, 128] | Not reported |
| BALB/c | Similar to A/J; glucose tolerance [121] | $Lep^{ob/ob}$ mice exhibit reduced adiposity and increased thermogenesis and are fertile [129] |
| C3H | High glucose tolerance with robust insulin secretion [121] | Not reported |
| AKR | Sensitive to diet-induced obesity with hyperinsulinemia and insulin resistance [48] | Not reported |
| CAST/Ei | Lean at 12 weeks on a high-fat diet [130] | Not reported |
| Nonobese Diabetic | 45% fat diet-induced transient hyperglycemia with severe obesity [75] | Not reported |
| New Zealand Obese | Resemble metabolic syndrome in humans; high-fat diet-induced obesity and hyperglycemia [24, 25] | Not reported |
| FVB | High glucose levels with lower levels of insulin on normal chow [75] | $Lepr^{db/db}$ mice display insulin resistance, severe hyperglycemia, and marked hyperinsulinemia compared to C57BL/6 [131] |
| Kuo Kondo | Obesity; hyperleptinemia; increased glucose and HbA1c; hyperinsulinemia similar to C57BLKS/J $Lepr^{db/db}$ mice [30] | $A^y$ mutation in *agouti* results in frank diabetes with nephropathy [34] |
| TallyHo | Natural model of obesity with type 2 diabetes [132] | Not reported |
| Nagoya-Shibata-Yasuda | Exhibit obesity; all males and 1/3 of females exhibit glucose intolerance [133] | Not reported |
| ALS/Lt | Sensitive to alloxan-induced diabetes [134] | Introduction of $A^y$ mutation induces diabetes in 100% of males and 60% of females at 24 weeks of age [135] |
| M16 | Increased body weight, fat and food intake; both males and females develop hyperinsulinemia; only males develop moderate hyperglycemia [29] | Not reported |
| LG and SM | High-fat diet-stimulated body weight gain and increased plasma glucose more in SM than LG mice [136] | Not reported |
| Tsumura, Suzuki, Obese Diabetes | Obesity and moderate diabetes [26, 27] | Not reported |
| Akita | Mutation in insulin 2 gene; nonobese [137] | Not reported |

mTOR signaling pathway via various mechanisms [82–86]. Metformin treatment has been shown to result in a gene expression profile similar to that of long-term caloric restriction [87], which can reduce the incidence of many age-related diseases, including cancer [88, 89]. Metformin treatment inhibits high-energy diet-stimulated colon cancer cell growth [90] and breast tumor growth in HFD-fed mice but did not inhibit tumor growth in mice fed normal chow [91]. Although the effects of metformin in obesity-related cancer biology are not clear, these reports suggest that the tumor suppressive effect of metformin may involve the amelioration of a systemic metabolic profile associated with a high-energy diet and obesity.

Elevated leptin levels, often found in obesity, may affect cancer cell growth. Recently, Ribeiro et al. injected androgen-insensitive murine prostate carcinoma RM1 cells into control male C57BL6 and genetic (*ob/ob* mice and *db/db* mice) and HFD mouse models of obesity [92]. They found that low-leptin models (*ob/ob* and HFD mice) exhibited large tumors, whereas high-leptin (*db/db*) mice exhibited small tumors, suggesting that leptin may inhibit RM1 tumor growth [92]. In contrast, Gonzalez et al. reported that leptin

may accelerate the growth of breast tumors in mice via induction of VEGF-VEGFR2-mediated angiogenesis [93], although their study used immunodeficient SCID mice and not a mouse model of obesity [94]. Similar leptin-induced proliferation and invasiveness has been shown in endometrial cancer [95]. Bartucci et al. reported that colorectal cancer stem cells express leptin receptors, and therefore leptin may induce tumor growth and interfere with the cytotoxic effects of the anticancer drug 5-FU [96]. The reports regarding the role of leptin in carcinogenesis are still very controversial and require further followup studies.

*3.3. Obstructive Sleep Apnea and Obesity.* Obstructive sleep apnea (OSA) is an important obesity-associated health problem that is characterized by obstruction of the airway and depletion of oxygen tone in the blood. OSA may be associated with the onset of hypertension, diabetes, and coronary heart disease. Although OSA is of clinical importance, the etiology of OSA is not yet clear, perhaps due to the lack of appropriate animal models. The first animal model reported to exhibit sleep apnea was the English bulldog [97]. These animals exhibit respiration disorders and decreased $O_2$ saturation that worsen during rapid-eye-movement sleep. Most bulldogs experience less than 90% $O_2$ saturation for prolonged durations [97]. Two varieties of obese pigs were also found to be good models of OSA [98, 99]. Although these models provide important information about the pathomechanisms of OSA, large-animal-based research is technically difficult. Therefore, for the development of experimental therapies and drugs, rodent models are superior. In 1996, Van Lunteren et al. reported altered respiratory-associated muscle contraction in genetically obese ZFR [100]. Later, this model was found to exhibit sleep apnea syndrome [101]. ZFRs have since been used for various experimental therapies and have provided important information about OSA [102–104].

Although these dog, pig, and rat models help improve our understanding of the pathophysiology of OSA, mouse models are critical in identifying the genes conferring disease risk [105]. Tagaito et al. developed a gas-delivery system that alters $O_2$ levels depending on the sleep-wake status of C57BL/6 male mice. However, this model is not a natural OSA model and is not a good representation of OSA [106]. Recently, NZO mice were used as a model mouse for sleep apnea syndrome [107]. NZO mice exhibit polygenic obesity and metabolic syndromes, such as insulin resistance, diabetes, hyperlipidemia, and hypertension (Table 1), much like a human sleep apnea patient. This report suggests that the NZO mouse may be a useful model for testing new drugs and experimental therapies for OSA.

## 4. Why Do Humans Gain Weight? Why Do Humans Like to Eat Fat?

All the data above might be focused mainly on the pathogenesis of obesity/obesity-related complications. Most publications may shed light on the pathology of obesity by forcing HFD or genetic mutations in rodents; however, the conditions are very different from the real problems that humans are facing. For example, although leptin-deficient rodents have been used in many obesity-associated studies, leptin/leptin receptor mutations are rare in humans [70–72]. The main difference between experimental animal models and human obesity is that humans do not have induced gene mutations and are not forced to eat HFDs. Instead, humans tend to enjoy eating such diets. If we can answer the question of why some individuals prefer to eat high-fat food and others do not, we would have a direct solution for obesity. Little evidence is currently available on this topic, but some seminal results have been shown [108, 109]. It has also been reported that the variation in fat consumption (ranging from 26 to 83% of total energy) is dependent on the response of inbred mouse strains to the macronutrient diet selection paradigm [110]. This theory suggests that there are strain-specific differences in food selection behavior, which could potentially be mediated by differences in brain neuropeptides [111–116]. These reports indicate that further investigation on this topic in conjunction with human epidemiological and genetic studies is required.

## 5. Conclusion

We have summarized many current animal models of obesity and obesity-associated human diseases. However, animal models have not yet been established for some devastating obesity-associated human diseases, including polycystic ovary syndrome [117, 118], which is extremely prevalent and constitutes one of the most common endocrinopathy in women of reproductive age. Suitable animal models are fundamental to testing novel therapeutic strategies against disease. Therefore, intensive and continuous efforts should be made to establish novel obesity-associated animal models that mimic human health problems.

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