A useful list of spontaneously arising animal models of obesity and diabetes

Eleazar Shafrir and Ehud Ziv
Department of Biochemistry and Diabetes Research Unit, Hadassah University Hospital and Hebrew University-Hadassah Medical School, Jerusalem, Israel

TO THE EDITOR: over the years, we have had the opportunity to edit books and compendia that characterize diverse animal models of obesity and diabetes. Most of those animal models have been either selected through inbreeding or characterized following spontaneously arising mutations. It is now timely to provide, in a summary manner, a concise list of such models as an update and reference for future research. The major defects are described in the references cited. In some cases, insulin resistance has been linked to impaired insulin signaling at various levels, including negative feedback at the level of the insulin receptor substrate (IRS)-1 (5, 15, 24). However, in most cases the mechanism of the diabetogenic changes has not been exhaustively investigated. We hope that this list will guide studies geared at elucidating specific defects in the signal flow and how these studies may explain the metabolic failures leading to the diabetic proneness of the models as well as the mechanism of the ensuing complications. These animal models should also enable the discovery of therapeutic modalities with relevance to human diabetes and should continue to be a useful tool along with specific target-generated transgenic and knockout animals so amply used to understand metabolism and energy balance.

Obesity and diabetes in mice with mutations in leptin or leptin receptor genes. Since the discovery that ob is a mutation in the leptin structural gene and db is a mutation in the leptin receptor gene, the nomenclature for these mutations has been changed to reflect their molecular basis. The Lepob mutation on chromosome 6 was discovered in the Jackson Laboratory, Bar Harbor, ME, and recognized by marked obesity and hyperphagia. This mutation was subsequently transferred to the B6 inbred strain background. On this genetic background, the mutation produces juvenile-onset obesity, hyperinsulinemia, and insulin resistance with mild hyperglycemia and a sustained hyperplasia of the pancreatic β-cells.

The Leprdb mutation is a recessive mutation on chromosome 4 that occurred spontaneously in the C57BLKS/J inbred strain. The obesity/diabetes syndrome is associated with progressively severe hyperglycemia and correlated with pancreatic cell necrosis and islet atrophy at the end stage. The ob mutation is predominately obese and exhibits only mild hyperglycemia.

The current genetic nomenclature for these mice is as follows: Lepob, common name “obese” gene product; leptin or leptin mRNA and Leprdb-IJ, common name “diabetic” gene product leptin receptor or leptin receptor mRNA. Detailed information on these strains can be found in Chua et al. (2).

Zucker diabetic fatty rat with a leptin receptor defect. The Zucker diabetic fatty (ZDF) rat exhibits leptin receptor defects. This type of obesity, although associated with insulin resistance, is unlike common forms of human obesity. The ZDF rat was developed into a reproducible type 2 diabetic model at Indiana University (16) from a Zucker rat colony (leprfa) in which certain individuals exhibited a propensity to diabetes. The male rat is characterized by hyperinsulinemia and hyperglycemia at 6–7 wk of age, with glucose reaching levels of 500 mg/dl and insulin levels dropping successively. The female rat requires a high-fat diet for the expression of diabetes. The ZDF rat carries a genetic defect in β-cell transcription that is independent of the leptin receptor mutation, causing obesity and insulin resistance likely to be inherited in the β-cell gene.

Goto-Kakizaki rat with impaired β-cell mass and function due to polygenic inheritance. The Goto-Kakizaki rat is a nonobese substrain of Wistar rat origin with inherited chronic hyperglycemia. It was selected through a group of eight generation-inbreeding Wistar rats displaying high glucose levels during a glucose tolerance test. They present “starfish-shaped” islet abnormalities and pancreatic hormone deficiencies, resembling the polygenic basis of human type 2 diabetes (14).

New Zealand obese mouse. This is a model of obesity, glucose intolerance, and metabolic syndrome of polygenic nature. This animal exhibits hepatic and peripheral leptin insensitivity, insulin resistance, impaired insulin secretion, hypercholesterolemia, and hypertension (6). It displays classic features of obesity, including excessive body weight hyperphagia and reduced energy expenditure. Such obesity is responsible for its impaired glucose metabolism.

JCR:LA-cp rat: exhibiting metabolic syndrome with micro- and macrovascular disease. The prediabetic state in the JCR:LA-cp rat is characterized by abdominal obesity, hypertriglyceridemia and insulin resistance, and a marked damage to the vascular system, which is associated with atherosclerosis, vasculopathy, and ischemic end-stage disease (19). It is a unique model of the obesity/insulin resistance syndrome with cardiovascular implications of polygenic derivation.

SHROB rat: a model of metabolic syndrome. The spontaneously obese SHROB (Koletzky) rat is an overtly nondiabetic rat with the primary and secondary characteristics associated with the human metabolic syndrome, including insulin resistance. It exhibits a single recessive trait, a nonsense mutation causing loss of hypothalamic leptin receptors designated as fak (12), and its insulin-signaling defects were initially reported by Friedman et al. (7).

Otsuka Long-Evans Tokushima fatty rat with metabolic syndrome and diabetic nephropathy. The Otsuka Long-Evans Tokushima fatty (OLETF) rat was developed by selective breeding of a line of Long-Evans rats with diabetic characteristics along with a control line designated as Long-Evans Tokushima. OLETF rats show hyperphagia with obesity, hyperlipidemia, insulin resistance, and glucosuria, and these rats are prone to glomerular lesions (11).

Neonatally streptozotocin-induced diabetic rats. Rats with diabetes induced by injection of streptozotocin on the day of birth, or soon thereafter, are used to study the long-term consequences of reduced β-cell mass that resemble those seen...
in human type 2 diabetes. The neonatally streptozotocin-treated rats become transiently diabetic for 3 to 5 days after birth but recover thereafter with altered β-cell function and mass and impaired response of insulin secretion to glucose administration. They are suitable to evaluate the effect of various diabetes modulators and complications (18).

*Rhesus monkey macaca mulatta* with features of type 2 diabetes. The nonhuman primate *Macaca mulatta* provides the most human-like model of metabolic disorders in diabetes representative of other monkey species prone to diabetes. On an ad libitum diet they gradually become overweight or obese and progress to classical biochemical and pathophysiological symptoms of type 2 diabetes (8). Specific defects in this animal model have been reported by Angeloni and Hansen (1).

*Psammomys obesus* gerbil with nutritionally induced type 2 diabetes and β-cell loss. The *Psammomys obesus* is a desert gerbil in which transition from native diet to laboratory rodent chow induces hyperinsulinemia followed by hyperglycemia. However, the hyperinsulinemia, which is a compensatory response for the insulin resistance, is not sustained. As a result, pancreatic insulin is depleted, and the secretion pressure leads to β-cell apoptosis. The reason for insulin resistance is overexpression of protein kinase C (PKC)ε isoform, which inhibits the activity of tyrosine kinase α and promotes serine phosphorylation on IRS, thereby inhibiting to tyrosine phosphorylation and downstream insulin signaling. Peptides from the catalytic domain of PKC abrogated the serine phosphorylation and restored insulin signaling and normoglycemia (13). *Psammomys* is a good model for research of insulin resistance and testing of antidiabetic drugs (24).

*Torii* rat with type 2 diabetes and human-like retinopathy lesions. Type 2 diabetes was discovered among males in an outbred colony of Sprague-Dawley rats. When sister-brother repeatedly mated with females of the same strain, the diabetes was established in males with numerous ocular complications such as cataract, retinopathy, neovascular glaucoma, and optic neuropathy (20).

*Cohen* diabetic rat. Two contrasting rat strains were derived by selective inbreeding. One strain develops type 2 diabetes when fed a sucrose-rich, copper-poor diet, and the other does not. The diabetes is due to β-cell dysfunction and reduced insulin secretion. Cohen rats exhibit retinopathy and nephropathy, reduced fertility, and testicular degeneration. These rats have been crossed with spontaneously hypertensive rats to develop a hypertensive strain that presents diffuse glomerulosclerosis and hypertensive myocardial and vascular changes (22). *KK* and *KKV* mice with type 2 diabetes and obesity. A strain of native mice originating from the Japanese natural environment habitat was found to lapse into spontaneous diabetes with moderate obesity and hyperglycemia, hyperlipidemia, insulin resistance, and renal glomerular changes. To strengthen the characteristics of diabetes in this KK mouse, the (A) dominant obese gene (from the agouti locus of yellow obese mice) was transferred by repeated crossing. The color of the hair changed from black to yellow (KKV). The mice genetic nature is polygenic and differs from the lepdb and lepob groups, whose diabetic state is induced by gene mutations (21).

*Nob* mouse as a model of diet-induced type 2 diabetes and obesity. BL6 mice are susceptible to obesity-linked diabetes when maintained on a high-fat diet. They also present abnormalities in the autonomic nervous function, β-cells, and expression of uncoupling protein-2 in adipocytes. It is of interest that this mouse was used to receive the *ob* and *db* genes in the Jackson Laboratory, but it is itself prone to nutritionally induced diabetes and obesity as well as hypertension (17).

*Rats, mice, and dogs subjected to diet-induced obesity*. Homeostatic and nonhomeostatic mechanisms exist in animals and humans regulating energy balance, the function of which can basically be regarded to protect against starvation. However, excess food intake leads to tissue deposition, primarily in adipocytes, resulting in untoward changes in metabolism. Several animals without genetic mutations undergoing diet-induced obesity and developing type 2 diabetes are reviewed by Coscun et al. (3).

REFERENCES


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