Hypoglycemic disorders and glycated hemoglobin
protein glycation

- Nonenzymatic proces
- Complex cascade of reactions
- Present even in healthy individuals
- Soluble and structural proteins can be glycated
1.) initiation

- Nonenzymatic condensation of aldehyde and amine group
- Formation of Schiff base (aldimine)
- Spontaneous intramolecular isomerization
- Formation of stable Amadori products (ketoamine)
• Rate of glycation depends on:
  – Glucose concentration in organisme
  – Rate of anomerization of sugar

• Reaction rate is inversely proportional to the number of carbon atoms in a molecule of the sugar
  → lowest for a hexose, highest for a triose
2.) propagation

• Amadori products can be:
  – Irreversibly oxidized
  – Degraded into the 1-, 3- or 4-deoxyglucosones

• Glucosone derivatives are very reactive → propagation of Maillard reaction, irreversible molecular changes of proteins
  – Heterocyclic products
  – Inter- and intramolecular bridges
3.) termination

• Reactions of deoxyglucosones and amines results in formation of
  – Pyrrols, pyrrolinones and pyrrolinone reductones

• These reacts with amine and carbonyl derivates and form thermodynamically stable products called **AGES** (Advanced Glycation End Products)
Impotrance of glycated proteins

• Suitable indicator of long-term glucose concentration

• Information on the course of glycaemia over time (depending on a half-life of the protein)

• Diagnosis of hyperglycaemia

• Checking kompenzation of DM, dietary measures and insuline treatement

• Determination of glycated hemoglobin, albumin
Determination of glycated albumin

• Fructosamine test

• Glycemia for at least 14 - 21 days

• Not routine determination (nonspecific)
Determination of glycated hemoglobin

- Determination of HbA$_{1c}$ is the most correct.

- Glycation of N-terminal valine and lysine residues.

- Informs about glycemia in last 6 - 8 weeks.

- mmol/mol glycated hemoglobin
  - 20-45 mmol/l
Methods of determination

• Routinely used method is HPLC determination
  – Rapid and reliable
  – Without the need previous separation of HbA\textsubscript{1c}

• Other methods: imunoassay, enzymatic and ELFO methods
DM complications

**Acute**
- Hypoglycaemia
- Hyperglycaemia
- Ketoacidosis
- Hyperosmolality and iont metabolism impairment

**Chronic**
- Nephropathy
- Neuropathy
- Retinopathy
- „diabetic foot“
- Dyslipidemia, high blood pressure...
hyperthyreoidism

diabetes

Liver disease

Impaired glucose tolerance

Healthy person

malabsorption

c (glu) [mmol/l]

time (hours)
HYPOGLYCEMIC DISORDERS
• Glucosis < 2,5 mmol/l

• Hormonal reaction to hypoglycemia
  – Insulin
  – Catecholamines
  – Glucagon
  – Corticotropin and hydrocortisone
  – Grow factor
Clinical manifestations of hypoglycemia (HG)

• Acute
  – Anxiety, tremor, feelings of ill-will
  – Palpitation, tachycardia, sweating, hungr
  – Ataxia, convulsions, coma

• Subacute and chronic
  – Lack of symphatetic hyperactivity
  – Gradual development of the confusion, lethargy and sleepiness
  – Hypothermia
  – Development of a seizure and coma
Diagnosis of hg

• Analysis of symptoms

• Glucose determination

• Evaluation of hypoglycemia - controlled fasting test
  • Suitable also in case of intentional induction of hypoglycemia
    – Imaging examinations
Classification of hg disorders

Symptomatic HG on an empty stomach

- With hyperinsulinism
  - Insulin reaction
  - Tumors of β-cells
  - Autoimunity
  - Intentional overdose

- Without hyperinsulinism
  - Liver disorders
  - Hypocortisolism
  - Alcohol intoxication

Asyptomatic HC

- Prolonged starvation

- Long-lasting intensive physical exercise

- Pregnancy
Symptomatic Hg with hyperinsulinism

- Reaction to insulin
  - Treatment choice
  - Insufficient food intake
  - Exercise
  - Insufficient contraregulation
  - Insulin intoxication
• Tumors of pancreatic β cells
  – Insulinomas (80% solitary, benign)
  – Familial
  – Associated with tumors of the parathyroid gland and pituitary
  – 99% located in pancreas
  – Neurological symptoms dominate, weak adrenergic response
Symptomatic hg without hyperinsulinism

- Low glucose output from liver
  - Direct damage to the liver parenchyma
  - Insufficient intake of amino acids
  - Congenital disorders of carbohydrate metabolism

- Ethanol HG
  - Impaired gluconeogenesis
  - Easy replacing by alcohol stupor
  - Depletion of liver glycogen $\rightarrow$ parenteral administration of glucagon is not effective

- Non-pancreatic tumors
Sources used:

• Obšil, Pavlíček, Glykace proteinů a fosfolipidů: Maillardova reakce in vivo. Chemické listy 91, 1997, 558-569.

