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REVIEW ARTICLE

Study of the pathogenesis and treatment of diabetes mellitus through animal models

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Abstract Most research in diabetes mellitus (DM) has been conducted in animals, and their replacement is currently a chimera. As compared to when they started to be used by modern science in the 17th century, a very high number of animal models of diabetes is now available, and they provide new insights into almost every aspect of diabetes. Approaches combining human, in vitro, and animal studies are probably the best strategy to improve our understanding of the underlying mechanisms of diabetes, and the choice of the best model to achieve such objective is crucial. Traditionally classified based on pathogenesis as spontaneous or induced models, each has its own advantages and disadvantages. The most common animal models of diabetes are described, and in addition to non-obese diabetic mice, biobreeding diabetes-prone (BB-DP) rats, streptozotocin-induced models, or high-fat diet-induced diabetic C57Bl/6J mice, new valuable models, such as dogs and cats with spontaneous diabetes, are described.

Abbreviations: AUC, area under the curve; BB-DP, BioBreeding Diabetes-Prone; BB/OK, BioBreeding/Ottawa Kalsburg; cDM, canine diabetes mellitus; DM, diabetes mellitus; *DLA*, Dog Leukocyte Antigen; FPG, fasting plasma glucose; GIR, glucose infusion rate; GTT, glucose tolerance test; *GLUT-2* and *-4*, Glucose Transporter; GAD, GAD65, Glutamate Decarboxylase; A1c, HbA1c, glycated hemoglobin; HFDID, high-fat diet-induced diabetic; HPLC, high-performance liquid chromatography; HLA, human leukocyte antigen; IDD, insulin deficiency diabetes; *IRS-1*, *IRS-2*, Insulin Receptor Substrate 1-2; IR, insulin resistance; ITT, insulin tolerance test; IPGTT, intraperitoneal GTT; IPITT, intraperitoneal ITT; IVGTT, intravenous; IA2, Islet Antigen 2; ICA, Islet Cell Antibodies; LADA, latent autoimmune diabetes of the adult; LETL, Long Evans Tokushima lean; Lep^{ob}, *ob/ob*, mutation in Leptin gene; MHC, major histocompatibility complex; $Lepr^{db}$, *db/db*, $Lepr^{fa}$, *fa/fa*, mutation in Leptin receptor; NOD, non-obese diabetic; OGTT, oral GTT; *PI3-K*, Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha gene; POC, point-of-care; PBGM, portable blood glucose meter; STZ, streptozotocin; T1D, type 1 diabetes; T2D, type 2 diabetes; TNFa, tumor necrosis factor alpha; ZDF, Zucker diabetic fatty; ZFR, Zucker fatty rat.

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PALABRAS CLAVE
Modelo animal;
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Gato

Estudio de la patogénesis y tratamiento de la diabetes mellitus a través de modelos animales

Resumen La mayoría de la investigación desarrollada en diabetes ha sido realizada mediante el uso de modelos animales, siendo su reemplazo todavía una quimera. Comparado con los primeros usos de estos modelos por la ciencia moderna, a partir del siglo XVII, el número de modelos animales disponible en la actualidad es muy elevado, ofreciendo nuevas perspectivas dentro de casi todos los aspectos de la enfermedad. Los abordajes que combinen estudios en humanos, *in vitro* y modelos animales son probablemente la mejor estrategia para mejorar el entendimiento de los mecanismos de la enfermedad aún subyacentes y, en este sentido, la elección del modelo que más se ajuste a dichos objetivos es determinante. Clasificados tradicionalmente en función de su patogénesis, en espontáneos o inducidos, cada modelo ofrece sus propias ventajas y desventajas. Se describen aquí los modelos de diabetes más comunes y, aparte del ratón Non-obese-Diabetic, la rata BioBreeding Diabetes-Prone, u otros modelos inducidos por estreptozotocina o dieta con alto contenido graso, se describen otros valiosos modelos de diabetes, como son el perro y el gato con diabetes espontáneas tipo 1 y tipo 2.

Review

The consequences of diabetes mellitus (DM) on people's lives have motivated the search for better understanding of the mechanisms of the disease, as well as better treatments.[1] Even though in vitro and in silico studies have improved in the last decades, they cannot completely replace the information inferred from animal models, given the complex etiology and multi-systemic interactions present in diabetes.[2] Most of the research in diabetes is performed in animals[3,4] and animal replacement[5] is still a chimera. The combined approach of human, in vitro and animal studies is probably the best strategy to improve our understanding of underlying mechanisms.[4]

The modern, more standardised use of animal models of DM started during the 17th century by Brunner,[6] though even earlier uses of animal research have been reported.[7] Claude Bernard, father of 'vivisection', identified the existence of differentiated endocrine and exocrine pancreas using animal models.[7] Some of the most important discoveries of biomedical research and DM were made with pancreatectomised dogs: the discoveries of pancreatic function by Von Mering and Minkowski[8] and the insulin hormone by Banting and Best.[9] Presently, a variety of animal models of DM are present and many additional advances have been possible: leptin's discovery, new insights into pathogenesis and complications and the development of new treatments, among others.[2,10,11]

These models are mainly classified based on which type of diabetes they mimic and whether they are spontaneous or induced.[2,10–13] Furthermore, progress in genetics has allowed to generate specific transgenic models, almost *à la carte*, extending the range of spontaneous or more susceptible/resistant models.[14] Sometimes, when they develop DM, the disease can be inconsistently classified as spontaneous or induced depending on the author,[2,13] as they are genetically induced, but clinical signs and symptoms of DM appear spontaneously.

Another group of models that should be regarded is humanized models. They are developed either as spontaneous or induced diabetic models, and they have allowed research progress in regenerative medicine for diabetes, but also in many other fields (*reviewed by Kennedy et al. 2016*).[15]

Spontaneous diabetes models

Diabetes occurs spontaneously in many animal species, including the horse, dolphin, and even hippopotamus, among many others (*reviewed by E. Gale*).[3] Some of these species have provided important results as veterinary patients or as animal models, enabling better understanding of underlying mechanisms of DM. The principal advantages when compared with induced models are that they are presumed to share mechanisms of disease with the human condition, especially in polygenic models.[3,11,12]

The past decade has seen remarkable advances in the understanding of genetics and pathophysiology of spontaneous models of immune mediated diabetes and the creation of new models. The most commonly used spontaneous models of T1D are the non-obese diabetic (NOD) mouse and the BioBreeding Diabetes-Prone (BB-DP) rat.[10] Other spontaneous T1D models include Long Evans Tokushima lean (LETL) rat and the New Zealand white rabbit. These models provide useful tools for the study of the autoimmune process and prevention of T1D. For T2D, the most frequently used spontaneous models are the Zucker fatty (ZFR) and Zucker diabetic fatty rats (ZDF) and the ob/ob and db/db mice.

Nevertheless, although their contribution is considerable, successful animal outcomes have failed to be translated to humans.[4] Consequently, the choice of appropriate, single or combined animal models should be made to fit specific purposes, according to their validation to the aim.[2,4] The most relevant, spontaneous models are described below.