Development of New Animal Models for Type 2 Diabetes Mellitus and Pharmacological Screening

INTRODUCTION

Diabetes is a major threat to global public health that is rapidly getting worse and the biggest impact on adults of working age in developing countries. At least 177 million subjects worldwide have diabetes and this figure is likely to more than double by 2030 to reach 366 million (WHO report 2000). This global pandemic principally involves type 2 diabetes, and is associated with several contributory factors including increased longevity, obesity, unsatisfactory diet, sedentary lifestyle and increasing urbanization. Worldwide more than 100 million people have been diagnosed with type 2 diabetes mellitus, and it has been estimated that many millions still remain undiagnosed and untreated. This common disease compromises both quality and length of life, and places a substantial burden on health care system (King H et al 1998).

Type 2 diabetes mellitus is a heterogeneous disorder characterized by a progressive decline in insulin action (insulin resistance), followed by the inability of β cells to compensate for insulin resistance (pancreatic β cell dysfunction) (Srinivasan K et al 2005). Insulin resistance is the condition in which normal amounts of insulin are inadequate to produce a normal insulin response from fat, muscle and liver cells.

Due to complex interaction among multiple susceptibility genes and between genetic and environmental factors, genetic analysis of diabetes is difficult and poorly understood in humans. Moreover, diabetes research in humans is impeded by obvious ethical considerations, because provocation of disease is strictly impermissible in man. Animal models of diabetes are therefore greatly useful and advantageous in biomedical studies because they offer promise of new insights into human diabetes. The animal models of type 2 diabetes can be obtained either spontaneously or induced by chemicals or dietary or surgical manipulations and/or by combination thereof.

Animals that spontaneously develop T2D include nonhuman primates and cats; however, only a small and unpredictable proportion of these animals develop T2D, so diabetes prevention studies would require costly maintenance of huge colonies of primates over
many years. Rodent models circumvent these problems and therefore most of the available models are based on rodents because of their small size, short generation interval, easy availability and economic considerations.

**Spontaneous or genetically derived diabetic animals:** Spontaneously diabetic animals of type 2 diabetes may be obtained from the animals with one or several genetic mutations transmitted from generation to generation (e.g., ob/ob, db/db mice) or by selected from non-diabetic outbred animals by repeated breeding over several generation [e.g.,(GK) rat].


<table>
<thead>
<tr>
<th>Model category</th>
<th>Obese</th>
<th>Non obese</th>
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<tbody>
<tr>
<td><strong>Spontaneous or genetically derived</strong></td>
<td>db/db mouse, ob/ob mouse, KK mouse, Zucker fatty rat, ZDF rat Obese rhesus monkey</td>
<td>Cohen diabetic rat, GK rat</td>
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<tr>
<td><strong>Diet/nutrition induced</strong></td>
<td>Sand rat, Spimy mouse</td>
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<tr>
<td><strong>Chemically induced</strong></td>
<td>GTG treated obese mice</td>
<td>Low dose ALX or STZ adults rats, mice etc. Neonatal STZ rat.</td>
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<tr>
<td><strong>Surgical diabetic animals</strong></td>
<td>VMH lesined dietary obese diabetic rat</td>
<td>Partial pancreatectomized animals eg. Dog, primates, pig and rats.</td>
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<tr>
<td><strong>Transgenic diabetic animals</strong></td>
<td>B 2 receptor knockout mouse Uncoupling protein knockout mouse</td>
<td>Transgenic or knockout mice involving genes of insulin and insulin receptor and its components of downstream insulin signaling eg. IRS-1, IRS-2, GLUT-4 and others.</td>
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**Diet/nutrition induced diabetic animals:** Sand rat: Psammomys obesus (P. obesus; Sand rat) remains normal in its natural habitat but develop obesity and diabetes in captivity when fed on standard laboratory chow (high energy diet) instead of its usual low energy vegetable diet (mainly of Atriplex). In later stages of development, these animals show decrease in

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adipose tissue, depletion of β cell granules, apoptosis and develop ketoacidosis. Then, they require insulin support for survival.

Chemically induced diabetic animals:

*Goldthioglucose obese diabetic mouse:*

Type 2 diabetes with obesity is induced in mice by goldthioglucose (GTG) (150-350 or 200 mg/kg, ip) injection. Mice gradually develop obesity, hyperinsulinaemia, hyperglycaemia, insulin resistance over a period of 16-20 wk after GTG injection72. *Alloxan and streptozotocin- induced adult diabetic animals: (Lenzen S. (2008))

ALX acts by selectively destroying the pancreatic β islets leading to insulin deficiency, hyperglycaemia and ketosis. ALX causes diabetes in many rodent and non rodent animals and is most preferably used in case of rabbit because of the relative ineffectiveness of streptozotocin (STZ) in rabbits for induction of diabetes and development of well characterized diabetic complications.

ALX is disadvantageous as the percentage incidence of diabetes is quite variable. Further, the incidence of ketosis and resulting mortality is high. The reversal of hyperglycaemia due to pancreatic regeneration is early and common in case of ALX treated animals. Because of these limitations, ALX is now almost replaced by STZ for induction of diabetes in laboratory animals.

Streptozotocin is an antibiotic derived from *Streptomyces achromogenes* and structurally is a glucosamine derivative of nitrosourea. Like ALX, it causes hyperglycaemia mainly by its direct cytotoxic action on the pancreatic β cells. Its nitrosourea moiety is responsible for β cell toxicity, while deoxyglucose moiety facilitates transport across the cell membrane.

ALX and STZ diabetic animals are most widely used for screening the compounds including natural products for their insulinomimetic, insulinotropic and other hypoglycaemic/antihyperglycaemic activities.

Recently, a new animal model of type 2 diabetes has been produced by combination of STZ and NAD administration in adult rats. As NAD is an antioxidant which exerts protective effect on the cytotoxic action of STZ by scavenging free radicals and causes only minor damage to pancreatic β cell mass producing type 2 diabetes.
Some investigators have attempted to replicate the disease process that naturally occurs in human beings from the progression of insulin resistance to type 2 diabetes in outbred animals. It has been achieved either by injecting chemicals (STZ) into animals which are genetically insulin resistant in its background (e.g., SHR, ZFR) or by combination of diet [high fat (HFD) or high fructose diet] plus STZ treatment. Feeding of above special diets produces hyperinsulinaemia and insulin resistance initially followed by treatment with STZ that causes the β cell damage and frank hyperglycaemia in the presence of almost absolute normal insulin circulating concentrations in nongenetic, outbred animals such as rats and mice.

Because of the disadvantages of the different animal models of type 2 diabetes mellitus, there exists a continued quest among the investigators for establishing the ideal animal model for type 2 diabetes either by way of modification of the existing methods or by developing new methodologies or a combination of both.