Rodent models of diabetes mellitus

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Agenda

- Animal models in general
- Pros and cons of rodent models
- Examples of different rodent models of diabetes
  - Genetically modified models
  - Chemically induced models
  - Surgically induced models
  - Dietary models
- Conclusion

Animal models

- **Aims**
  - Disease mechanisms – metabolic pathway
  - Diet strategies, medication → safety, effect

→**Translational value** for human medicine!

Van der Worp et al. 2010, Varga et al. 2010

Some models for own species, e.g. feline Diabetes (*Henson & O'Brien 2006, Hoenig et al. 2000, Häring et al. 2013,…*)





- Rodents/rabbits
- Large animals
- Non human primates (NHP)

Rodent models – Pros



- Availability and maintenance
- Handling
- Short reproductive cycle
- Rather high ethical tolerance
- Standardised housing and hygiene (e.g. SPF)
- Knowledge about genomics – genome engineering easily possible

➔Widespread use of these species

Renner et al. 2016

Rodent models – Cons



- Size
  - Surgery
  - Sampling
- Life expectation
- Training?
- Degree of applicability for human medicine questionable
  - Difference in GIT physiology (rabbit, guinea pig)
  - Difference in metabolism
  - Drug safety testing

Renner et al. 2016

Genetic models of diabetes - examples

Type I

- **NOD mouse** (*Makino et al. 1980*)
- **BB rat** (*Nakhooda et al. 1977, Chapel & Chapel 1983*)

Spontaneous onset → selective breeding for hyperglycaemia

Type II

- **Goto Kakizaki rat** (GK) (*Goto et al. 1976*)
- **KK mouse** (*Nakamura & Yamada 1977, Reni & Mealadio 2005*)
- **Zucker rat** (*Clark et al. 1983, Peterson et al. 1990*) Fatty phenotype = diabetic
- **db/db mouse** (*Hummel et al. 1966, Kitada et al. 2016*) Defective leptin receptor → obesity, IR
- **ob/ob mouse** (*Houseknecht et al. 1998*) leptin deficient → obesity, IR



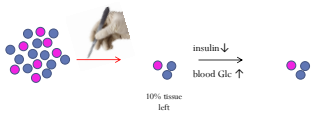
Chemically induced models of DM II

- Direct cytotoxic destruction of pancreatic beta-cells (other cells intact)
  - Streptozotocin (STZ)
  - Alloxan (ALX)
- Easy to generate

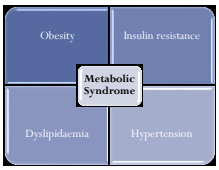
Srinivasan & Ramarao 2007

Surgically induced models of DM II

- Partial pancreatectomy (*Bonner-Weir et al. 1983*)



Models for DM type II



- Monogenetic or chemical models insufficient for translational research (*Buettner et al. 2006*, Srinivasan & Ramarao 2007)

➔ **nutritive intervention to mimic the pathogenesis**

Diabetes type II – Desert rodents

- Desert rodents adapted to low energy diet in natural habitat
- **Spiny Mice** presented with high energy diets (sucrose / fat)
  - Pancreatic hypertrophy
  - Low insulin secretion
  - Low response to Glc
  - →Diabetes develops in relatively old animals

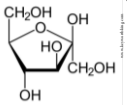
Acomys cahirinus

- **Desert Gerbil**
  - Partly inborn insulin resistance
  - Predisposition to obesity
  - Fed a high energy diet
  - →fast development of hyperglycaemia

Psammomys obesus

Shafrir et al. 2006

Diabetes type II – Fructose



- High fructose feeding for 2 wk
  - Hepatic insulin resistance
  - Altered lipid metabolism: higher conversion rate to fat in the liver
- Insulin receptor activity↓
- Yet no obesity / manifest Diabetes mellitus provoked in those models
- Frc ≠ insulin stimulus → no leptin signalling → increased BW gain

Taghibiglou et al. 2001, Elliott et al. 2002, Rutledge et al. 2007

Diabetes type II – high fat diet

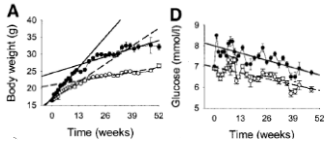
- Common strain: **C57BL/6J** mice *(Surwit et al. 1988)*
- For example: *Winzell &Ahrén 2004*

	High fat diet	Control diet
	% of kcals	
Fat	58	11.4
Carbohydrate	25.6	62.8
Protein	16.4	25.8

Diabetes type II – high fat diet

- For example: *Winzell &Ahrén 2004*
- **C57BL/6J** mice

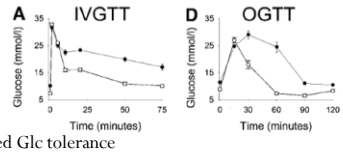
- HFD
- CON



Diabetes type II – high fat diet

- *Winzell &Ahrén 2004*

- HFD
- CON



→Impaired Glc tolerance

→Hyperinsulinaemia – islet dysfunction

→Early stage of Diabetes mellitus

Diabetes type II – high fat diet

- For example: *Ikemoto et al. 1996*

Table 1. Composition of the High-Carbohydrate Diet and High-Fat Diets

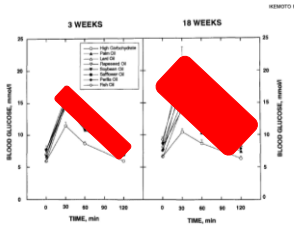
Component	High-Carbohydrate (%)	High-Fat (%)
Oil	4.0	32.0
Casein	23.7	33.1
Sucrose	10.0	17.6
α-Starch	50.0	—
Vitamin mix	1.0	1.4
Mineral mix	7.0	9.8
Cellulose powder	4.0	5.6
DL-Methionine	0.4	0.5
Energy (kcal/100 g)	343.4	489.8
Fat energy kcal/100 g	36.8	294.7
%	10.7	60.2

7 HFD groups
- Palm
- Lard
- Rapeseed
- Soybean
- Safflower
- Perilla
- fish

- Composition for isocaloric energy intake when fed ad libitum (preliminary trials – feed intake)

Diabetes type II – high fat diet

- For example: *Ikemoto et al. 1996*



At 3 wk
Significantly **higher blood Glc in HFD** mice

At 18 wk
significantly higher blood Glc in HFD mice
+ differences between fat sources

Combination diet + STZ

- **Dietary interventions**
  - high fat
  - high fructose
- **Plus low dose STZ**

e.g. *Chen &Wang 2005*, *Luo et al. 1998*,*Wilson & Islam 2012*

High fat diet – on step further

- **Father rats on HFD**

→female offspring impaired Glc tolerance (*Ng et al. 2010*)

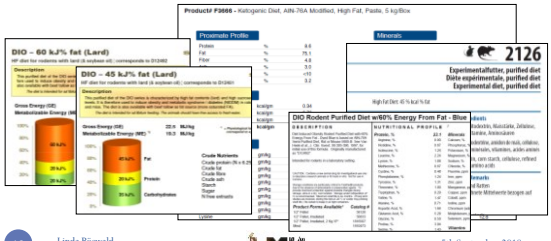
- **Mother mice/rats on HFD** during pregnancy (*Burgueno et al. 2013, Dahlhoff et al. 2014*)

→epigenetic influence on offspring

  - Even when raised by lean mother
  - Male offspring: insulin resistance and steatohepatitis as adults
  - Female offspring: hyperglycaemia

High fat diet – discussion

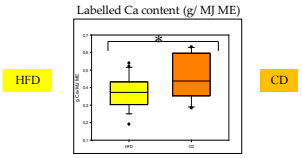
- "high fat diet" not a standardised term *(u.a. Buettner et a. 2006)*
- Nutrient composition varying HFD vs. control *(Böswald & Kienzle 2018)*



High fat diet – discussion

Frommelt et al. 2014:

- Male Wistar rats fed HFDs with varying fat contents
- Calcium digestibility reduced in high fat diets by ≥ 30%
  - Ca soaps
- Phosphorus digestibility increased → less insoluble Ca/P complexes



Conclusion

- Lots of rodent models have been established
  - Different approaches
  - Different phenotypes
- Valuable for basic research
- Translational usefulness limited
- Careful interpretation of nutritional trials

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Literature II/II

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Diabetes type II – high fat diet

- Common strain: **C57BL/6J** mice *(Surwit et al. 1988)*
- For example: *Winzell &Ahrén 2004*

Table 2. Fatty Acid Composition (%) of the Dietary Oils

Fatty Acid	Palm	Lard	Rapeseed	Soybean	Safflower	Perilla	Fish
12:0	0.4						
14:0	1.1	1.7					3.0
16:0	44.6	24.0	3.8	9.9	6.8	6.1	18.2
16:1	0.2	2.6	0.2				4.2
18:0	4.2	14.4	1.7	4.1	2.5	1.7	4.9
18:1	39.5	43.9	59.4	23.6	13.8	18.4	18.8
18:2 (n-6)	9.2	9.1	20.2	53.7	75.7	14.3	1.3
18:3 (n-3)	0.2	0.7	7.1	7.1	0.2	58.3	0.8
20:4 (n-6)		0.1					2.0
20:5 (n-3)							6.8
22:6 (n-3)							22.8
Others	0.7	3.5	7.6	1.6	1.0	1.2	17.2
S:M:P ratio	10:8:2	10:12:2	10:96:41	10:16:42	10:14:75	10:24:92	10:10:14
n-6/n-3 ratio	46.1	13.1	2.9	7.6	378.5	0.3	0.1

Abbreviation: S:M:P, saturated, monounsaturated, and polyunsaturated fatty acid.