Diabetes mellitus

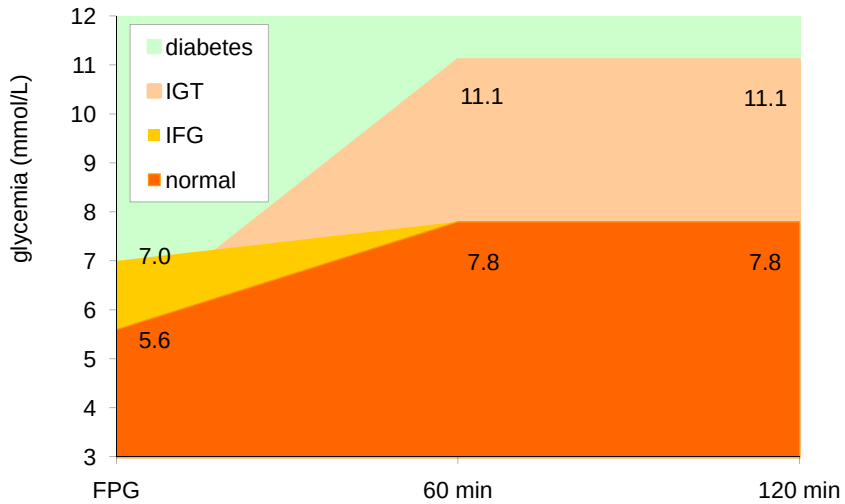
Definition of diabetes mellitus (DM)

- DM is a group of metabolic disorders characterized by **hyperglycemia** resulting from a lack of insulin effect
  - due to either defect in insulin secretion or insulin action
- **chronic hyperglycemia** leads to long-term cell, tissue & organ damage = **diabetic complications**
  - retina
  - kidney
  - nerves

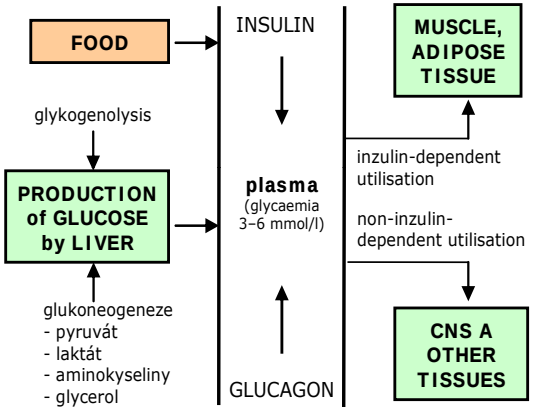
Diagnosis of DM

- diabetes
  - classical symptoms + random plasma glycemia ≥11.1 mmol/l (venous plasma)
    - random = any time of the day
    - symptoms include polyuria and polydipsia
  - FPG (fasting plasma glucose) ≥7.0 mmol/l
    - fasting means at least 8 h from the last meal
  - 2-h PG (postprandial glucose) ≥11.1 mmol/l during oGTT
    - oGTT: according to the WHO consists of FPG examination followed by a standard load of 75g of glucose (diluted in water) and examination of glycemia in 60th and 120th minute
- impaired glucose tolerance (IGT)
  - excluded <7.8 mmol/l
  - 2-h PG ≥7.8 - <11.1 mmol/l during oGTT
- impaired fasting glucose (IFG)
  - diabetes excluded by FPG ≤5.6 mmol/l
  - FPG ≥5.6 – <7 mmol/l

Interpretation of glycemia

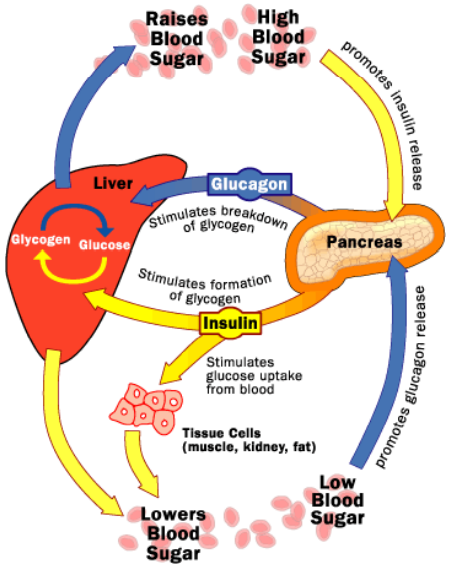


Regulation of glycemia

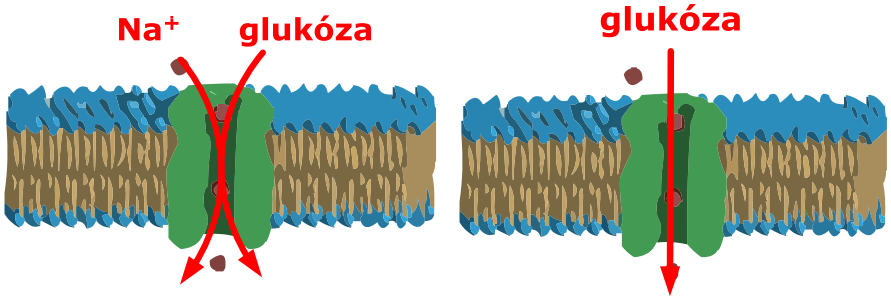


- humoral
  - principal
    - **insulin**
    - **glucagon**
  - auxiliary
    - glucocorticoids
    - adrenalin
    - growth hormone
- neural
  - sympaticus
    - hyperglycemia
  - parasympaticus
    - hypoglycemia

Main contra-regulation: insulin/glucagon

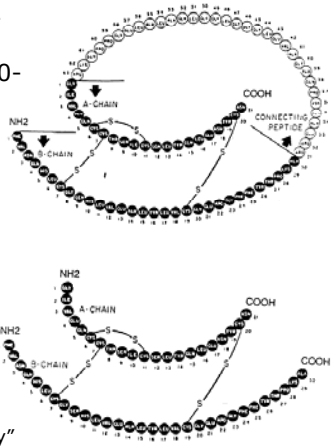


The way glucose enters the cell???

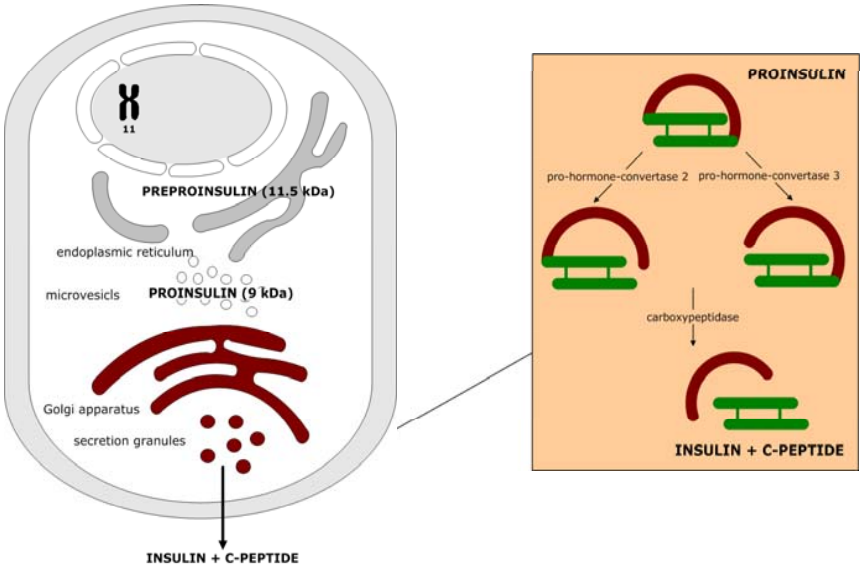


Insulin

- exocytosis from B-cells of islets of Langerhans into portal circulation
  - 50% degraded during first pass through liver
  - parallel cleavage of the C-peptide
- total daily production in healthy subject ~20-40 U
  - 1/2 **basal** (postabsortive) secretion
    - pulsatile (5 - 15 min intervals)
  - 1/2 **stimulated** (postprandial)
    - early phase (ready insulin)
      - ☛ Glc/K_{ATP}-dependent
    - late phase (synthesis de novo)
      - ☛ other secretagogues
- stimulation of secretion
  - <<<glucose
  - <<amino acids
  - <GIT hormones (incretins)
  - FFA
    - variable stimulation (length of chain & (un)saturation)!!
    - since insulin is acting also as peripheral "satiety" signal, reaching the satiety is delayed after fatty meal

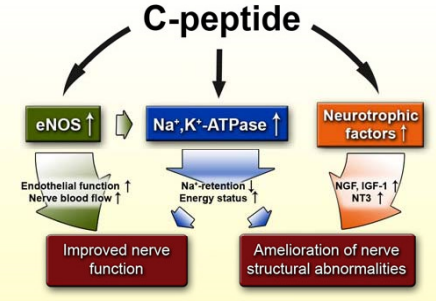


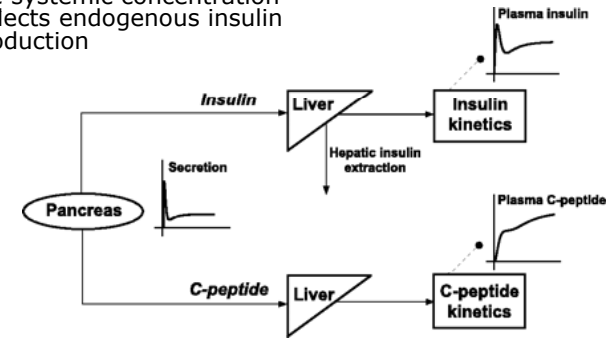
Insulin synthesis



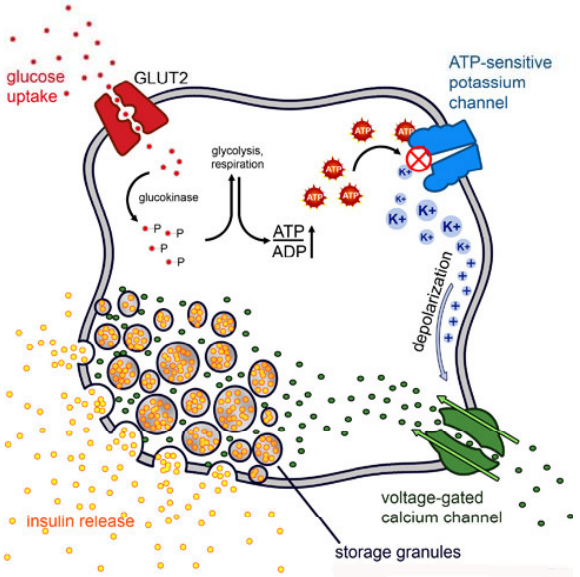
C peptide

- activity
  - certain beneficial vascular effects (nitric oxide)
- mainly diagnostic use
  - equimolar to insulin
  - unlike insulin, C-peptide is not degraded from portal blood in liver
  - the systemic concentration reflects endogenous insulin production

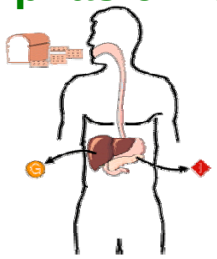


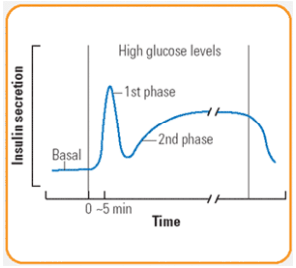


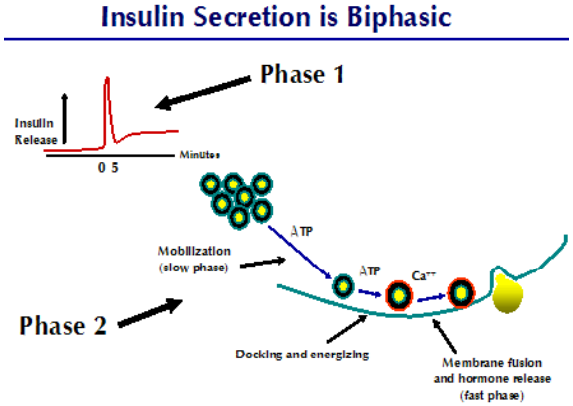
Coupling: glycemia – insulin secretion



Summary: coupling of glycemia → biphasic insulin secretion

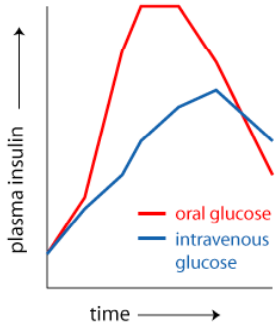




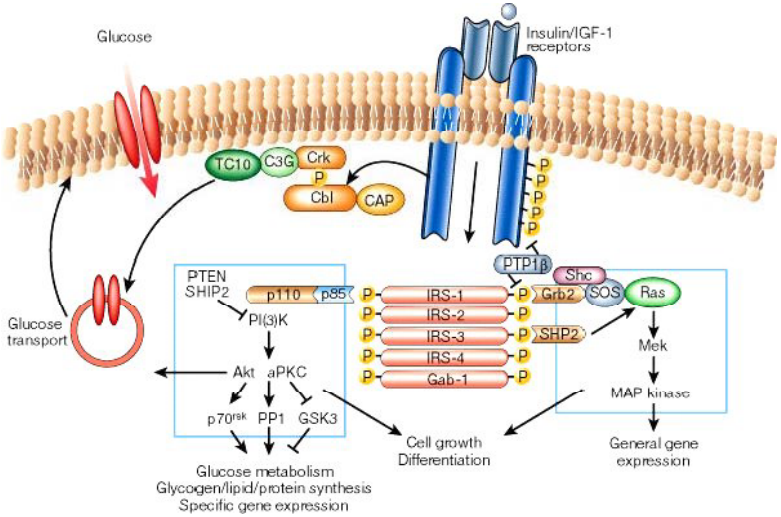


Incretins – enteroinsular axis

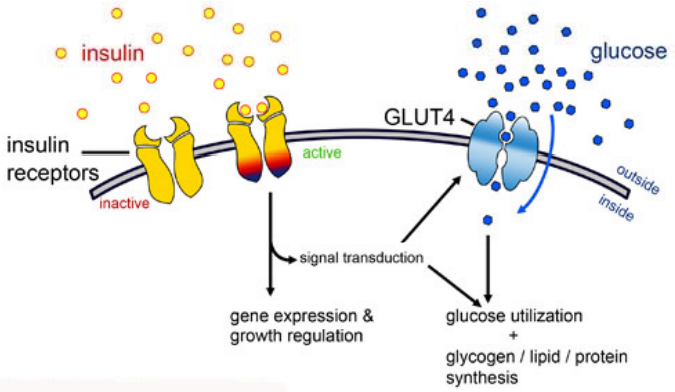
- GIT hormones produced by endocrine cells of small intestine stimulating insulin secretion even **before elevation of blood glucose**
  - Ins-secretion after oral Glc >> after i.v. Glc
    - hypoglycemia – if the patient still conscious then better to give Glc per os
- "forward" regulatory mechanism – anticipation of increase of Glc
- 2 major incretin hormones
  - GIP (glucose-dependent insulinotropic peptide or gastric inhibitory peptide)
  - GLP-1 (glucagon-like peptide-1)
- treatment of T2DM [= delayed effect of Glc on Ins stimulation] by incretin analogues
    - GLP-1 analogue - exenatide (GLP-receptor agonist)
    - DPP-4 inhibitors (dipeptyl peptidase 4 - proteolytic degradation of incretins) - gliptins
  - improvement of Glc-stimulated Ins secretion after meal
  - supression of postprandial glucagon release
  - delayed gastric emptying
  - protection of β-cells from apoptosis



Insulin receptor



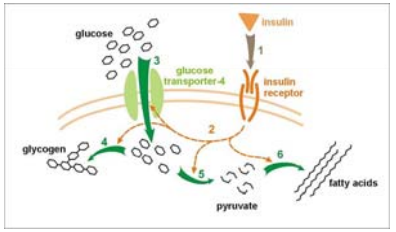
Insulin receptor signal cascade



- insulin receptor
  - tyrosinkinase type (2 α and 2 β subunits)
  - (1) cascade of phosphorylations (down-stream kinases)
    - balanced activation or inhibition of hormones
      - ☛ activation of anabolic pathways (i.e. glycegenogenesis, lipogenesis)
      - ☛ inhibition of catabolic pathways (e.g. lipolysis, glycogenolysis) and gluconeogenesis
  - (2) translocation of GLUT4

Classification of tissues according to insulin action:

- **insulin-sensitive**
  - **muscle**
  - **adipose tissue**
    - glucose uptake facilitated by **GLUT4**, which becomes integrated into cell membrane after insulin receptor activation



  - **liver**
    - metabolic actions
- **insulin-insensitive**
  - **all others incl. muscle, adipose and liver**
    - glucose uptake is realized by facilitated diffusion by **GLUT1, 2, 3, 5, …** permanently localized in the cell membrane
    - transport of glucose depends solely on
      - ☛ concentration gradient
      - ☛ type and density of GLUTs

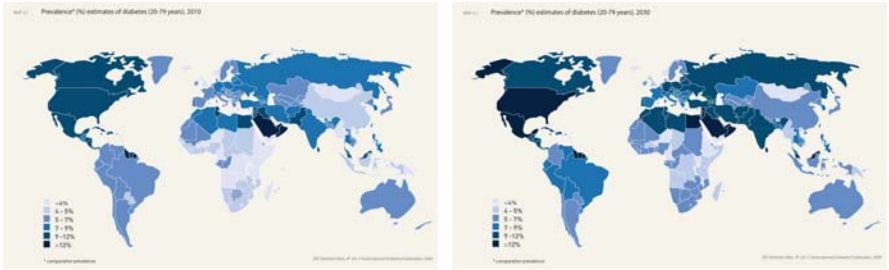
Diabetes mellitus

- **heterogeneous** syndrome characterized by **hyperglycemia** due to **deficiency of insulin action** as a result of
  - absolute insulin deficiency
    - **destruction of the β-cells of the islets of Langerhans**
  - relative deficiency of insulin secretion and/or action
    - abnormal molecule of insulin (mutation of insulin gene)
    - defective conversion of preproinsulin to insulin
    - circulating antibodies against insulin or its receptor
    - **secondary failure of β-cells of the islets of Langerhans**
    - insulin resistance in peripheral tissues
      - receptor defect
      - **post-receptor defect**
- prevalence of DM in general population 5%, over the age of 65 already 25%

Prevalence (%) of diabetes (population 20-79 years)

2010 – 4.3 bil. (from a total of 7 bil.)
285 mil. diabetics
0.75 mil. diabetics in Czech rep.

2030 – 5.6 bil. (from a total of 8.5 bil.) **30 %**
438 mil. diabetics **54 %**
1.2 mil. diabetics in Czech Rep. **60 %**



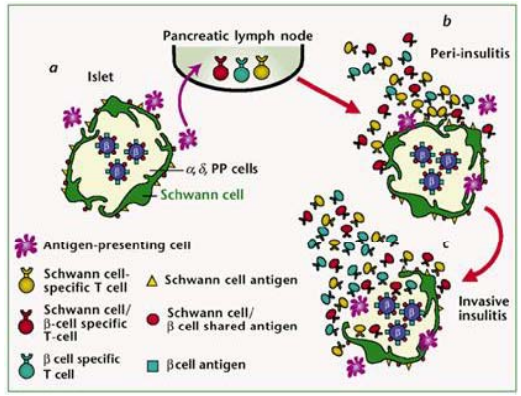
[*IDF Diabetes Atlas*, 4th ed. ©International Diabetes Federation, 2009]

Classification of DM

1. Diabetes mellitus type 1 (T1DM) ~5%
2. Diabetes mellitus type 2 (T2DM) ~90%
3. Other specific types: a. genetic defects of B-cell - monogenic DM (MODY1 - 6) - mutation of mitochondrial DNA b. genetic defects leading to insulin resistance - type A insulin resistance, leprechaunismus, Rabson-Mendenhal syndrome, lipoatrophic DM c. diseases of exocrine pancreas - pancreatitis, tumor, cystic fibrosis, hemochromatosis d. endokrinopathies - Cushing syndrome, acromegaly, pheochromocytoma, hyperthyreosis e. iatrogenic DM (i.e. drugs and toxins) f. other genetic syndromes associated with DM - Down, Klinefelter, Turner syndromes, …
4. Gestational diabetes mellitus

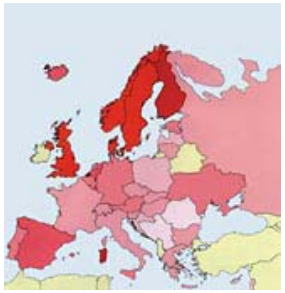
T1DM (formerly IDDM)

- selective autoimmune destruction of β cells of IofL in genetically predisposed individuals
- genetic susceptibility
  - chromosome 6 – MHC class III
    - DR3-DQ2 and DR4-DQ8
  - chromosome 11 - insulin gene
- cytotoxic autoimmunity mediated by T-lymphocytes
  - there are also antibodies against β cell structures (ICA, GAD, IAA), but they are rather markers of autoimmunity than causal agent

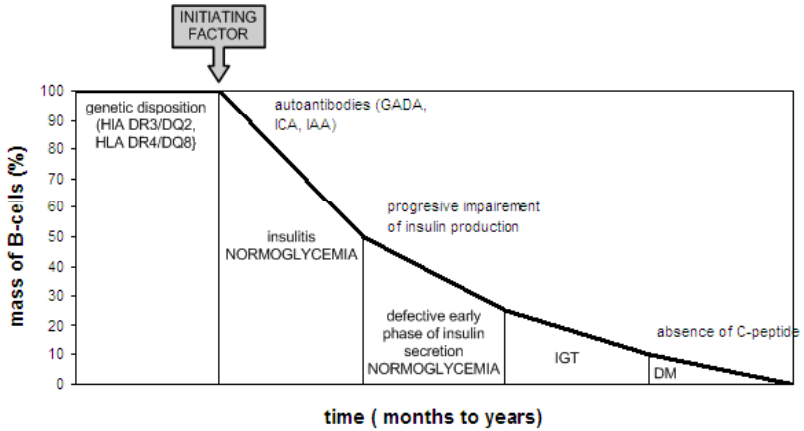


T1DM

- autoimunity has to be triggered by various factors
  - infection
    - viruses
      - rubella, measles, coxsackie B, CMV, EBV, enteroviruses, retro-viruses
    - mechanism is unclear
      - cytolytic (⊗ sequestration of antigens
      - formation of neoantigens
      - molekular mimicry or superantigens
  - environmental factors (according to the epidemiologic evidence)
    - diet – early exposition proteins of cow's milk
      - bovine insulin
    - vitamin D – reason for **northern-southern geographical gradient**?
    - toxins (diet, water, bacteria)
    - gluten???
- manifestation typically in childhood
- absolute dependence on exogenous supplementation by insulin

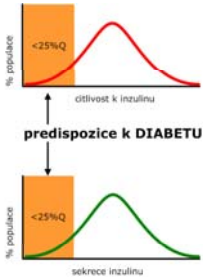


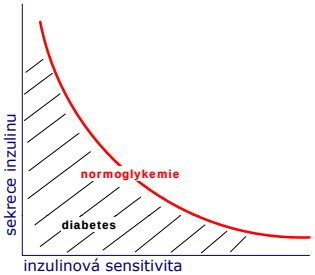
Natural history of T1DM



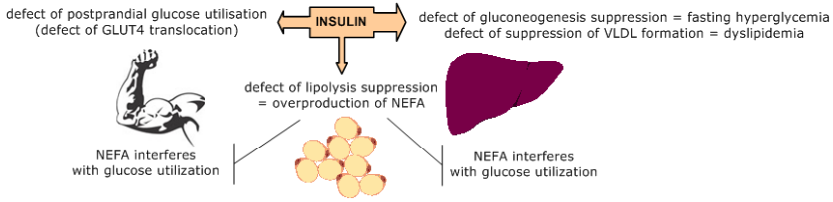
T2DM (formerly NIDDM)

- insulin sensitivity is a continuos trait with distinct interindividual variability, it can be assessed by:
  - hyperinsulinemic euglycemic clamp
  - calculated indexes (based on relationship between glycemia and insulin during fasting or oGTT) – e.g. HOMA, QUICKI, …
- main pathophysiologic feature of T2DM is an **imbalance** between insulin secretion and its effect
  - **in the time of clinical manifestation there are both insulin resistance and impairment of insulin secretion**
- what is "chicken" and what is "egg"??
  - insulin resistance
    - genetic predisposition (polygenic) – thrifty phenotype
    - acquired factors
      - competition of GIs with NEFA!!! (diet)
      - effect of adipokines from adipose tissue (obesity)
      - ↓ mobilisation of GLUT4 in physical inactivity
      - down-regulation of ins. receptor due to hyperinsulinemia
  - impairment of secretion
    - inherited factors
      - fewer B-cells (~20-40%)
      - defect of 1. phase of Ins secrection (~80% reduction)
    - acquired factors
      - – gluco- and lipotoxicity for B-cells
- 90% of subjects are obese – **metabolic syndrome!!!**

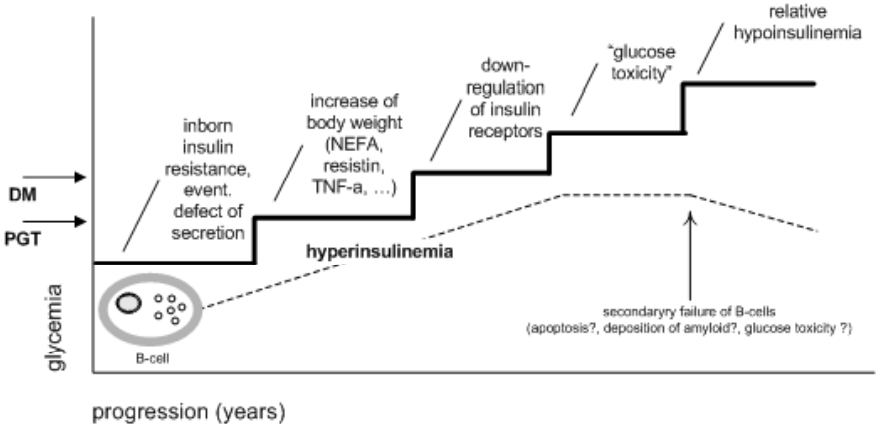




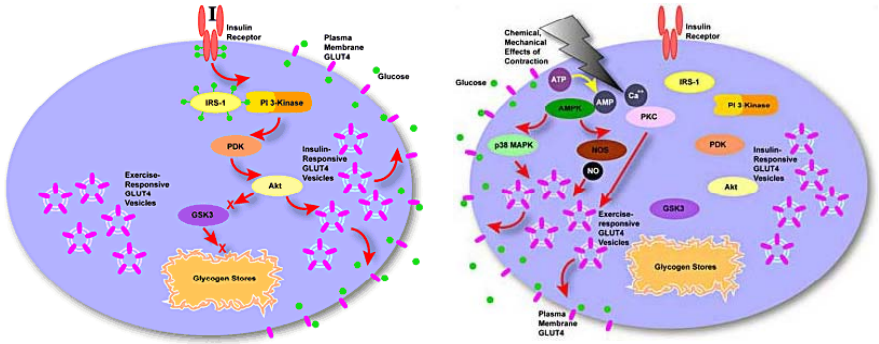
Pathogenesis of T2DM



Natural history of T2DM



Insulin- and "sport"-dependent translocation of GLUT4



- 2 intracellular "pools" of GLUT4
  - insulin-dependent (see cascade of Ins-receptor)
  - Ca^{2+} / NO / AMPK?-dependent
    - this mechanism is responsible for improvement of insulin sensitivity in physically active subjects

Main characteristics of T1DM and T2DM

	T1DM	T2DM
onset	childhood	adults
genetic disposition	yes (oligogenic)	yes (polygenic)
clinical manifestation	often acute	mild or none
autoimmunity	yes	No
insulin resistance	no	yes
dependence on insulin	yes	No
obesity	no	yes

Clinical presentation of DM

- due to the increase of blood osmolality, osmotic diuresis and dehydratation
  - classical
    - polyuria, thirst, polydipsia
    - tiredness
  - others
    - temporary impairment of visus
    - recurrent infections
    - perio-/parodontitis
- extreme hyperglycemia
  - ketoacidotic coma
  - non-ketoticidotic hyperglycemic coma
  - lactic coma

Complications of DM

- microvascular
  - diabetic retinopathy
  - diabetic nephropathy
  - diabetic neuropathy
    - sensoric
    - motoric
    - autonomous
- macrovascular
  - accelerated atherosclerosis (CAD, peripheral and cerebrovascular vascular disease)
- combined
  - diabetic foot (ulcerations, amputations and Charcot´s joint)
- others
  - periodontitis
  - cataract
  - glaucoma

Pathogenesis of complications