Experimental diabetes mellitus

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seminars and practicals from pathophysiology
(May 2003)
Definition of DM

• DM is a group of metabolic disorders characterized by hyperglycemia as a reason of impaired effect of insulin

• chronic hyperglycemia leads to organ damage (retina, kidney, nerves)
Diagnosis of DM

• classical symptoms of diabetes + random plasma glycemia ≥11.1 mmol/l
  – any time of the day
  – symptoms include polyuria, polydipsia and rapid loose of weight
• FPG ≥7.0 mmol/l
  – fasting means at least 8 h from the last meal
• 2-h PG ≥11.1 mmol/l during GTT
  – according to WHO standard load of 75g of
Interpretation of glycemia

- **FPG:**
  - $< 6.1$ mmol/l = normal glycemia
  - $6.1 - 7.0$ mmol/l = IGT (impaired glucose tolerance)
  - $\geq 7.0$ mmol/l = diabetes

- **oGTT – 2h PG:**
  - $< 7.8$ mmol/l = normal glucose tolerance
  - $7.8 - 11.1$ mmol/l = IGT
Oral glucose tolerance test

- FPG (Fasting Plasma Glucose)
- 2-h PG (2-hour Postload Plasma Glucose)
- glykemie (mmol/l)

- Normal
- PGT (Postload Glucose Tolerance Test)
- Diabetes Mellitus
Practicals

1. i.p. ANESTEZIA
2. 1 week before 1/2 animals ALLOXAN i.v. 30mg/kg
3. blood sample from tail vein
4. measurement of FPG on glucometer
5. application of 20% glucose 2ml/100g i.p
6. repeated measurement of glycemia on glucometer in 30 a 90 min time intervals
7. urine sample for determination of glukosuria

results:
- graph FPG - 30mPG - 90mPG
- comparison of DM x non-DM
Pathophysiology of diabetes mellitus
Regulation of glycemia

plasma
- balance between intake and disposal

HEPATIC GLUCOSE PRODUCTION
- glycogenolysis
- gluconeogenesis
  - pyruvate
  - lactate
  - aminoacids
  - glycerol

MUSCLE, ADIPOSE TISSUE
- insulin dependent disposal
- non-insulin dependent disposal

BRAIN AND OTHER TISSUE

FOOD

glykemie 3 - 5mmol/l
Regulation of glycemia

- **humoral**
  - **principal**
    - insulin
    - glucagon
  - **modulatory**
    - glucocorticoids
    - adrenalin
    - growth hormon

- **neural**
  - **sympaticus**
    - hyperglycemia
  - **parasympaticus**
    - hypoglycemia
Mutual interchange of substrates in intermediate metabolism

GLUCOSE
- glucose-6-P
- pyruvate
- lactate
- acetyl-CoA
- citrate cycle
- respiratory chain and oxidative phosphorylation
- keton bodies
- free fatty acids
- ATP
- lactate cycle in liver

GLYCOGEN
- glukóza-1-fosfát
- glycogenesis
- glycogenolysis

glycerol
- gluconegensis
- glucogennic aminoacids

liver, muscle
liver, kidney, intestine
Insulin

- gene in 11th chromozome
- preproinzulin → proinzulin → inzulin + C-peptide
- exocytosis into portal circulation
  - 50% degraded during first pass through liver
- total daily production 20 - 40 U
  - 1/2 basal secretion, 1/2 stimulated
- basal secretion pulsatile
  - 5 - 15 min intervals
- stimulated – glucose, aminoacids, FFA, GIT hormons
  - early phase (ready insulin)
Intracellular cascade of insulin receptor

- Insulin
- Metabolic effects
- Gene expression
- Phosphorylation of signal protein
- IRS-1
- GLUT-4
- PI3-kináza
- Metabolic effects
- Gene expression
Two kinds of tissue from the point of view of insulin action:

- insulin-sensitive
  - muscle, adipose tissue, liver
  - facilitated diffusion by GLUT 4
  - integration into cytoplasmic membrane regulated by insulin

- insulin-nonsensitive
  - others
  - facilitated diffusion by GLUT 1, 2, 3, 4, and 5
  - transport of glucose depend solely on concentration gradient
Diabetes mellitus

• heterogenous syndrome characterized by hyperglycemia due to deficiency of insulin action (as a result of complete depletion or peripheral resistance)

• prevalence of DM in general population 5%, over the age of 65 20%
Causes of insulin deficiency

• absolute
  – destruction of β cells in the Langerhan´s islands

• relative
  – insulin
    • abnormal product of β cells
    • abnormal molecule of insulin (mutation)
    • defective conversion of preproinsulín to insulin
    • circulating antibodies against insulin or receptor
  – insulin resistance in peripheral tissue
    • receptor defect
## Classification of DM

### I. DIABETES MELLITUS

<table>
<thead>
<tr>
<th>Type</th>
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<tbody>
<tr>
<td>Diabetes mellitus of type 1 (T1DM)</td>
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<tr>
<td>Diabetes mellitus of type 2 (T2DM)</td>
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<tr>
<td>Gestational diabetes mellitus</td>
</tr>
</tbody>
</table>

### Other specific types

1. genetic defects of β cell function (MODY)
2. genetic abnormalities of insulin receptor
3. exocrine pancreas disorders
4. endocrinopathies
5. iatrogenic
6. rare genetic syndromes
7. others

### II. IMPAIRED GLUCOSE TOLERANCE (IGT)

- with obesity
- without obesity
Symptoms of DM

• chronic
  – polyuria
  – polydipsia
  – weight loss
  – impairment of visus
  – cutaneous infections

• acute
  – hyperglycemic coma
    • ketoacidotic
    • non-ketoticidotic
DM of type 1 (IDDM)

- selective destruction of $\beta$ cells of LO in genetically predisposed individuals
  - MHC-II (loci DR3, DR4 a DQ $\beta$)
- autoimmunity mediated by T-lymphocytes
  (antibodies against $\beta$ cells (ICA, GAD) as well)
  - started by infection (virus)
  - manifestation typically in childhood
- dependence on exogenous
DM of type 2 (NIDDM)

• imbalance between secretion and affect of insulin
• genetic predisposition – polygenic
  – insulin resistance
  – impairment of secretion
• clinically manifested T2DM has concomitant insulin resistance and impairment of secretion
  – due to epigenetic factors
  – typically in older adults
Insulin resistance

• state, when physiologic amount of insulin does not cause adequate response
  – unsupresed hepatic gluconeogenesis leads to fasting hyperglycemia
  – ineffective insulin-dependent glucose disposal in muscles leads to postprandial hyperglycemia

• compensatory hyperinsulinism

• further worsening by down-regulation of insulin receptors
Main characteristics of T1DM and T2DM

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>T1DM</th>
<th>T2DM</th>
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<tbody>
<tr>
<td>onset</td>
<td>childhood</td>
<td>adults</td>
</tr>
<tr>
<td>genetic disposition</td>
<td>yes (oligogenic)</td>
<td>yes (polygenic)</td>
</tr>
<tr>
<td>clinical manifestation</td>
<td>often acute</td>
<td>slow or none</td>
</tr>
<tr>
<td>autoimunity</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>insulin resistance</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>depends on insulin</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>obesity</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>
Complications of DM

- retinopathy
- nephropathy
- peripheral neuropathy
- diabetic foot (ulcerations, amputations and Charcot’s joint)
- atherosclerosis (CAD)
- hypertension
- abnormalities of lipoprotein metabolism
- periodontitis