EDITORIAL

Contribution of animal models to the research of the causes of diabetes

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Abstract

In most publications, animal models of diabetes have mainly been investigated for their multiple etiologies as well as for changes leading to diabetes and their genetic derivation. Aspects which seem important and need a special research endeavor are the causes of diabetes complications in the different species, the molecular basis of their induction and possible arrest and prevention. A list and discussion of the intensively studied rodents is presented of spontaneous or nutritional background causing Type 2 diabetes but omitting models produced by transgenic manipulations or gene knockout techniques.

INTRODUCTION

Animal models of diabetes have been described in several recent publications[1-3]. In most publications it is mainly the multiple heterogenous etiologies that have been investigated as well as the mechanism of changes leading to diabetes and the genetic derivation. Other aspects which seem important and need a special research endeavor are the causes of diabetes complications in the different species, the molecular basis of their induction and possible arrest and prevention. A list and discussion of the intensively studied rodents is presented of spontaneous or nutritional background causing Type 2 diabetes but omitting models produced by transgenic manipulations or gene knockout techniques.

OBESE-DIABETIC MICE DB/DB AND OB/OB

These are intensively studied mice models of obesity and diabetes affecting a common pathway, a defect in the leptin receptor (db) and a defect in the leptin gene (ob). The nomenclature for these species currently used is \textit{Lepr}^db and \textit{Lepr}^ob. Apart from the basal deficiencies caused by the respective mutations, there are apparent complications in the tissue immune system, muscle and adipose tissue metabolism, endocrine pancreas and pancreatic beta cells leading to beta cell loss and insulin dependence. In addition, with time, these animals suffer from vasculopathy, neuropathy, nephropathy and myocardial disease.
KK AMD KKA^y DIABETIC MICE, MODELING FOR TYPE 2 DIABETES AND OBESITY[5]

The KK spontaneously diabetic mouse was established by inbreeding of the local strains of Japanese mice. It exhibits moderate obesity, polyphagia, polyuria, persistent glucosuria and moderate hyperglycemia with hyperlipidemia. Yellow obese gene (A) has been transferred into KK mice by repeated crossing of yellow obese mice with KK mice (black fur at weaning), resulting in more moderate diabetic changes than in the original KK mice but with a stronger expression of obesity. Regional differences in leptin gene downregulation expression have been found in adipose tissue during fasting. Among the complications, there are renal lesions similar to human nephropathy including glomerular basement membrane thickening and proteinuria. These mice have been recommended as useful for drug testing because of their low weight and clear responses.

SHROB (KOLETZKY) RAT[6]

The spontaneously hypertensive and obese rat, emerging from the SHR corpulent lines of rats, exhibits many primary and secondary characteristics of human metabolic syndrome as a nonsense mutation affecting all forms of leptin receptor, designated fa^f: Hyperphagia, enhanced lipogenesis, extensive growth of adipose tissue, impaired glucose tolerance without overt hyperglycemia, marked hyperinsulinemia with insulin hypersecretion from enlarged islets, insulin resistance, reduced expression of insulin receptor (IR) and insulin receptor substrate protein (IRS1) and a defect in the insulin signaling pathway.

Since the SHROB rat is not hyperglycemic, the complications in this animal cannot be directly linked to glucose hyperoxidation. Glomerulopathy with proteinuria occur involving focal segmental nephrosclerosis and hypertensive vascular lesions, most probably due to overactivity of the rennin-angiotensin system.

Atherosclerosis is related to impaired clearance of circulating leptin due to complete absence of functional leptin receptor. Retinal neurovascularization, progressive capillary dropout and vascular abnormalities and retinal hemorrhage are also evident.

JCR: LACP RAT[7]

This animal, inbred from the corpulent hyperphagic rat \( \phi \) strains, also presents when young with most of the manifestations of metabolic syndrome with particular micro and macrovascular lesions. It shows insulin resistance, hyperinsulinemia but without loss of hypersecretion capacity, hyperlipidemia including both cholesterol and triglycerides, vasculopathy, atherosclerosis and a unique cardiovascular disease with cardiac ischemia which calls for the application of a cardioprotective pharmacological agent. It slowly progresses to full blown type 2 diabetes. The origin of the lesions is polygenic related to the unknown components of the genome derived from corpulent rat strains.

Among the complications are vasculopathy and atherosclerosis with thrombi linked to the arterial surface and intimal lesions in the vascular smooth muscle cells, glomerular sclerosis and impaired wound healing.

ZUCKER DIABETIC FATTY RAT[8]

Several diabetic males and females were identified in the obese Zucker fa/\( \alpha \) colony and selectively inbred. After 10 generations the Zucker diabetic fatty (ZDF) trait was established. The rats are hyperglycemic and hyperinsulinemic until the total failure of beta cells associated with reduction of islet mitochondrial enzymes. They are also mildly hypertensive and hyperlipidemic. Two mutations of the leptin receptor reduce its affinity for interaction with leptin and are responsible for ZDF obesity. The rise in triglyceride rich lipoproteins appears to be correlated with the change from the hyperinsulinemic to insulinoenic stage. A decrease in the endothelial-dependent vasodilation and decreased resting blood flow have been observed, indicating a disturbed endothelial regulation. Ocular changes include retinal hypercellularity and thick capillary basement membrane. Reduced wound healing and reduced nerve conduction velocity with nerve edema have been reported.

COHEN DIABETIC RAT[9]

The Cohen diabetic rat is a model of nutritionally induced type 2 diabetes originally developed by A.M. Cohen in Jerusalem. A diabetogenic diet rich in sucrose and poor in copper was fed to the “Sabra” albino rat strain of the Hebrew University with two contrasting results. A sensitive group developed full blown type 2 diabetes whereas a resistant group remained without hyperglycemia. The sensitive group developed beta cell dysfunction, reduced insulin secretion with insulin resistance. The hyperglycemia was reversible by diet adjustment.

Chief complications were nephropathy with mesangial expansion and thickening of the glomerular basement membrane, proliferative retinopathy, testicular atrophy and gastrointestinal disorders, skeletal pathology and embryopathy.

GOTO KAKIZAKI RAT[10]

Goto kakizaki (GK) rat is a nonobese substrain of Wistar origin, developing type 2 diabetes due to impaired beta cell mass function and glucotoxicity stemming from polycgenic inheritance. The GK rats were initiated by Y Goto and coworkers in Sendai, Japan by repeated selecting and breeding of animals with a reduced glucose tolerance chosen from a large pool of rats for several generations. The diabetes in the chosen isolated rats was reproducible.
even after > 100 generations. The primary defect was in the beta cell with “starfish - shaped” abnormalities but with somewhat differing phenotypical properties in substrain colonies maintained by various investigators.

Among the complications investigated in GK rats are nephropathy with thickening of the glomerular basement membrane, reduced nerve conduction velocity and segmental demyelination, osteopathy, altered retinal endothelial retinopathy and cell/pericyte ratio.

**OTSUKA LONG EVANS TOKUSHIMA FATTY RATS**[^11]

Three kinds of diabetes models have been developed by selective breeding in a group of Long Evans rats obtained from Charles River Co in Canada by K Kawano and associates in Tokushima, Japan: a line of type 2 diabetic rats known as Otsuka Long Evans Tokushima Fatty (OLETF) which were hyperphagic consuming up to 30 g of food daily; a line known as Long Evans Tokushima Lean resembling type 1 insulin-dependent diabetes; and a Long Evans Tokushima non-diabetic control line. The OLETF rats exhibited glucose intolerance and insulin resistance, hypertriglyceridemia with marked triglyceride infiltration into pancreatic islets, obesity and increased blood pressure. The onset of diabetes with its complications was significantly attenuated by diet restriction.

The outstanding complication was nephropathy with proteinuria. Glomerular oxidative lesions were evident similar to those in human nephropathy, fibrin-cap, capsular drop and aneurysmal dilatation of intraglomerular vessels.

**PSAMMOMYS OBSUS GERBIL**[^12]

*Psammomys obesus* (previously named “sand rat”) is a gerbil living in the desert or semi desert areas of North Africa and the Near East. The gerbil is not hyperphagic or diabetic in the wild but is ill adapted to nutritional excess. When transferred to the laboratory, it becomes hyperinsulinenic and hyperglycemic with marked insulin resistance when its native diet of salt bush (*Atriplex halimus*) is substituted for a laboratory rodent diet. After a few weeks on the laboratory diet, the animals develop insulin resistance with hyperinsulinemia, then gradually lose their pancreatic beta cells and their insulin levels markedly decrease. It is of interest that their insulin resistance is related to the inhibition of IR action, a shift in the tyrosine to serine phosphorylation on IRS and a blockade of insulin signaling. Insulin resistance and the change in phosphorylation pattern is related to the increase in the activity of an enzyme of the protein kinase isoenzyme group protein kinase C epsilon (PKCε) which inhibits the tyrosine phosphorylase. The intraperitoneal injection of a peptide removed from the catalytic region of PKC inhibited the inhibitory serine phosphorylation of IRS by PKCε and enabled the functioning of downstream insulin signaling.[^13] *Psammomys* is a good model for studies of insulin signaling pathway in muscles.

Most diabetes complications of *Psammomys* are related to insulin resistance and hyperglycemia. Cataracts are often evident and retinal lesions also occur. Among other complications, angiopathy, degeneration of intervertebral discs, spondylitis and hearing impairment have been described as well as nephropathy due to Na-K ATPase hyperactivity.

**CONCLUSION**

There is no need to underscore the huge contribution of animal models to the investigation of the causes of diabetes. However, much remains to be researched on the road of understanding and preventing the complications of the disease, particularly the processes of the development of diabetic tissue lesions. This is of outstanding importance to the amelioration and prevention of human diabetes and promoting pharmacological approaches to combating diabetes.

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