Rodent models of type II diabetes

Definitions

Insulin resistance:
Glucose metabolism does not respond to insulin.

Glucose intolerance:
Difficulty clearing the blood for glucose after a meal.

Postprandial hyperglycemia:
The liver does not stop glucose production after a meal, as it normally would.

Basal hyperglycemia:
Basally elevated blood glucose levels independent of meals.

Fasting hyperglycemia:
Elevated blood glucose levels even after fasting.

Effective and successful rodent models and study set-ups are essential to ensure optimal selection of promising drugs against Type II diabetes.

Disease

Type II diabetes is a late onset disease and the patients are frequently overweight. The disease is characterized by abnormalities in insulin secretion and a decrease in functional efficiency of circulating insulin, resulting in an insulin resistance. As a consequence, type II diabetic patients are hyperglycemic and the development of secondary lesions (e.g. hypertension, atherosclerosis, autonomic dysfunctions) seems largely to relate to the severity and chronicity of hyperglycemia.

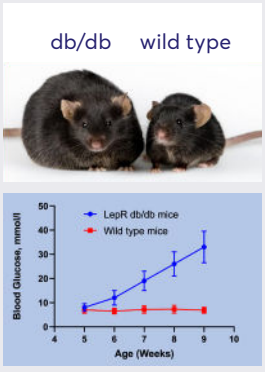
Type II diabetes typically develops through a progressive series of increasingly severe phases:

Pre-diabetes: Impaired glucose tolerance, postprandial hyperglycemia and decreased sensitivity to insulin.

Phase I: Postprandial as well as basal hyperglycemia, insulin-producing beta-cells in pancreas are increasingly dysfunctional.

Phase II: Fasting hyperglycemia and significant beta-cell atrophy.

Phase III: Beta-cells no longer release insulin. Insulin replacement therapy is required.



Models

Two principal types of rodents models of Type II diabetes exist: Dietary Induced Obese (DIO) and genetic models. The two types of models have different characteristics as outlined below:

	Human	DIO models	Genetic Models
Human disease model	-	**Prediabetic**	**Phase 1, 2 & (3)**
Genetics/Degree of obesity	Polygenetic/ Moderate	Polygenetic/ Moderate	Monogenetic/ Severe
Genetics/Degree of diabetes	Polygenetic/ Moderate	Polygenetic/ Moderate	Polygenetic/ Severe
Insulin resistance	Moderate to Severe	Moderate	Severe
Basal hyperglycemia	Yes	No	Yes

Thus, DIO models are prediabetic whereas genetic models rapidly develop overt diabetes.
As in humans, rodent models of Type II diabetes are obese.

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Important note:
Representative data are shown throughout this document. However, biological variability might cause deviations from shown data.

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Dietary Induced Obese (DIO) Models

Because the consumption of western high calorie diet and sedentary lifestyles obesity is rapidly becoming the most important health problem challenging most developed countries. In addition to promoting obesity, diets with high caloric content are associated with an increased risk for developing type 2 diabetes. Animal models, in which obesity and type 2 diabetes are induced by feeding a diet enriched in caloric content are therefore of increasing interest to develop new therapeutic strategies.

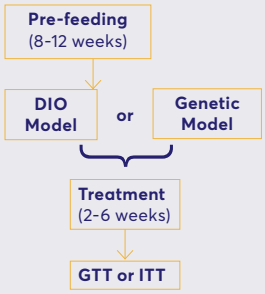
At Scantox we work with DIO Models in both mice (C57BL/6J) and rats (Sprague Dawley or Wistar). The animals are feed with high calory diets for 8-12 weeks before enrollment in studies.

Genetic Models

We routinely use Lep ob/ob and LepR db/db mice, as well as Zucker Fatty rats and ZDF (Zucker Diabetic Fatty) rats as genetic type II diabetic models. All these animal models are obese and insulin resistant. Differences between the strains are listed below:

Efficacy studies in diabetic models

Irrespective of the choice of rodent Type II diabetes model, studies using these models for investigation of test substance efficacy are usually composed of the same subset of activities:



		Mice		Rats	
	HUMAN	Lep ob/ob	LepR db/db	Zucker Fatty	Zucker Diabetic Fatty
Obesity	Moderate, variable onset	Severe, early onset	Severe, early onset	Severe, early onset	Severe, early onset
Hyperglycemia	Moderate. Men most susceptible.	Mild and transient	Severe	Normal or mild	Severe in males, but not in females
Hyperinsulinemia	Moderate before onset of diabetes later in life	Severe throughout life	Severe from early in life	Severe early, but transient	Severe from early in life
Insulin Resistance	Yes	Yes	Yes	Yes	Yes
β-cell Dysfunction	Yes	No	Yes	No	Yes

Generally, in drug discovery and testing, the db/db mouse is the most popular animal model used by pharmaceutical companies to test glucose lowering agents, insulin sensitizers, insulin secretagogues, and anti-obesity agents, although ob/ob mice, Zucker fatty rats and ZDF rats are also widely used for specific purposes.

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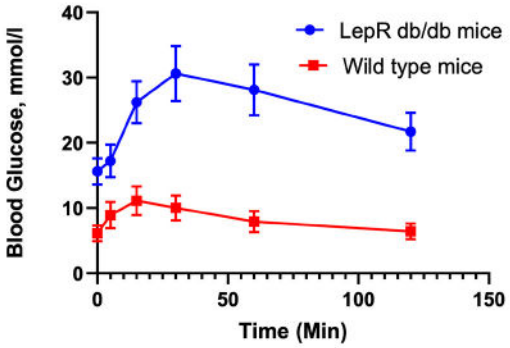
Central to the study design is a treatment period with repeated dosing of the test substances. In this period the diabetic status of the animals is monitored by bi-weekly measurements of fasting blood glucose and body weights. During and after the treatment period the animals may be subjected to glucose tolerance tests (GTTs) and sometimes insulin tolerance tests (ITTs). Finally, in advanced mechanistic studies, glucose clamps may be performed. The duration of treatment and number of additional tests are determined by the nature of the test item and the specific aim of the investigation.

Glucose Tolerance Test

The glucose tolerance test measures the clearance of a glucose load from the body. It is used to detect disturbances in glucose metabolism that can be linked to diabetes or metabolic syndrome. Animals are fasted before the test. Test articles are administered 30 minutes before glucose challenge. Fasted blood glucose levels are then determined before the challenge solution of glucose is administred. Subsequently, the blood glucose level is measured at different time points during the following 2 hours.



The most common methods for the administration of glucose in mice during glucose tolerance tests are peroral gavage (p.o.) or intraperitoneal injection (i.p.) injection. Both routes of administration are generally accepted as appropriate; however, there are differences in the dynamics of the plasma glucose and insulin response to p.o. and i.p. delivery. The plasma glucose levels are significantly lower in response to oral GTT compared with the same glucose dose administered i.p. This is mainly due to the fact that glucose absorption from the gut leads to the release of gastrointestinal hormones which significantly potentiate glucose-induced insulin release with consequently lower blood glucose levels compared with i.p. injection.

Insulin Tolerance Test (ITT)

To complement the analysis of glucose tolerance in vivo, it is recommendable to include some measurements of insulin resistance to the study. Here, the ITT is the first-choice method. It is technically relatively similar to the GTT as it involves monitoring of blood glucose levels over time, but in response to intravenous insulin administration rather than glucose challenge.

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