Animal Models of Diabetes and Insulin Resistance

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An Organ System..... Course.
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Species Differences
Body Mass
- Body Temperature and Basal Metabolic Rate -

Species Differences
Body Mass
- Blood Pressure and Heart Rate -
**Differences between Human and Rodents**

- **Body Mass**
  - Blood Glucose Level and Glucose Kinetics

<table>
<thead>
<tr>
<th>Species</th>
<th>Glucokinase</th>
<th>Regulatory protein</th>
<th>Blood K0.5</th>
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</thead>
<tbody>
<tr>
<td>Human</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Dog</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Rat</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Mouse</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Rabbit</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Pig</td>
<td>+</td>
<td>+</td>
<td>~100</td>
</tr>
<tr>
<td>Cat</td>
<td>-</td>
<td>-</td>
<td>Low</td>
</tr>
<tr>
<td>Cattle</td>
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<td>-</td>
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<tr>
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<td>-</td>
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<tr>
<td>Xenopus</td>
<td>+</td>
<td>+</td>
<td>? 2.6</td>
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<tr>
<td>Toad</td>
<td>+</td>
<td>+</td>
<td>? 52</td>
</tr>
<tr>
<td>Turtle</td>
<td>+</td>
<td>+</td>
<td>?</td>
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</table>

**Differences between Human and Rodents**

- **Phosphoenolpyruvate carboxykinase Distribution in the Liver**

| Species | Human Mouse Guinea Pig Chicken |
|---------|-----------------------------|-------------------------------|
| Cytoplasm | 30–50 | 80–90 | 15–20 | 5          |
| Mitochondria | 50–70 | 10–20 | 80–85 | 95         |

- Intracellular Distribution
- Periportal
- Mitochondria
- Cytoplasm
- + + + + +
- + - +
- + + +
- + + +
- + + +

- Perivenous
- Mitochondria
- Cytoplasm
- + + +
- + + +
- + + +
### Differences between Human and Rodents

- **Hepatic Architectures**

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Rat/Mouse</th>
<th>Guinea Pig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innervation</td>
<td>Rich</td>
<td>Poor</td>
<td>Rich</td>
</tr>
<tr>
<td>Gap Junction</td>
<td>Poor</td>
<td>Rich</td>
<td>Poor</td>
</tr>
</tbody>
</table>

### Mouse Models

**Difference between Strains**

- **A: Glucose Tolerance Test**
- **B: Fast & Full Glucose Levels**
- **C: Insulin Tolerance Test**
- **D: Insulin Levels**

### Animal Models of Obesity

**Origin: Single Gene**

1. **ob/ob**: the obese mouse (C57BL/6J ob mice)
   - the protein product of this gene is leptin
   - Metabolic-endocrine anomalies - no response to satiety signal (hyperphagia, hyperinsulinemia, insulin resistance, decreased insulin receptor function, defective thermogenesis)
   - Pancreatic function - profuse and lasting insulin oversecretion (hyperplasia and hypertrophy)
   - Lesions and complications - minor complications (infertility)
2. **db/db**: the diabetic mouse (C57BL/Ks db mice)

- Mutation of leptin receptor
- Metabolic-endocrine anomalies - no response to satiety signal (hyperphagia - hyperinsulinemia with obesity, then hypoinsulinemia and ketosis - insulin resistance - decreased insulin receptor function - defective thermogenesis
- Pancreatic function - labile islets - hypertrophy and enhanced replication followed by cell degeneration
- Lesions and complications - renal and vascular lesions - neuropathy

3. **fa/fa**: Zucker fatty rat

- Mutation of leptin receptor
- Metabolic-endocrine anomalies - no response to satiety signal (hyperphagia - hyperinsulinemia - insulin resistance - decreased insulin receptor function - defective thermogenesis
- Pancreatic function - profuse and lasting insulin oversecretion - hyperplasia and hypertrophy
- Lesions and complications - minor complications - infertility

4. **fa/fo**: Zucker diabetic fatty rat

- Mutation of leptin receptor
- Metabolic-endocrine anomalies - no response to satiety signal (hyperphagia - hyperinsulinemia with obesity, then hypoinsulinemia and ketosis - insulin resistance - decreased insulin receptor function - defective thermogenesis
- Pancreatic function - labile islets - hypertrophy and enhanced replication followed by beta cell degeneration
- Lesions and complications - renal and vascular lesions - neurophathy

5. **Cpefat**: the fat mouse (fat/fat or Cpefat/Cpefat)

- Carboxypeptidase E is required for the cleavage of two arginine residues from the beta-chain of insulin during its processing from proinsulin.
- No immunoreactive carboxypeptidase E protein in pancreas and pituitary.
- A late-onset form of obesity (60 - 70g body weight at 24 weeks)
- Hyperproinsulinemia
- The obesity is likely to result from a complex pattern of alterations in neuropeptide activity and secretion within the hypothalamic-pituitary system rather than from hyperproinsulinemia.
### Animal Models of Obesity

**Origin: Single Gene**

6. tub/tub: the tubby mice
   - This gene product has not been identified.
   - The obesity develops slowly and only becomes evident at 8 to 12 weeks of age.

7. Ay/a: the yellow obese mouse
   - The agouti gene encodes a 131-amino acid protein that is normally uniquely expressed in the hair follicle.
   - Obesity is less pronounced than in ob/ob and db/db mice.
   - Obesity is of later onset (8 to 12 weeks of age).
   - Insulin resistance.
   - The clear sexual dimorphism of the associated hyperglycemia.
   - Apparently normal activity of the hypothalamic-pituitary-adrenal axis.

**Origin: Multigenic**

1. NZO mouse
   - Metabolic-endocrine anomalies - insulin resistance.
   - Insulinaemia is less severe than in ob mice.
   - Pancreatic function - loss of first phase release but persistent oversecretion.
   - Impaired islet glucose metabolism.
   - Lesions and complication - renal lesions.

2. BSB mouse

3. AKR mouse

4. OM rat

**Origin: Dietary**

1. High fat
2. High fat/high carbohydrate (sucrose)
3. High carbohydrate (sucrose)
4. Cafeteria diets

**Origin: Neuroendocrine**

1. Lesions
   - Electronic (ventromedial hypothalamus, paraventricular nucleus, amygdala).
   - Knife cut (hypothalamus, midbrain).
   - Chemical (glutathione, monosodium glutamate, bipiperidyl mustard, ibotenic acid, kainic acid).
   - Viral (scrapie or canine distemper virus).

2. Chemical infusions
   - NPY to paraventricular nucleus.
   - Norepinephrine to ventromedial hypothalamus.

3. Ovariectomy
4. Peripheral insulin
5. Antidepressants
6. Hibernation/migration
Animals with Obese-Type 2 diabetes-like Syndromes

Animals with long-lasting genetic diabesity
1. C57BL/6J obese (ob)
2. KK mice (yellow agouti Ay) and their hybrid
3. NZO mice
4. Zucker fatty rats
5. Wister-Kyoto diabetic rats
6. Wister-Kyoto fatty rats

Animals with beta cell-losing diabesity
1. Zucker diabetic fatty rats
2. C57BL/Ks diabetic mouse (db)

Animals with Obese-Type 2 diabetes-like Syndromes

Animals with nutritionally induced type 2 diabetes
1. Psammomys obesus (sand rat), a gerbil on a regular laboratory diet
2. Non-human primate Macaca mulatta on an ad libitum diet
3. C57BL/6J mouse on a high caloric fat-disaccharide diet

Animals with non-Obese-Type 2 diabetes-like Syndromes

1. Goto-Kakizaki (GK) rats
   - Metabolic-endocrine abnormalities - hyperglycaemic
   - insulin resistance
   - non-ketotic
   - Pancreatic function - islet deformation
   - secretion abnormality
   - gradual beta-cell loss
   - Lesions and complication - nephropathy
   - neuropathy

2. Cohen sucrose-induced rats
   - Metabolic-endocrine abnormalities - hyperglycaemic
   - transiently hyperinsulinaemic, then overtly diabetic
   - Pancreatic function - defective first phase and stimulated release
   - Lesions and complication - nephropathy
   - retinopathy
   - osteopathy
   - testicular degeneration

3. NON mice
   - Metabolic-endocrine anomalies - inborn insulin synthesis deficit
   (no autoimmune involvement)
   - develop obesity on high energy diet
   - Pancreatic function - mild oversecretion despite partial insulin deficiency
   - Lesions and complication - fatty glomerular lesions

4. WBN/Kob rats
   - Metabolic-endocrine abnormalities - gradual hypoinsulinemia due to fibrotic and inflammatory exo- and endocrine padestruction
   - Pancreatic function - disappearance of both beta and alpha cells
   - Lesions and complication - cataracts, renal and neural lesions