Animal Models of Diabetes and Insulin Resistance

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An Organ System..... Course.
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What is different between human and animals?

mouse  rat  dog  human
What is different between human and animals?

Body Mass

mouse    rat    dog    human
Species Differences
Body Mass
- Body Temperature and Basal Metabolic Rate -
Species Differences
Body Mass
- Body Temperature and Basal Metabolic Rate -
Differences between Human and Rodents

Body Mass
- Blood Pressure and Heart Rate -

Blood Pressure

<table>
<thead>
<tr>
<th>Animal</th>
<th>Blood Pressure (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>100</td>
</tr>
<tr>
<td>Rat</td>
<td>200</td>
</tr>
<tr>
<td>Mouse</td>
<td>300</td>
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</tbody>
</table>

Heart Rate

<table>
<thead>
<tr>
<th>Animal</th>
<th>Heart Rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>400</td>
</tr>
<tr>
<td>Rat</td>
<td>500</td>
</tr>
<tr>
<td>Mouse</td>
<td>700</td>
</tr>
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</table>
Differences between Human and Rodents
Body Mass
- Blood Glucose Level and Glucose Kinetics -

<table>
<thead>
<tr>
<th></th>
<th>Blood Glucose</th>
<th>Glucose Consumption</th>
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<tbody>
<tr>
<td>Human</td>
<td>100 mg/dl</td>
<td>10 mg/kg/min</td>
</tr>
<tr>
<td>Rat</td>
<td>100 mg/dl</td>
<td>10 mg/kg/min</td>
</tr>
<tr>
<td>Mouse</td>
<td>100 mg/dl</td>
<td>20 mg/kg/min</td>
</tr>
</tbody>
</table>
What is different between human and animals?

Body Mass

Life Span

mouse  rat  dog  human
**Zucker Diabetic Fatty (ZDF) Rats**
A model of human type 2 diabetes associated with obesity

**Plasma Glucose**
- Lean littermates
- ZDF rats

**Plasma Insulin**

**Plasma Glucagon**

**Hepatic Glucose Production**
- 6 hours fasted ZDF rats

**Glucokinase Protein**

**Regulatory Protein**

**Gluconeogenesis**

**Glycogenolysis**
What is different between human and animals?

Body Mass

Life Span

Anatomy

mouse  rat  dog  human
# 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><strong>Innervation</strong></td>
<td>Rich</td>
<td>Poor</td>
<td>Rich</td>
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<tr>
<td><strong>Gap Junction</strong></td>
<td>Poor</td>
<td>Rich</td>
<td>Poor</td>
</tr>
</tbody>
</table>

![Diagram showing differences between human, guinea pig, and rat/mouse with regards to Innervation and Gap Junction](image)

- **Human**
- **Guinea Pig**
- **Rat/Mouse**
What is different between human and animals?

- Body Mass
- Life Span
- Anatomy
- Enzyme Expression

mouse  rat  dog  human
## Differences between Human and Rodents
- Phosphoenolpyruvate carboxykinase Distribution in the Liver -

<table>
<thead>
<tr>
<th></th>
<th>Human</th>
<th>Rat Mouse</th>
<th>Guinea pig</th>
<th>Chicken</th>
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<tbody>
<tr>
<td><strong>Intracellular Distribution</strong></td>
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<tr>
<td>Cytoplasm</td>
<td>30~50</td>
<td>80~90</td>
<td>15~20</td>
<td>5</td>
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<tr>
<td>Mitochondria</td>
<td>50~70</td>
<td>10~20</td>
<td>80~85</td>
<td>95</td>
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<tr>
<td><strong>Intralobular Distribution</strong></td>
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<td>Periportal</td>
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<td></td>
</tr>
<tr>
<td>Cytoplasm</td>
<td>++</td>
<td>++++</td>
<td>++</td>
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<tr>
<td>Mitochondria</td>
<td>++</td>
<td>-</td>
<td>++</td>
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<tr>
<td>Perivenous</td>
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<tr>
<td>Cytoplasm</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Mitochondria</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>
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
Animal Models of Obesity

Origin: Single Gene

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 hypoinsulinaemia and ketosis
  - insulin resistance
  - decreased insulin receptor function
  - defective thermogenesis

- Pancreatic function
  - labie islets
  - hypertrophy and enhanced replication followed by cell degeneration

- Lesions and complications
  - renal and vascular lesions
  - neuropathy
Animal Models of Obesity

Origin: Single Gene

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
Animal Models of Obesity

Origin: Single Gene ???

4. fa/fa : Zucker diabetic fatty rat

• Mutation of leptin receptor

• Metabolic-endocrine anomalies - no response to satiety signal (hyperphagia)
  - hyperinsulinemia with obesity,
  then hypoinsulinaemia and ketosis
  - insulin resistance
  - decreased insulin receptor function
  - develop fasting hyperglycemia

• Pancreatic function
  - labie islets
  - hypertrophy and enhanced replication
  followed by beta cell degeneration

• Lesions and complications
  - renal and vascular lesions
  - neuropathy and nephropathy
  - cataract
Animal Models of Obesity

Origin: Single Gene

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.
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
Animal Models of Obesity

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**
Animal Models of Obesity

Origin: Dietary

1. High fat

2. High fat/high carbohydrate (sucrose)

3. High carbohydrate (sucrose)

4. Cafeteria diets
Animal Models of Obesity

Origin: Neuroendocrine

1. Lesions
   • Electronic (ventromedial hypothalamus, paraventricular nucleus, amygdala)
   • Knife cut (hypothalamus, midbrain)
   • Chemical (goldtioglucose, monosodium glutamate, bipiperidyl mustard, ibotenic acid, kainic acid)
   • Viral (scrapie or canine ditemper 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 hybride
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 anomalies - hyperglycaemic
     - transiently hyperinsulinaemic, then overtly diabetic
   • Pancreatic function - defective first phase and stimulated release
   • Lesions and complication - nephropathy
     - retinopathy
     - osteopathy
     - testicular degeneration
Animals with non-Obese-Type 2 diabetes-like Syndromes

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 anomalies - gradual hypoinsulinemia due to fibrotic
     - inflammatory exo- and endocrine pancreas destruction
   - Pancreatic function - disappearance of both beta and alpha cells
   - Lesions and complication - cataracts, renal and neural lesions