Genetically Obese Animals

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Contents

General Considerations

A long history of research in both rodents and humans strongly argues that energy, stored in the form of fat in adipose tissue, is homeostatically conserved. Energy homeostasis is a very complex long-term process composed of multiple interacting homeostatic and behavioral pathways, including glucose homeostasis, lipid homeostasis, the hypothalamic-pituitary-adrenal axis, short-term satiety, and other macronutrient pathways that together act to maintain constant levels of energy stores. Obesity, anorexia, cachexia, and failure to thrive are some of the syndromes that result from mutations in genes critical to energy homeostasis.

Historically, five such mutations were identified in the mouse: obese (*ob*) and diabetes (*db*), as well as agouti (A^y), fat (*fat*), and tubby (*tubby*) gene. The cloning and characterization of these mutant genes led to the discovery of leptin, the key adipocyte hormone encoded by the obese (*ob*) gene that communicates to the brain information regarding the level of energy stored in the form of fat. Discovery of the leptin receptor, encoded by the diabetes (*db*) gene, and the discovery that the product of the agouti (A^y) gene caused obesity by antagonizing the melanocortin-4 receptor (MC4-R) led to the identification of key neural circuits involved in the regulation of energy homeostasis. Since the characterization of these first obesity genes, however, a very large number of transgenic and knockout models with obesity, anorexia, cachexia, or obesity resistance have been created (Robinson et al. 2000).

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Obesity and diabetes are syndromes quite often linked in patients (maturity-onset diabetes) and hereditary animal models. The regulation of body weight in animals by leptin was reviewed by Friedman and Halaas (1998).

Symptoms of diabetes and obesity are overlapping in many animal models (see also chapter "► Genetically Diabetic Animals").

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Spontaneously Obese Mice

Obese-Hyperglycemic (ob/ob) Mice

Ingalls et al. (1950), Mayer et al. (1951), and Bleisch et al. (1952) observed hereditary diabetes in genetically obese mice. The obese-hyperglycemic mice were glycosuric, the non-fasting blood sugar levels were about 300 mg%, but neither ketonuria nor coma was observed. One of the most interesting features was insulin resistance; doses as high as 400 IU/kg had little effect on blood sugar. The serum insulin-like activity was high, the islands of Langerhans were hypertrophic, their insulin content was increased, and the liver glycogen stores were decreased. Kidneys and other organs did not show pathological changes. Obviously, the diabetic condition of this and other strains of obese-hyperglycemic mice is different from that of the human diabetic patient.

Three working groups identified in 1995 the OB protein (Pelleymounter et al. 1995; Halaas et al. 1995; Campfield et al. 1995), which was later named leptin and which is missing in ob/ob mice. Leptin is a hormone expressed in and secreted from adipose tissue. It signals to the hypothalamus the size of the fat stores and thereby regulates food intake. As ob/ob mice are leptin deficient, there is no break signal to the hypothalamus for food intake with the result of increased food uptake and with subsequent increased adiposity. In addition leptin regulates sympathetic outflow from the brain. Therefore, at normal animal house temperature of about 20–22 °C, ob/ob mice feel cold and subsequently increase food intake for compensation. Since 1977 it has been already known that ob/ob mice have a thermogenic defect and lower body temperature compared to wild-type littermates (Trayhurn et al. 1977).

Pelleymounter et al. (1995) investigated the effects of the *obese* gene product on body weight regulation in ob/ob mice. The OB protein was expressed in *E. coli* and purified to homogeneity as a 16-kDa monomer. Daily intraperitoneal injections of the recombinant OB protein to ob/ob mice lowered their body weight, percent body fat, food intake, and serum concentrations of glucose and insulin.

Halaas et al. (1995) reported that daily intraperitoneal injections of either mouse or human recombinant OB protein reduced the body weight of ob/ob mice but had no effect on *db*/*db* mice.

Campfield et al. (1995) found that peripheral and central administration of microgram doses of recombinant mouse OB protein reduced food intake and body weight of ob/ob and diet-induced obese mice but not in *db*/*db* obese mice.

Reduced oxygen consumption has been noted as early as 10–18 days of age in ob/ob mice (Boissenault et al. 1976; Trayhurn et al. 1977).

Other strains or substrains of mice with obesity and hyperglycemia have been described by Dickie (1962), Westman (1968), Stein et al. (1970), Coleman and Hummel (1973), and Herberg and Coleman (1977).

Strautz (1970) implanted ob/ob mice with Millipore diffusion chambers containing islets isolated from the pancreas of normal littermates.

Trayhurn et al. (1977) found a thermogenic defect in pre-obese ob/ob mice. Rectal temperature of 17-day-old pre-obese mice in response to an environmental temperature of 4 °C fell much more than in lean controls.

Chlouverakis (1972) performed parabiotic experiments of obese-hyperglycemic mice

(ob/ob) with lean littermates and determined body weight, glucose, serum insulin, and triglycerides as well as insulin sensitivity of diaphragm muscle and epididymal fat pad.

Parabiosis of obese (ob/ob) with diabetes (*db*/*db*) mice caused the obese partner to become hypoglycemic, to lose weight, and to die of starvation, while no abnormal changes were observed in the diabetic partner (Coleman 1973).

Cresto et al. (1977) compared the rate of insulin degradation in normal and in ob/ob mice.

Zhang et al. (1994) succeeded in positional cloning of the mouse *obese* gene and its human homologue.

Trayhurn et al. (1996) studied the effects of fasting and refeeding on *ob* gene expression in white adipose tissue of lean and obese (ob/ob) mice using a 33-mer antisense oligonucleotide as a probe for the rapid chemiluminescence-based detection of *ob* mRNA.

Sterility defect in homozygous obese female mice could be corrected by treatment with the human recombinant OB protein leptin (Chehab et al. 1996).

Roupas et al. (1990) used isolated adipocytes from ob/ob mice to study the diabetogenic action of growth hormone.

Rafael and Herling (2000) investigated the effect of leptin on energy balance in leptin-deficient ob/ob mice under conditions of thermoneutrality. It was found that food intake was reduced as long as body weight was above that of lean littermates. The closer the body weight of the obese mice came to that of lean mice, the obese mice increased their food intake gradually. It was concluded that leptin does not inhibit food intake per se but that leptin redirects energy from endogenous stores as long as they are present for energy expenditure.

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Yellow Obese (A^YA) Mouse

The yellow obese mouse is the only example of obesity inherited through a dominant gene and was described as early as 1883 by Lataste and in 1905 by Cuenot. It is located on chromosome 2 at linkage group 5, the agouti locus (Bateson 1903). Since the genes controlling obesity and the agouti coat colors are so closely linked, the obesity is associated with a change of pigmentation from black to yellow. Such an association allows the early identification of pre-obese mice as soon as the coat hair begins to grow.

Since the original description of the yellow (A^ya) mouse, a number of additional alleles have appeared at the agouti locus. The homozygous dominant yellow mutation (A^y/A^y) is lethal in utero (Robertson 1942; Eaton and Green 1962) with approximately 25 % of any litter from A^ya matings dying from an abnormal development after the trophoblast stage (Pedersen 1974).

Yellow (A^ya) mice develop a moderate form of obesity and diabetes. Increased body weight first appears at the time of puberty (8–12 weeks) (Dickie and Wooley 1946; Carpenter and Mayer 1958), after which body weight increases slowly to reach values of approximately 40 g. In contrast to other forms of obesity, yellow mice are characterized by increased linear growth. Plasma insulin concentrations are increased and food is stored more efficiently than in lean mice (Dickerson and Gowan 1967). Food intake returns to normal in older A^ya mice and the animals lose body weight (Hollifield and Parson 1957). The obesity may be exaggerated by being fed high-fat diets (Fenton and Chase 1951; Silberberg and Silberberg 1957; Carpenter and Mayer 1958). Food restriction may normalize body weight but

the animals still remain obese (Fenton and Chase 1951; Hollifield and Parson 1957). Metabolic rate of A^ya mice is depressed when related to body surface, although oxygen consumption per animal is identical to the homozygous recessive agouti (a/a) mouse (Bartke and Gorecki 1968).

Gill and Yen (1991) studied the effect of ciglitazone on endogenous plasma islet amyloid polypeptide (amylin) and insulin sensitivity in obese-diabetic viable yellow mice (VY/Wfl-A^{vy}/a).

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KK-A^Y Mouse

Iwatsuka et al. (1970) reported on yellow KK mice (also named KK-A^y mice), carrying the yellow obese gene (A^y). These mice develop marked adiposity and diabetic symptoms in comparison with their littermates, black KK mice. Blood glucose and circulating insulin levels as well as HbA_{1c} levels were increased progressively from 5 weeks of age. Degranulation and glycogen infiltration of B cells were followed by hypertrophy and central cavitation of islets. Lipogenesis by liver and adipose tissue were increased. Insulin sensitivity of adipose tissue was more remarkably reduced than in black KK mice to its complete loss at 16 weeks of age. Renal involvement is uniquely marked by early onset and rapid development of glomerular basement membrane thickening (Diani et al. 1987).

Sohda et al. (1990) evaluated ciglitazone and a series of 5-[4-(pyridylalkoxy)benzyl]-2,4-thiazolidinediones for hypoglycemic and hypolipemic activities in yellow KK mice.

Hofmann et al. (1992) evaluated the expression of the liver glucose transporter GLUT2 and the activity and the expression of phosphoenolpyruvate carboxykinase in the liver of obese KKA^Y mice after treatment with the oral antidiabetic agent pioglitazone.

Yoshida et al. (1991) compared brown adipose tissue thermogenesis, resting metabolic rate, insulin receptors in adipocytes, and blood glucose and serum insulin levels during a glucose overloading test in yellow KK mice with C57B1 control mice after a β_3-adrenoceptor agonist.

Yoshida et al. (1996) determined body weight, food intake, white adipose tissue weight, brown adipose tissue weight and its thermogenesis,

noradrenaline turnover, blood glucose and serum insulin levels, and GLUT4 in diabetic yellow KK mice compared with C57B1 mice after mazindol.

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Fat/Fat Mice

Fat mice carry an autosomal recessive mutation and display a range of abnormalities, including progressive adult-onset obesity, hyperinsulinemia, and infertility (Coleman and Eicher 1990). The mutant allele of *fat* was identified and shown to be a missense (serine → proline) mutation in carboxypeptidase E which abolishes enzyme activity in a variety of neuroendocrine tissues (Naggert et al. 1995). Carboxypeptidase E is required for both sorting and proteolytic processing of a variety of prohormones including proinsulin and POMC (Cool et al. 1997). As carboxypeptidase E is expressed in the CNS, defective processing of a variety of hypothalamic neuropeptides – such as POMC and MCH – may trigger obesity in these animals (Rovere et al. 1996).

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Tubby Mice

Tub is an autosomal recessive mutation in mice (Coleman and Eicher 1990) which display a tripartite phenotype of blindness, deafness, and

maturity-onset obesity. In response to weight gain, these mice gradually increase their food intake in proportion to body weight and increase plasma insulin levels thereby maintaining normoglycemia. The progressive retinal degeneration in *tubby* mice results from apoptotic loss of photoreceptor cells, with abnormal electroretinograms detected as early as 3 weeks of age (Heckenlively et al. 1995). The mouse obesity gene *tub* has been identified and characterized (Noben-Trauth et al. 1996; Kleyn et al. 1996).

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NZO Mouse

The New Zealand obese (NZO) mouse was first described in 1953 by Bielschowsky and Bielschowsky. The strain was developed by selective inbreeding of obese mice from a mixed colony, beginning from a pair of agouti mice, which also gave rise to the NZB black strain (Melez et al. 1980). NZO mice of both sexes exhibit high birth weights and are significantly heavier at weaning age. Severe obesity (including both visceral and subcutaneous fat depots) develops even when mice are maintained on a standard diet containing 4.5 % fat. NZO mice develop obesity, mild hyperglycemia, glucose intolerance, hyperinsulinemia, and insulin resistance. The adult NZO mouse normally attains a body weight of 50–70 g by 6–8 months, although weight gain continues slowly after this age (Cofford and Davis 1965; Herberg et al. 1970). Hyperglycemia and glucose intolerance increase continuously with advancing age of the animals.

Renal disease in NZO mice is seen by 6 months of age. NZO mice have a high prevalence of autoimmune disorders.

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Diabetes Obesity Syndrome in CBA/Ca Mice

CBA/Ca mice are commonly used for leukemogenesis research because this strain has a low spontaneous incidence of leukemia but has a relatively high inducibility of myeloid leukemia in response to benzene and radiation exposure. A mild spontaneous maturity-onset diabetes obesity syndrome occurs in a small proportion (10–20 %) of male CBA/Ca mice. Inbreeding can increase the incidence to 80 %. It occurs at 12–16 weeks of age and is characterized by hyperphagia, obesity, hyperglycemia, hypertriglyceridemia, hyperinsulinemia, and an impaired glucose tolerance. The mice are also resistant to exogenous insulin. Female mice remain normal except for a slight increase in serum insulin. The male obese-diabetic mice have a normal life expectancy.

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Transgenic Animals

Purpose and Rationale

Transgenic animals offer a new approach to study the development of obesity and therapeutic possibilities.

The potential for inserting new genetic material into mammals has produced numerous transgenic mice with increased or decreased quantities of body fat (Bray and Bouchard 1997).

Reduced body weight is a common effect of gene knockout mice (Reed et al. 2008). During a search for obesity candidate genes in a small region of the mouse genome, it was noticed that many genes when knocked out influence body weight. To determine whether this was a general feature of gene knockout or a chance occurrence, the Jackson Laboratory Mouse Genome Database for knockout mouse strains and their phenotypes was surveyed. Based on a data set of 1977 knockout strains, it was found that 31 % of viable knockout mouse strains weighed less and an additional 3 % weighed more than did controls. Assuming that the surveyed knockout genes are representative, then upward of 6,000 genes are predicted to influence the size of a mouse.

For the characterization of the specificity of a candidate compound to a specific target involved in body weight regulation, the use of respective knockout mouse (in which the specific target is knocked out) vs. wild-type mouse might be helpful: the compounds should only be active in wild-type mice but inactive in the respective knockout mouse model.

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Spontaneously Obese Rats

The occurrence of spontaneous obesity has been reported in several strains of rats:

Zucker-Fatty (ZF) Rat

The Zucker-fatty rat is a classic model of obesity combined with insulin resistance and hyperinsulinemia (Zucker 1965). Obesity is due to a simple autosomal recessive (*fa*) gene

mutation (Fa gene encodes the leptin receptor) and develops at an early age. Obese Zucker rats manifest mild glucose intolerance, hyperinsulinemia, and peripheral insulin resistance similar to human prediabetes. However, their blood sugar level is usually normal throughout life (Bray 1977; Clark et al. 1983; McCaleb and Sredy 1992; Abadie et al. 1993; Alamzadeh et al. 1993; Kasim et al. 1993; Galante et al. 1994).

Truett et al. (1991) found evidence that the rat obesity gene fatty (*fa*) has homology with the mouse gene diabetes (*db*). Both genes determine a leptin receptor defect.

Triscari and Sullivan (1987) reported a normalizing effect of an inhibitor of thromboxane synthase on the hyperinsulinemic state of obese Zucker rats and diet-induced obese rats.

Rouru et al. (1993) described the effect of chronic treatment with a 5-HT_1 receptor agonist on food intake, weight gain, plasma insulin, and neuropeptide Y mRNA expression in obese Zucker rats.

Santti et al. (1994) studied the potentiation of the anti-obesity effect of a β_3-adrenoceptor agonist in obese Zucker rats by exercise.

Savontaus et al. (1997) investigated the anti-obesity effect of an imidazoline derivative in genetically obese (*fa*/*fa*) Zucker rats.

Lynch et al. (1992) identified several adipocyte proteins, among them pyruvate decarboxylase contributing to the increased lipogenic capacity of young obese Zucker adipocytes.

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Zucker-Diabetic-Fatty (ZDF) Rat

The obese Zucker-diabetic-fatty (ZDF) rat derived from inbreeding of hyperglycemic Zucker obese rats. Male ZDF rats are obese and insulin resistant and progress spontaneously to overt diabetes (hyperglycemia: around 20 mmol/l blood glucose) at the age of around 8–10 weeks. Female ZDF rats are obese and insulin resistant and remain normoglycemic as long as they are fed with standard rat chow (low fat). On a high-fat diet, female ZDF rats experience the slow progression to overt diabetes similar to their male littermates. This transition to overt diabetes appears due to a progressive loss of pancreatic ß-cells. Body weight development is above that of lean littermates as long as they are young and normoglycemic; this reflects their fa genetic background. When they become overt diabetic, body weight development stops and in later diabetic stages declines due to the energy loss via glucosuria.

The phenotype of ZDF rat is due to (1) the autosomal recessive (*fa*) gene identical to that of ZF rats but (2) with an additional ß-cell gene defect (Griffen et al. 2001).

Zhang et al. (1996) reported downregulation of the expression of the obese gene by an antidiabetic thiazolidinedione in Zucker-diabetic-fatty rats and db/db mice.

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WDF/fa-fa Rat

The WDF/Ta-fa rat, commonly referred to as the Wistar fatty rat, is a genetically obese, hyperglycemic rat established by the transfer of the fatty (*fa*) gene from the Zucker rat to the Wistar-Kyoto rat (Ikeda et al. 1981; Kava et al. 1989; Velasquez et al. 1990). The Wistar fatty rat exhibits obesity, hyperinsulinemia, glucose intolerance, hyperlipidemia, and hyperphagia

similar to Zucker rats being, however, more glucose intolerant and insulin resistant than Zucker rats. Hyperglycemia is usually not observed in females but can be induced by addition of sucrose to the diet.

Kobayashi et al. (1992) found an increase of insulin sensitivity by activation of insulin receptor kinase by pioglitazone in Wistar fatty rats (*fa*/*fa*).

Mazusaki et al. (1996) found an augmented expression of the *obese* (*ob*) gene during the process of obesity in genetically obese-hyperglycemic Wistar fatty (*fa*/*fa*) rats.

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JCR:LA-cp Rat

Several substrains were developed from obese SHR rats, such as the JCR:LA-corpulent rat which exhibits a syndrome characterized by obesity, hypertriglyceridemia, and hyperinsulinemia with impaired glucose tolerance and is susceptible to vascular arteriosclerotic lesions (Russell and Amy 1986a, b; Russell et al. 1994).

Cp mutation encodes a leptin receptor defect, which is different to those defects encoded by *fa* mutation in rats or *db* mutation in mice. Compared to Zucker-fatty rats, the JCR:LA-cp (corpulent) rats have higher levels of the insulin-releasing hormone GIP (glucose-dependent insulinotropic polypeptide = gastric inhibitory polypeptide) and higher insulin levels (Pederson et al. 1991).

Vydelingum et al. (1995) found an overexpression of the obese gene in the JCR:LA-corpulent rat.

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OLETF Rat

A spontaneously diabetic rat with polyuria, polydipsia, and mild obesity was discovered in 1984 in an outbred colony of Long-Evans rats. A strain of rats developed from this rat by selective breeding has since been maintained at the Tokushima Research Institute (Otsuka Pharmaceutical, Tokushima, Japan) and named OLETF. The characteristic features of OLETF rats are (1) late onset of hyperglycemia (after 18 weeks of age), (2) a chronic course of disease, (3) mild obesity, (4) inheritance by males, (5) hyperplastic foci of pancreatic islets, and (6) renal complications (nodular lesions). The clinical and pathological features of disease in OLETF rats resemble those of human NIDDM.

Administration of diazoxide (0.2 % in diet), an inhibitor of insulin secretion, to OLETF rats from the age of 4–12 weeks completely prevented the development of obesity and insulin resistance (Aizawa et al. 1995).

Ishida et al. (1995) found that insulin resistance preceded impaired insulin secretion in OLETF rats.

Umekawa et al. (1997) determined induction of uncoupling protein and activation of GLUT4 in OLETF rats after administration of a specific β_3-adrenoceptor agonist.

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WBN/Kob Rat

Spontaneous hyperglycemia, glucosuria, and glucose intolerance have been observed in aged males of an inbred Wistar strain, named the WBN/Kob rat (Nakama et al. 1985; Tsichitani et al. 1985; Koizumi et al. 1989). These animals exhibit impaired glucose tolerance and glucosuria at 21 weeks of age. Obvious decreases in the number and size of islets are found already after 12 weeks of age. Fibrinous exudation and degeneration of pancreatic tissue are observed in the exocrine part, mainly around degenerated islets and pancreatic ducts in 16-week-old males. Recent publications on this obese rat strain focuses on spontaneous development of chronic pancreatitis (Ohashi et al. 1990; Mori et al. 2009).

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Obese SHR Rat

The strain of obese SHR rats was developed by Koletsky (1973, 1975) by mating a spontaneous hypertensive female rat of the Kyoto-Wistar strain with a normotensive Sprague Dawley male. After several generations of selective inbreeding, these obese SHR exhibited obesity, hypertension, and hyperlipidemia. In addition, some rats developed hyperglycemia and glucosuria associated with giant hyperplasia of pancreatic islets.

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