Diabetes mellitus

Regulation of glucose metabolism
Insulin a ins. sensitivity vs. resistance
Classification of DM
PP of primary types of DM – T1DM and T2DM
Acute and chronic complications of DM

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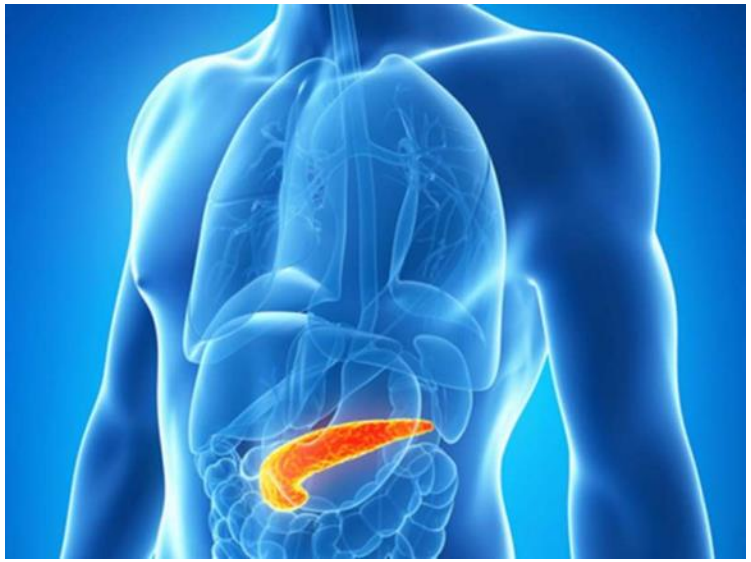
Definition of diabetes mellitus (DM)

- 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



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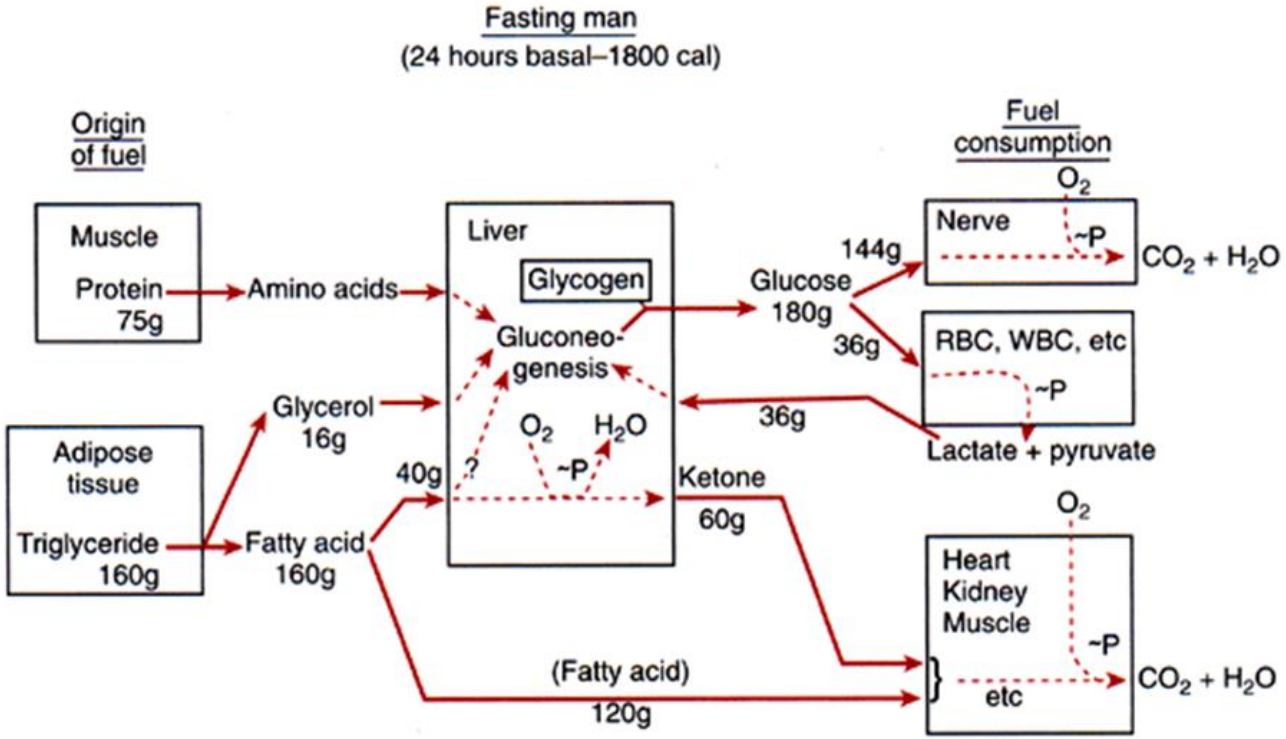
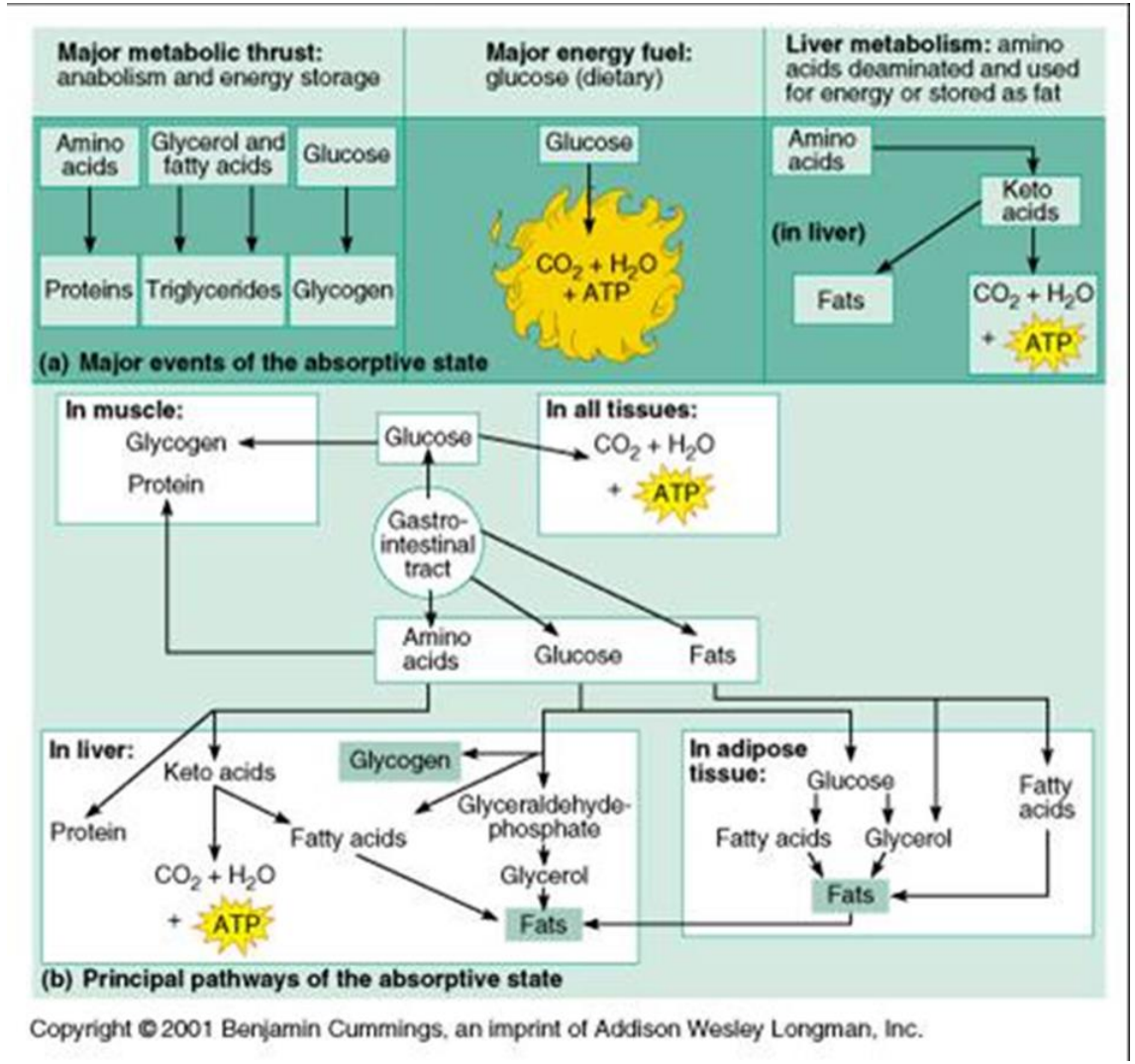
Fasting vs. absorptive state





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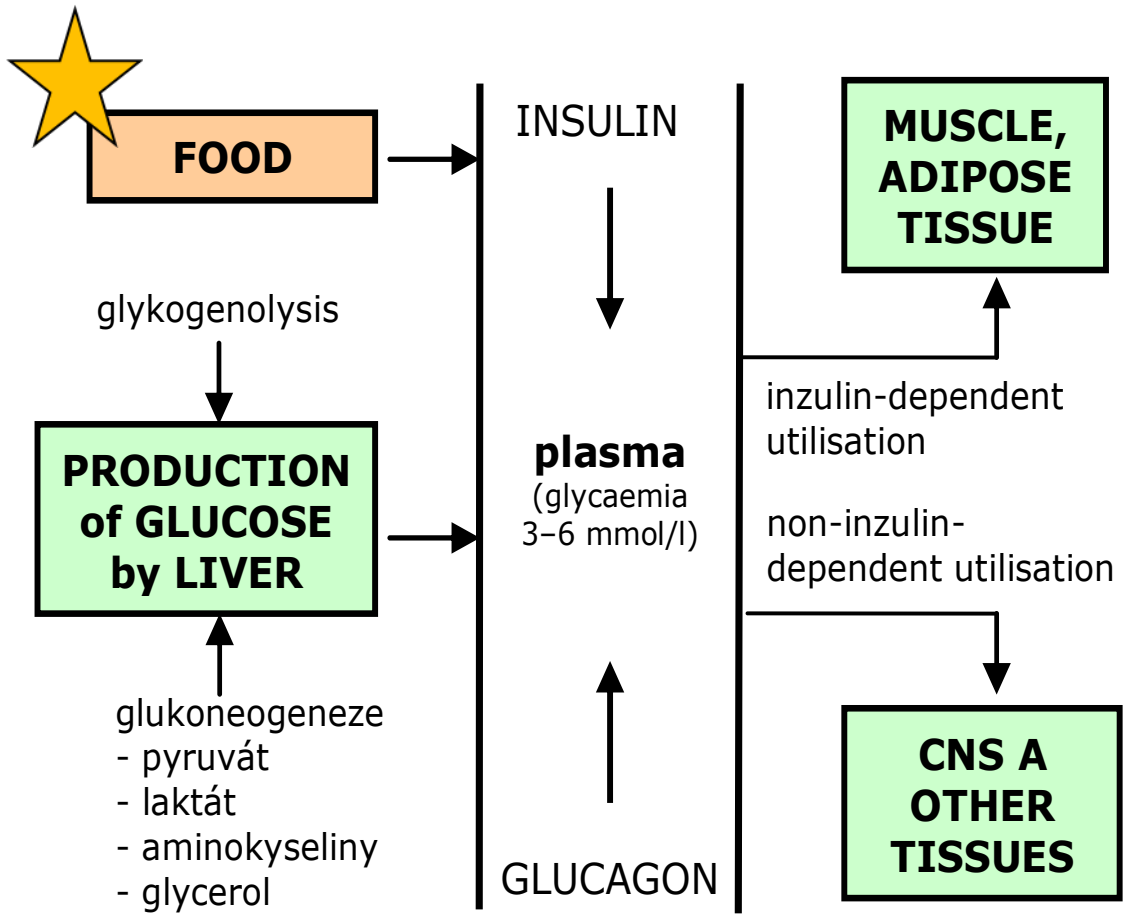
Regulation of glycemia



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

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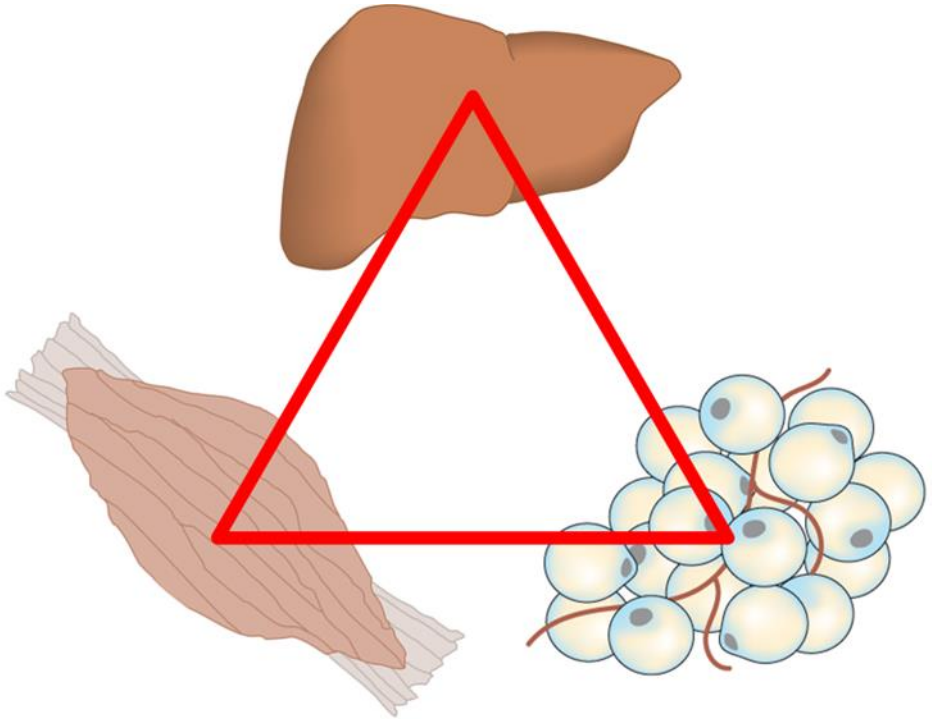
What happens (in healthy man) after meal = insulin orchestrates allocation and utilisation of nutrients

diabetic “triumvirate”



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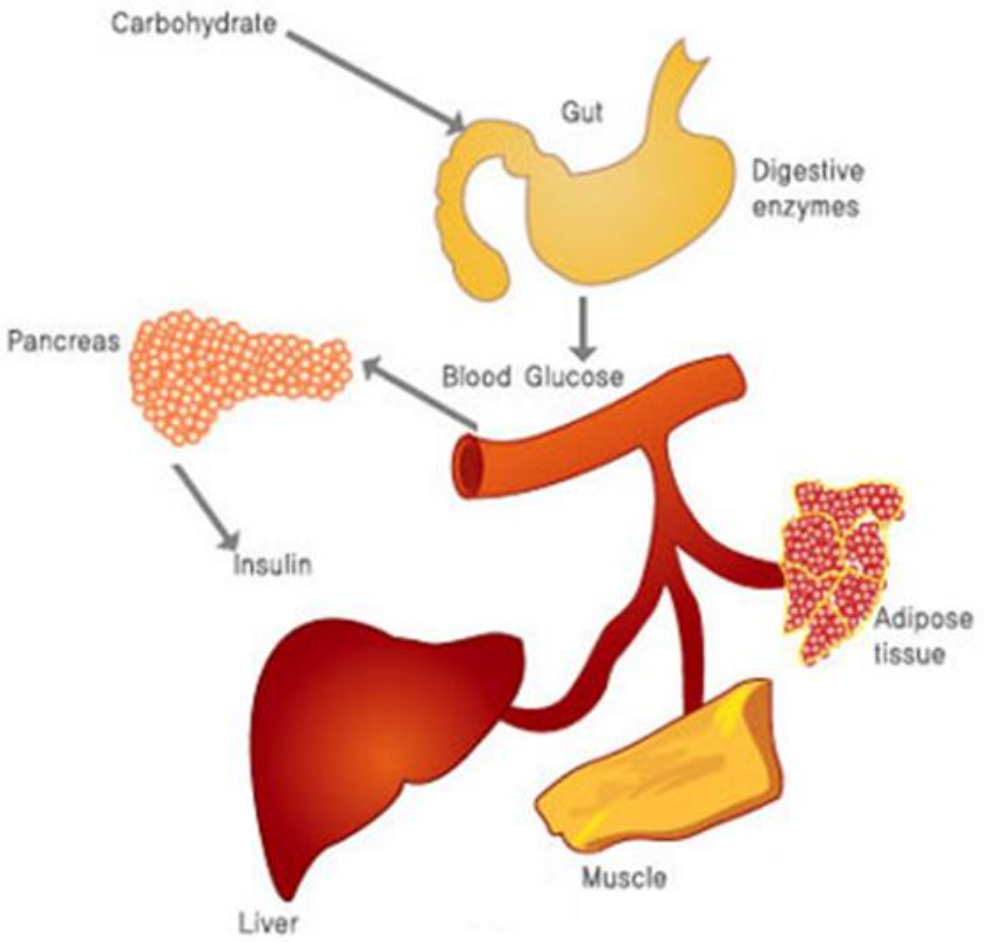
What happens (in healthy man) after meal = insulin orchestrates allocation and utilisation of nutrients



- liver
  - stimulation of glycogen formation (up to~ 5% of liver weight)
    - ↑ hexokinase, phosphophructokinase, glycogensynthase
    - ↓ G-6-P-kinase
  - inhibition of gluconeogenesis
    - ↓ PEPCK
  - fat formation
    - ↑ synthesis of FFA and VLDL
  - proteosynthesis
    - ↑ transport of AA
  - inhibition of ketogenesis
- muscle
  - translocation of GLUT4
  - formation of glycogen
  - proteosynthesis
    - ↑ transport of AA
- adipose tissue
  - translocation of GLUT4
    - Glc → glycerol
  - stimulation of adipogenesis
    - ↑ activity of LPL
      - hydrolysis of VLDL and resynthesis of TAG
    - ↓ hormone-sensitive lipase
- brain
  - insulin participates in the control of appetite/satiety

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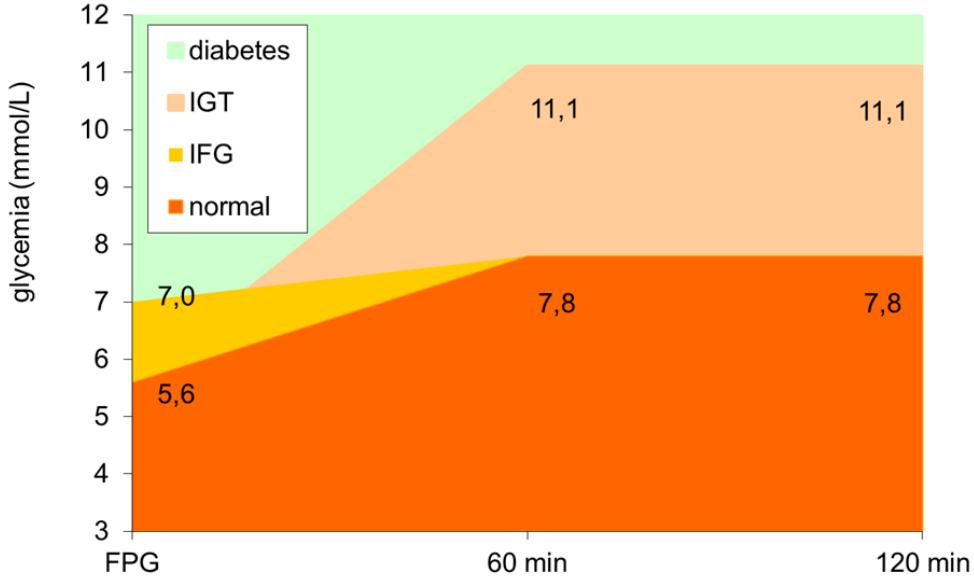
Diagnosis of DM

- 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



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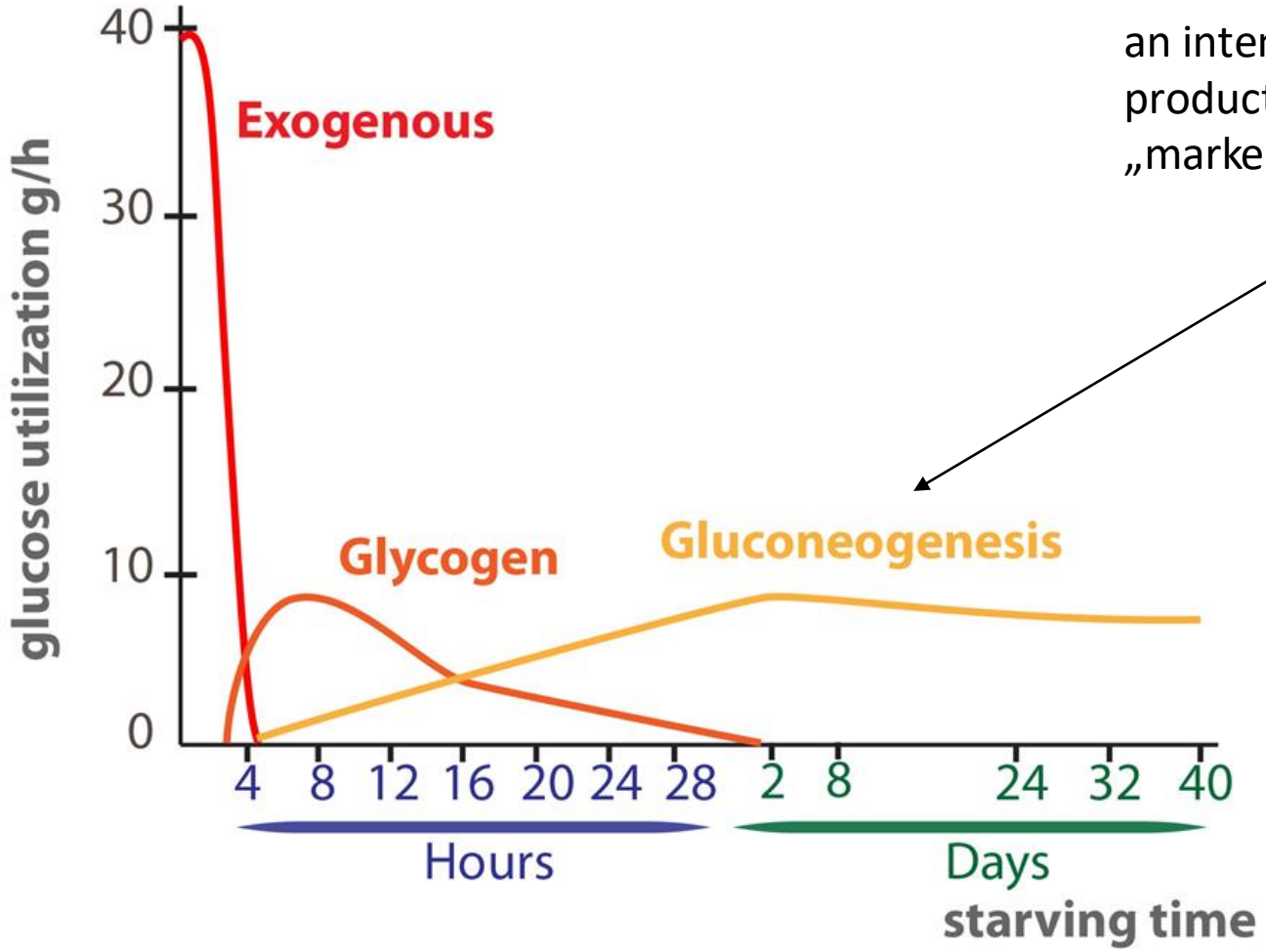
Importance of fasting plasma glucose measurement



an intensity of liver glucose production is a very sensitive „marker“ of insulin sensitivity

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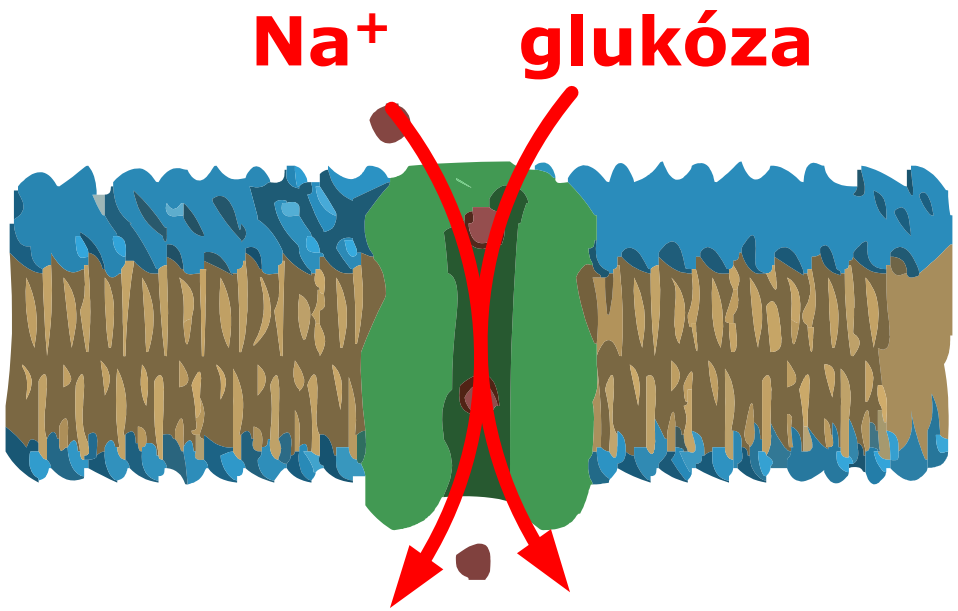
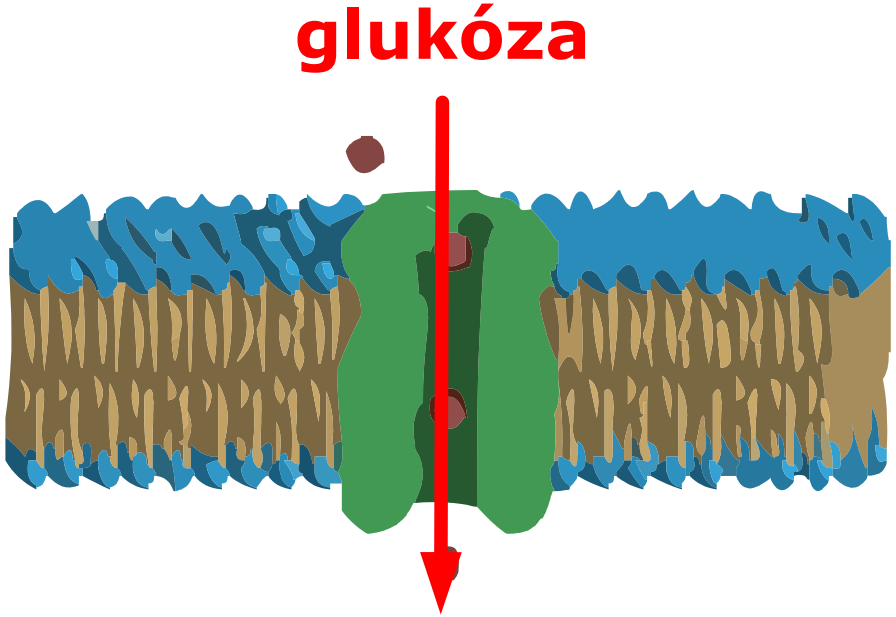
Q1: The way glucose enters the cell??





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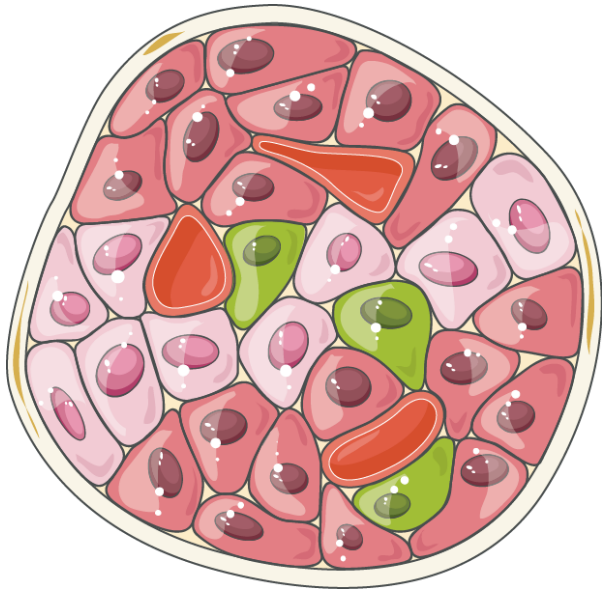

INSULIN SECRETION VS. INSULIN SENSITIVITY / RESISTANCE

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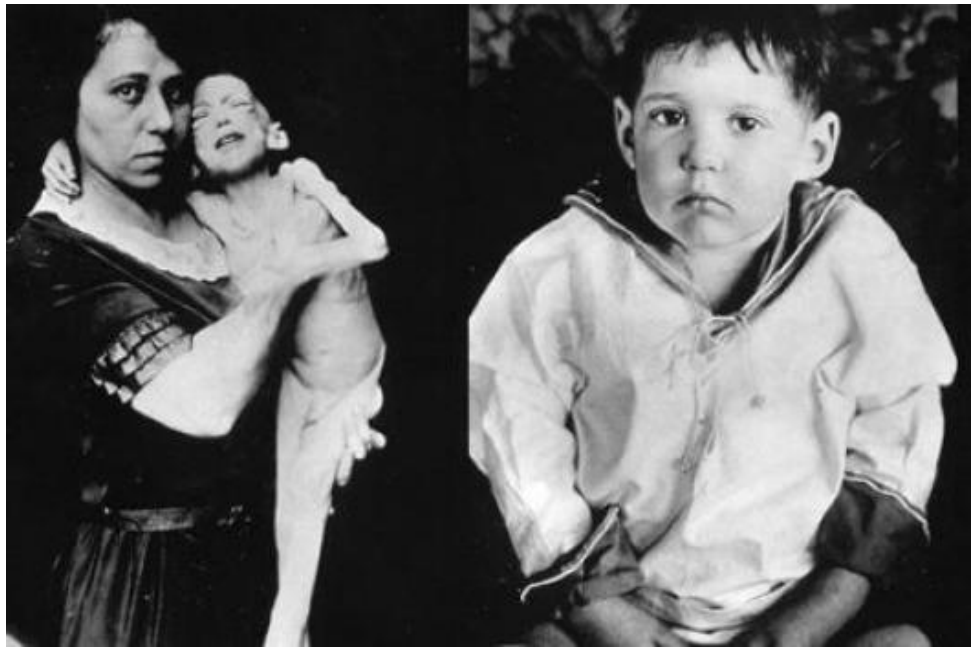
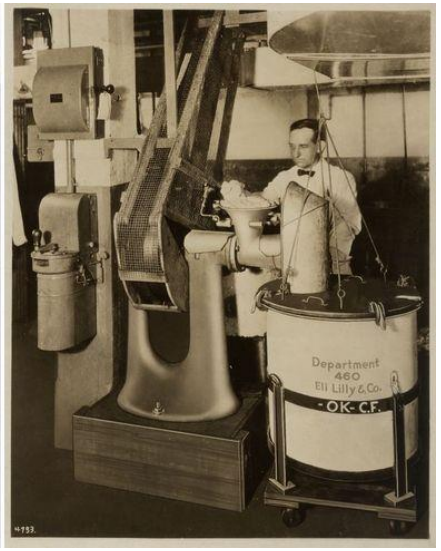
Insulin – world diabetes day

- 14/11 (od 1991)
- birthday of the man who co-discovered insulin, Frederick Banting
- Banting discovered insulin in 1922 alongside Charles Best under the directorship of John McLeod and with assistance of James Collip
- The Nobel Prize in Physiology or Medicine 1923 was awarded jointly to Frederick Grant Banting and John James Rickard Macleod "for the discovery of insulin"





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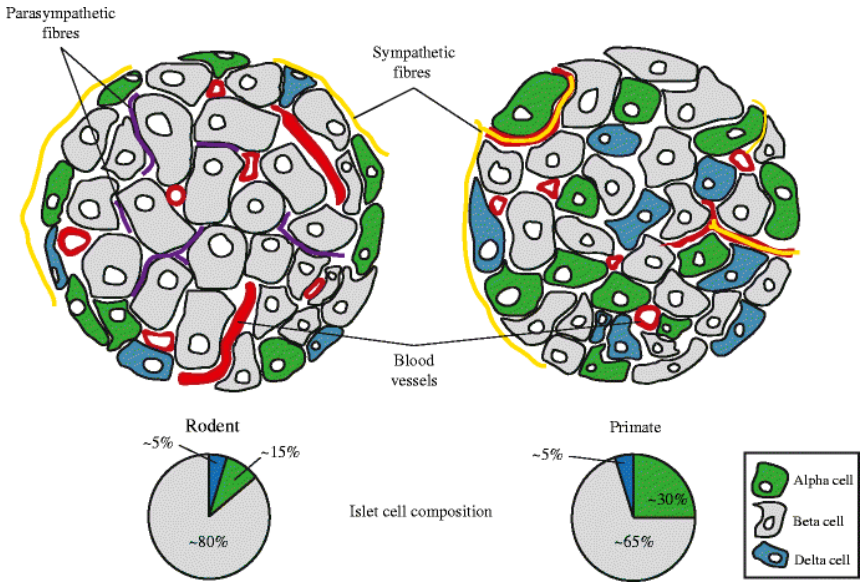
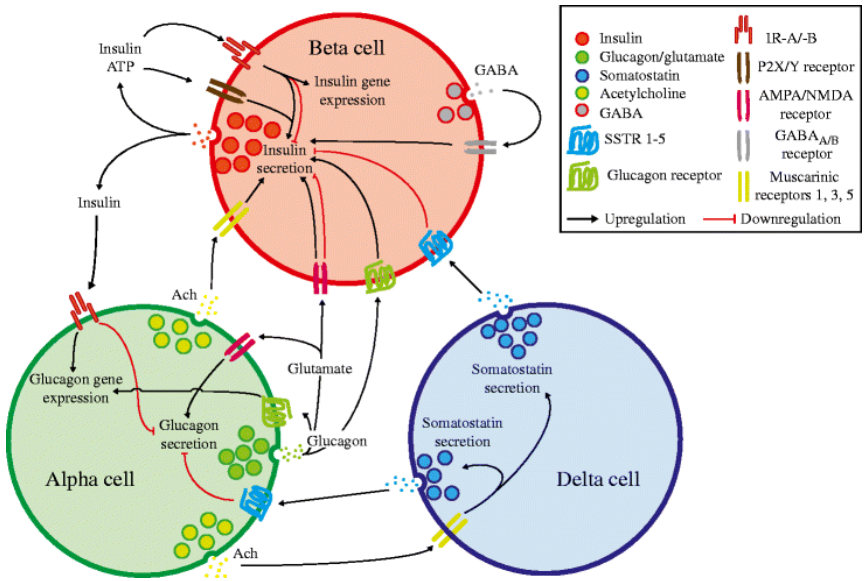
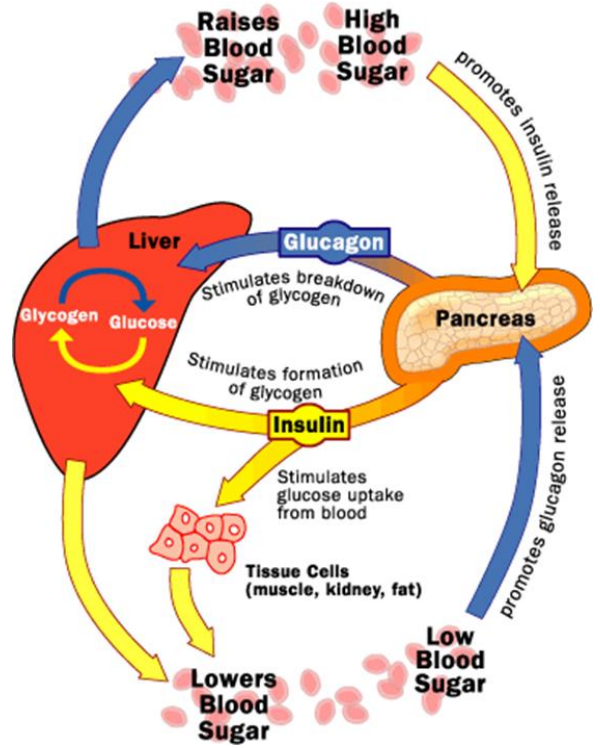
Langerhans islets - architecture

- The pancreatic islet blood flow is 5–10 times higher than that of the exocrine pancreas, and can be selectively enhanced whenever the need for insulin secretion is increased
- B-A-D flow hypothesis
  - that is why contra-regulation insulin/glucagon works so well







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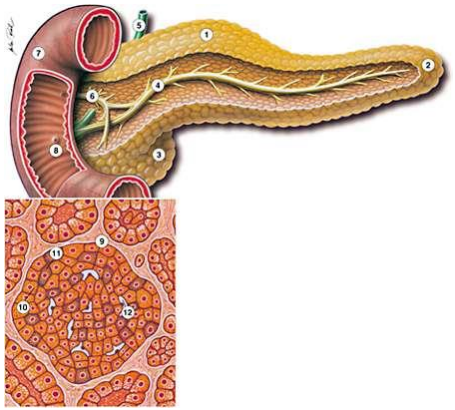
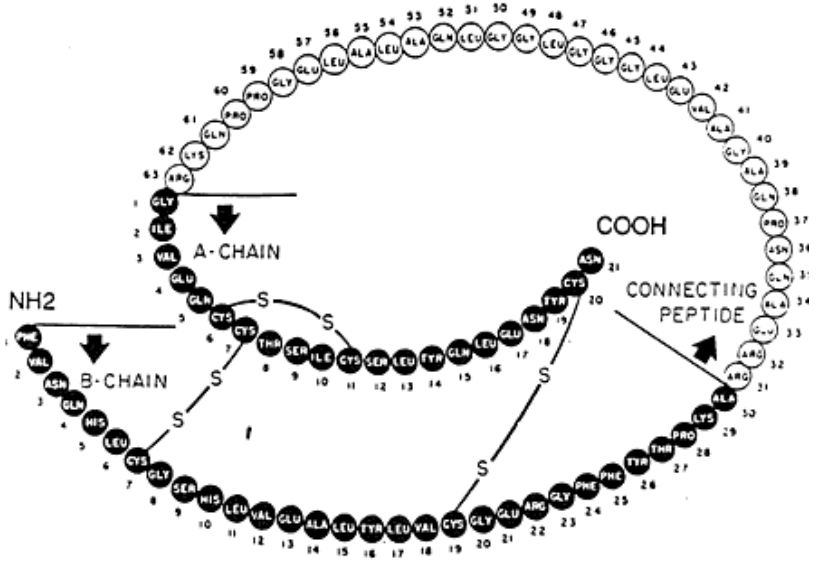
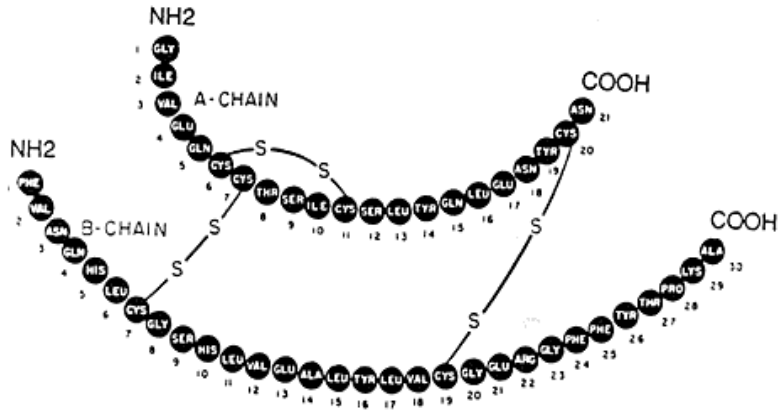
Insulin

- 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







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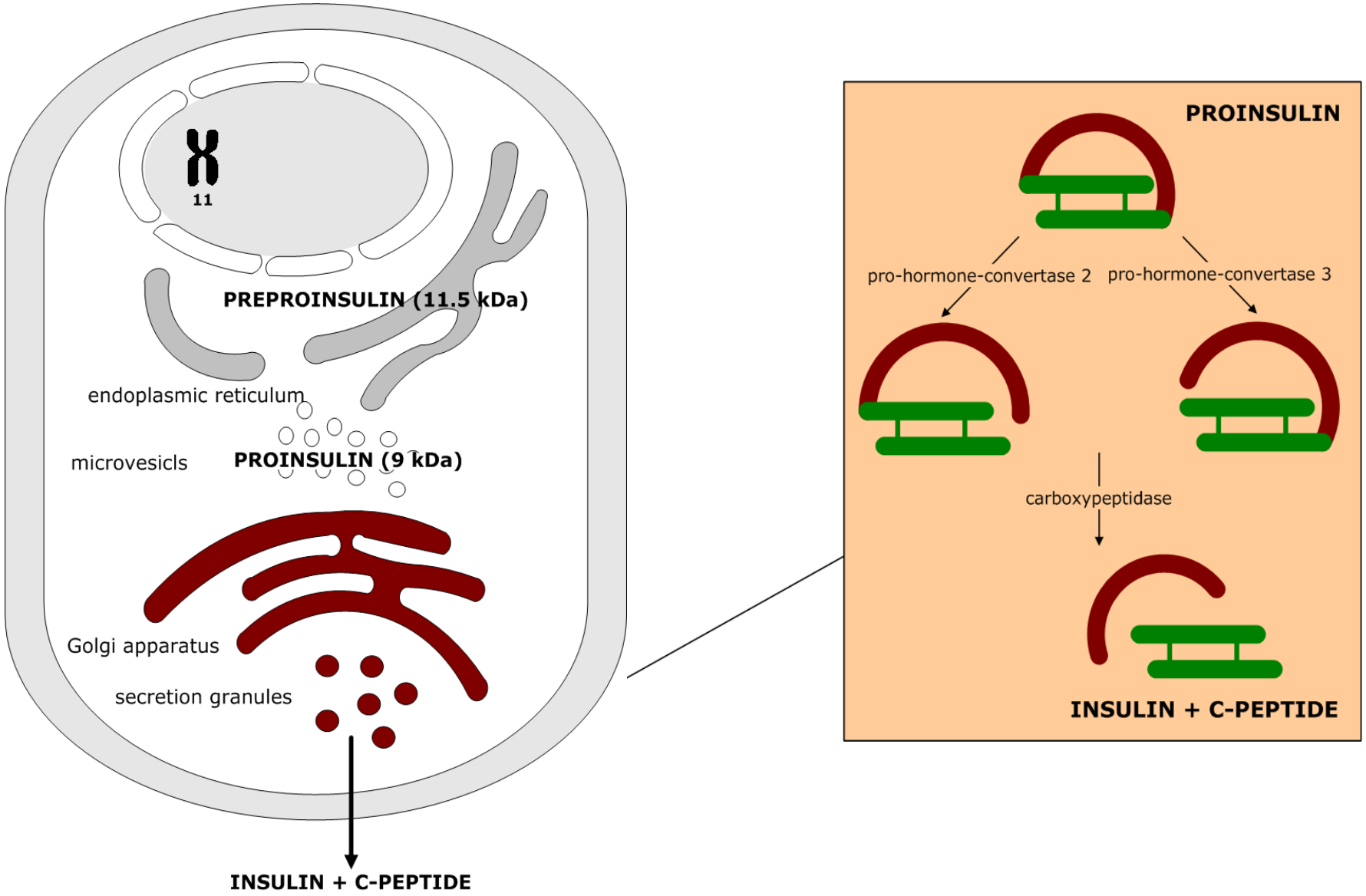
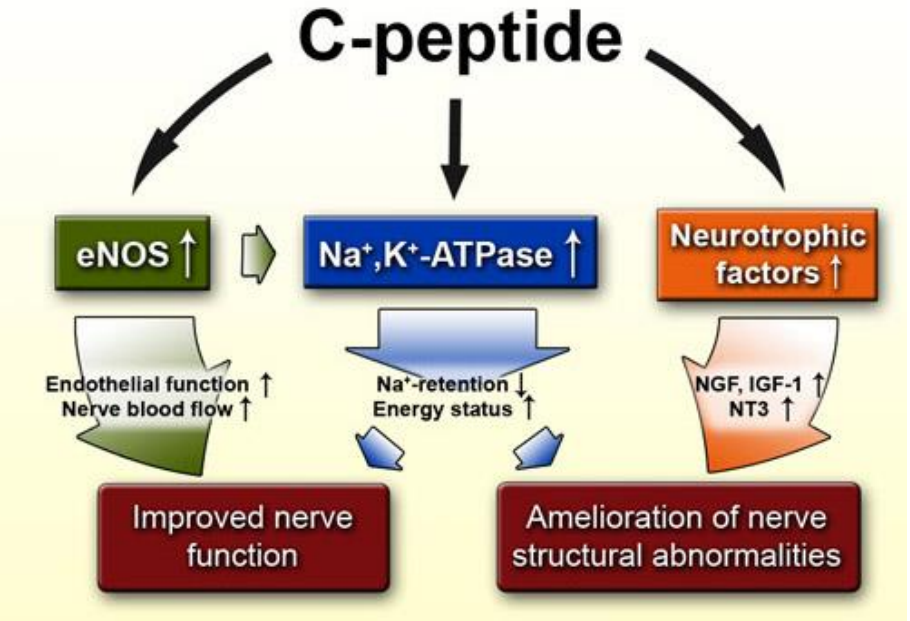
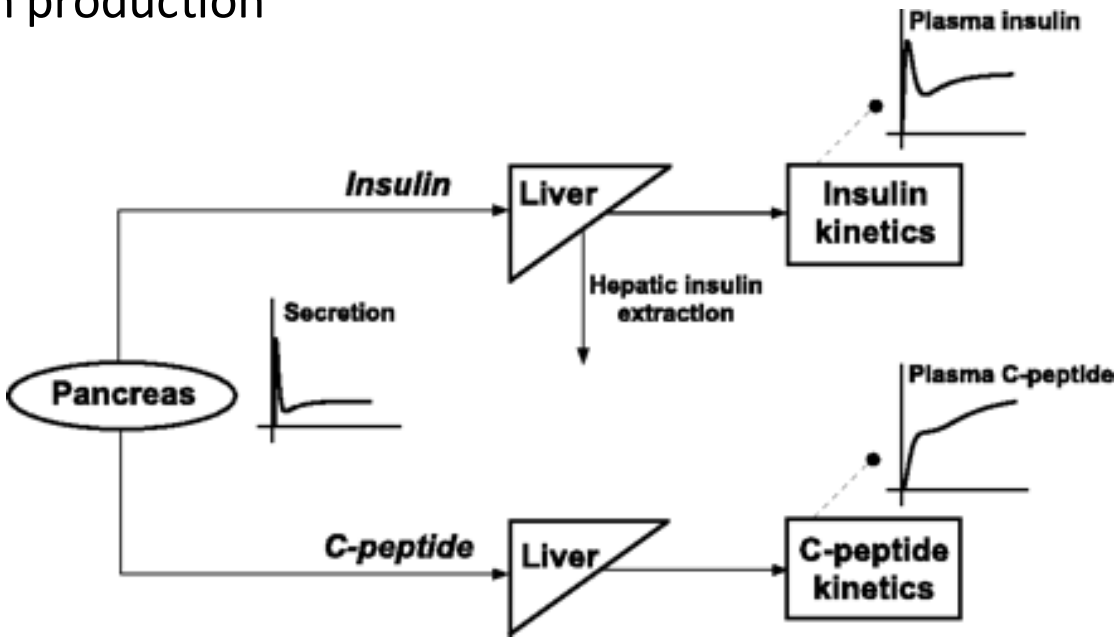
Insulin synthesis



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





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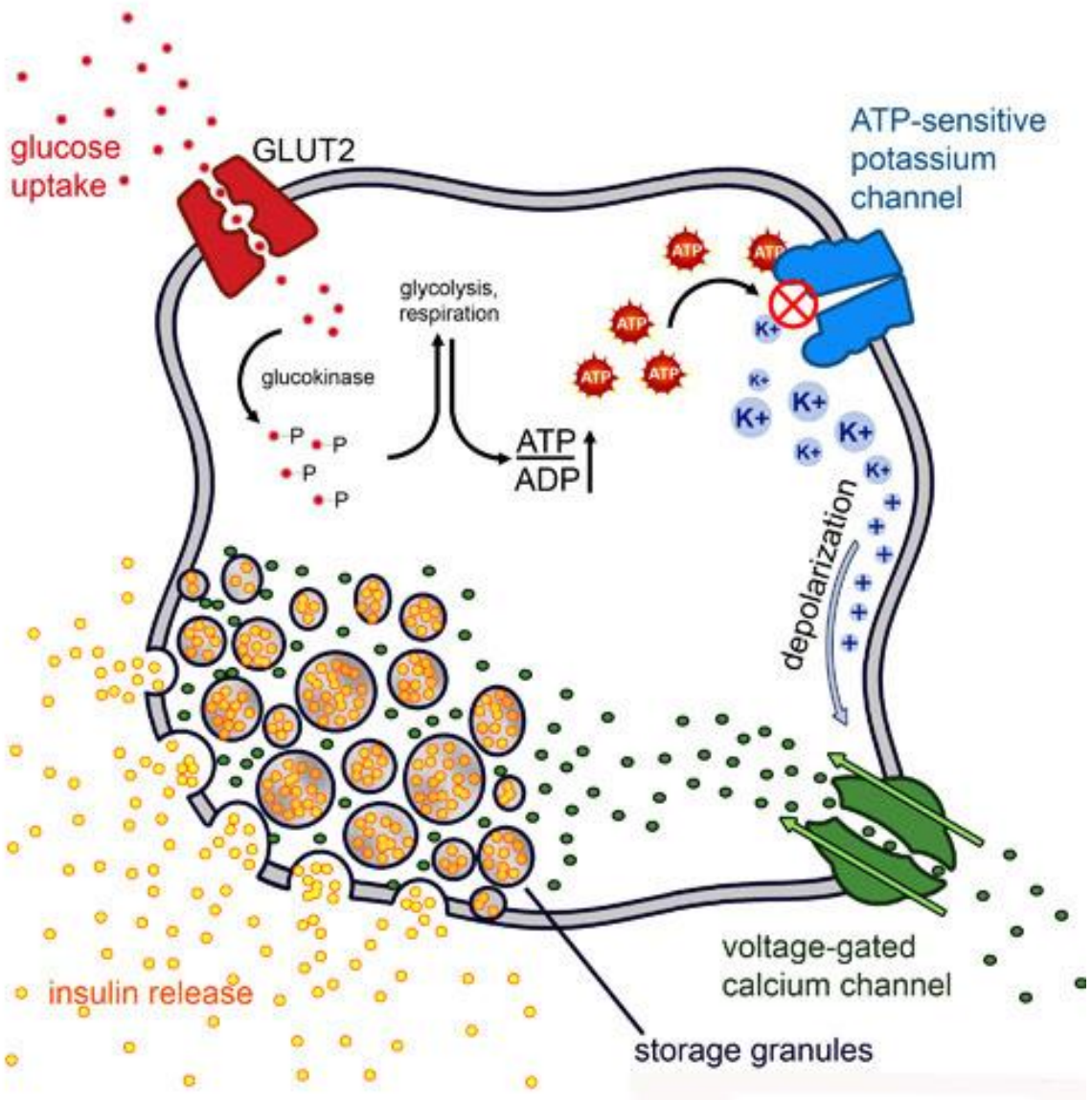
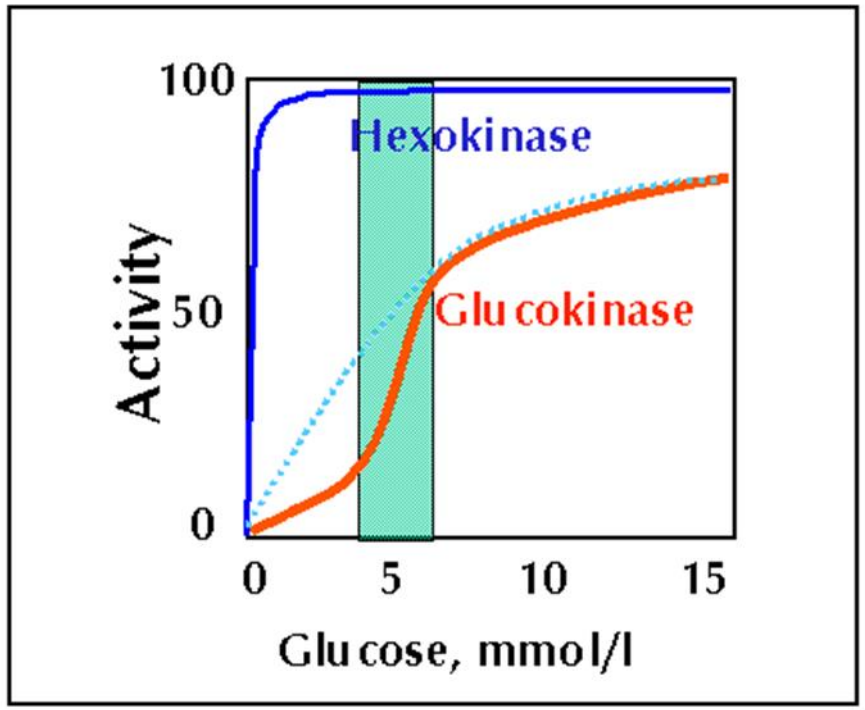
Coupling: glycemia – insulin secretion



Hexokinase vs. glucokinase



- **hexokinase** (ubiquitously with exception of liver and pancreatic b-cells)
  - activity increases with increased glucose but activity is inhibited by increased G6P
  - levels of enzyme are constitutive
  - only generates ATP when energy is required
- **glucokinase** (hepatocytes and b-cells)
  - is not normally active because its Km is lower than normal blood glucose levels
  - eating food increases glu in blood, activates glucokinase which converts glu to glycogen and fatty acids
  - activity increases with increased glucose but is not inhibited by increased glu6PO4
  - the levels of the protein are regulated by insulin
  - rate of reaction is driven by substrate-glucose not by demand for product-G6P
    - allows all glu available to be converted to G6P and then if excess present, it is converted to glycogen and from there to triglycerides and fatty acids

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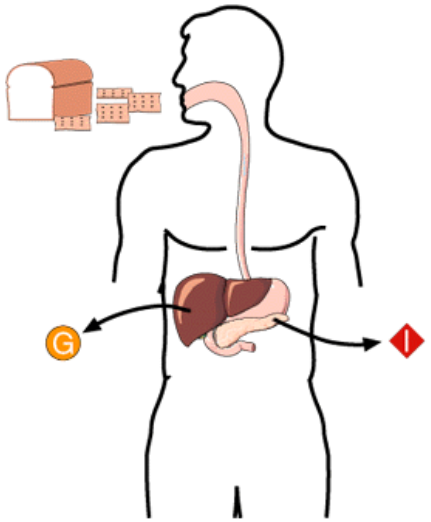
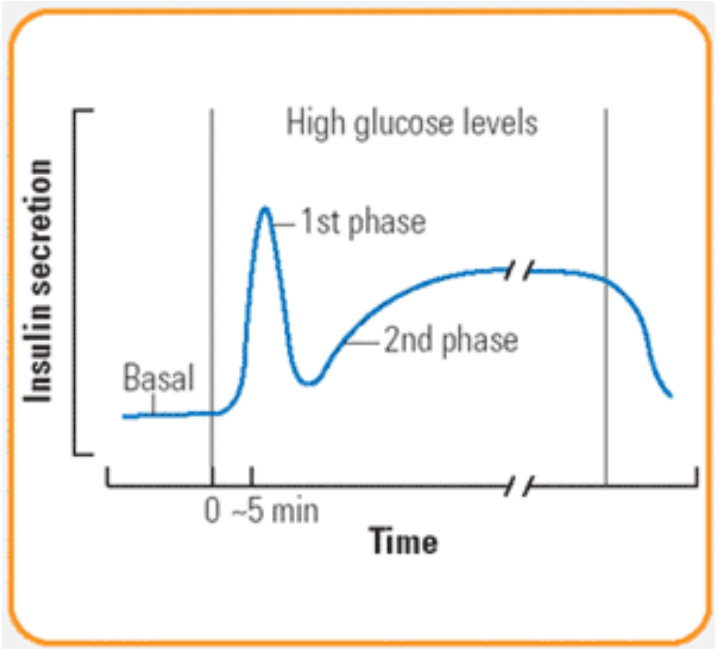
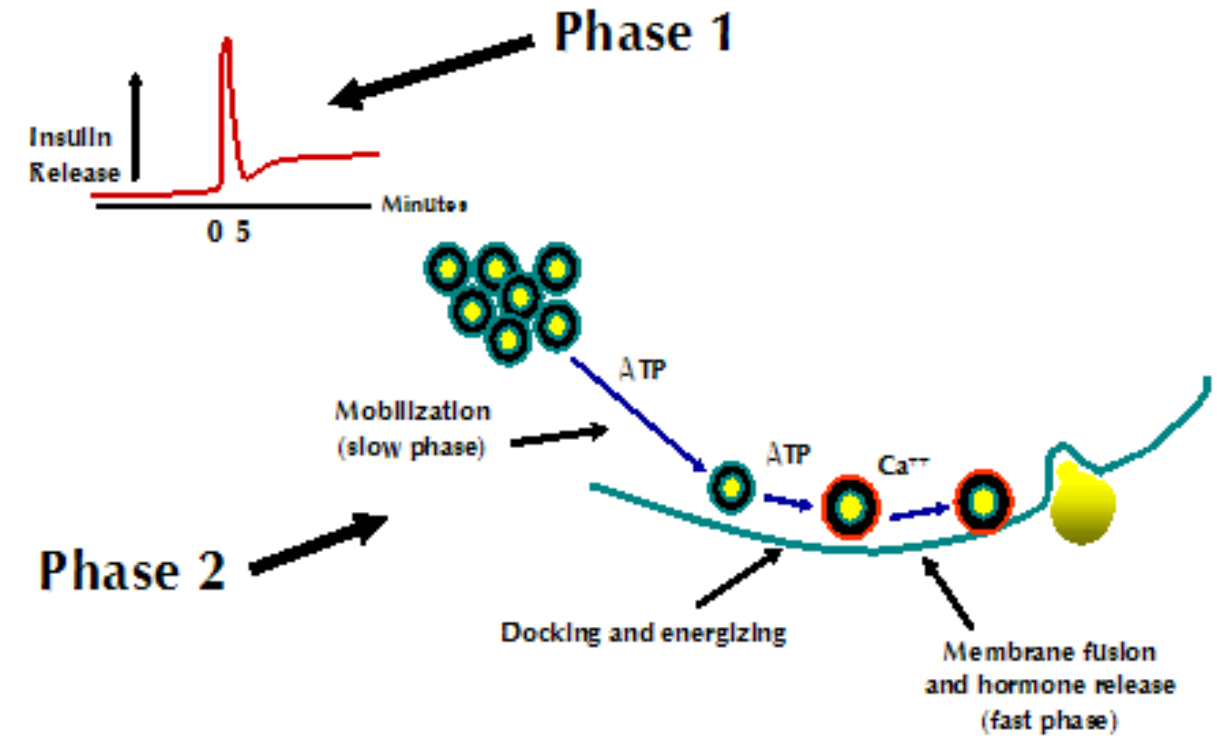




Insulin Secretion is Biphasic



- in vivo not so obvious
  - 1. phase – Glc/K_{ATP}-dependent
  - 2. phase – other secretagogues

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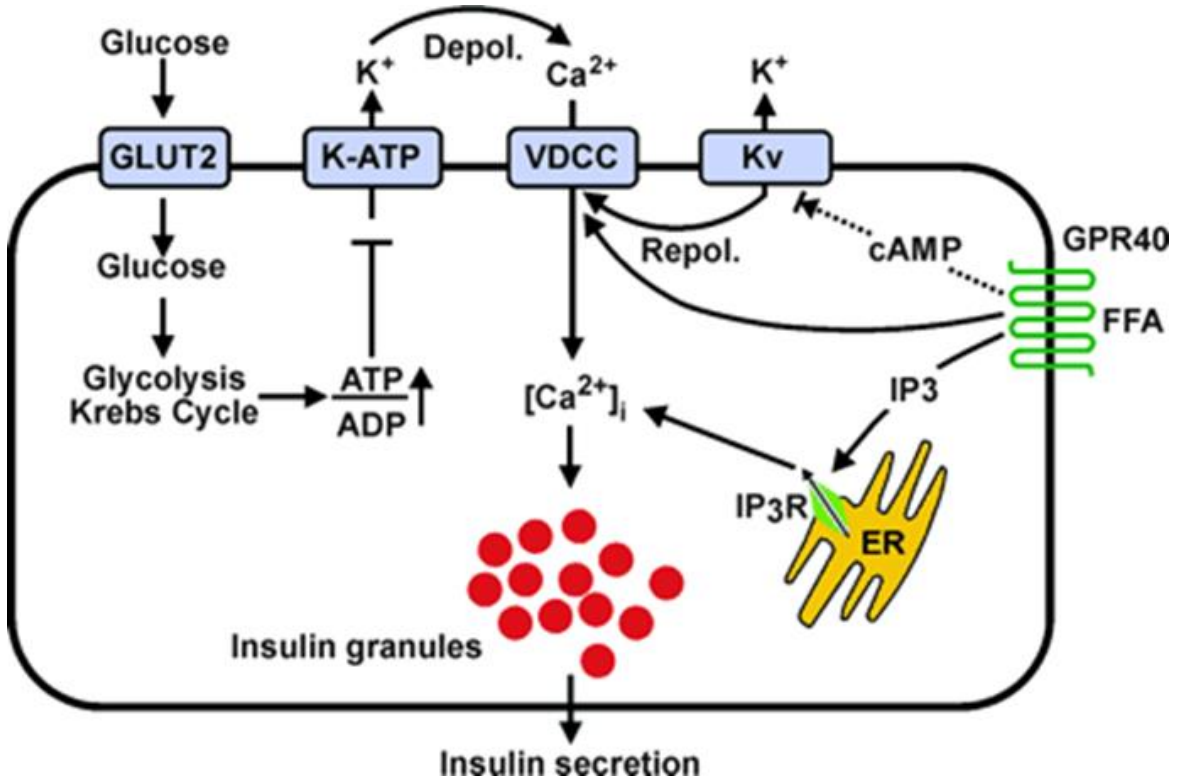
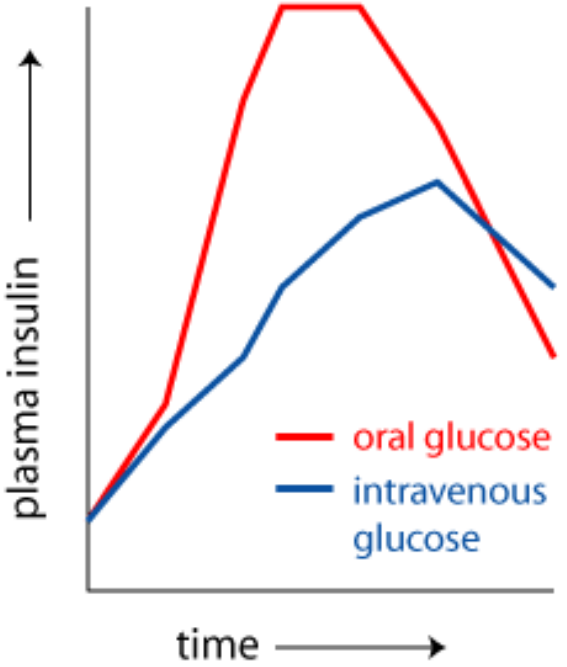
NEFA and insulin secretion

- NEFA can enter cells (incl. B-cells)
  - directly by diffusion across the membrane (short-chain FA) → metabolism (oxidation) → ATP …. insulin secretion
  - via receptor (GPR40) → see the figure
- however, long term exposure to NEFA, esp. long-chain saturated (e.g. palmitate), suppress secretion of insulin and damages B-cells



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



Gula monster (Heloderma suspectum)

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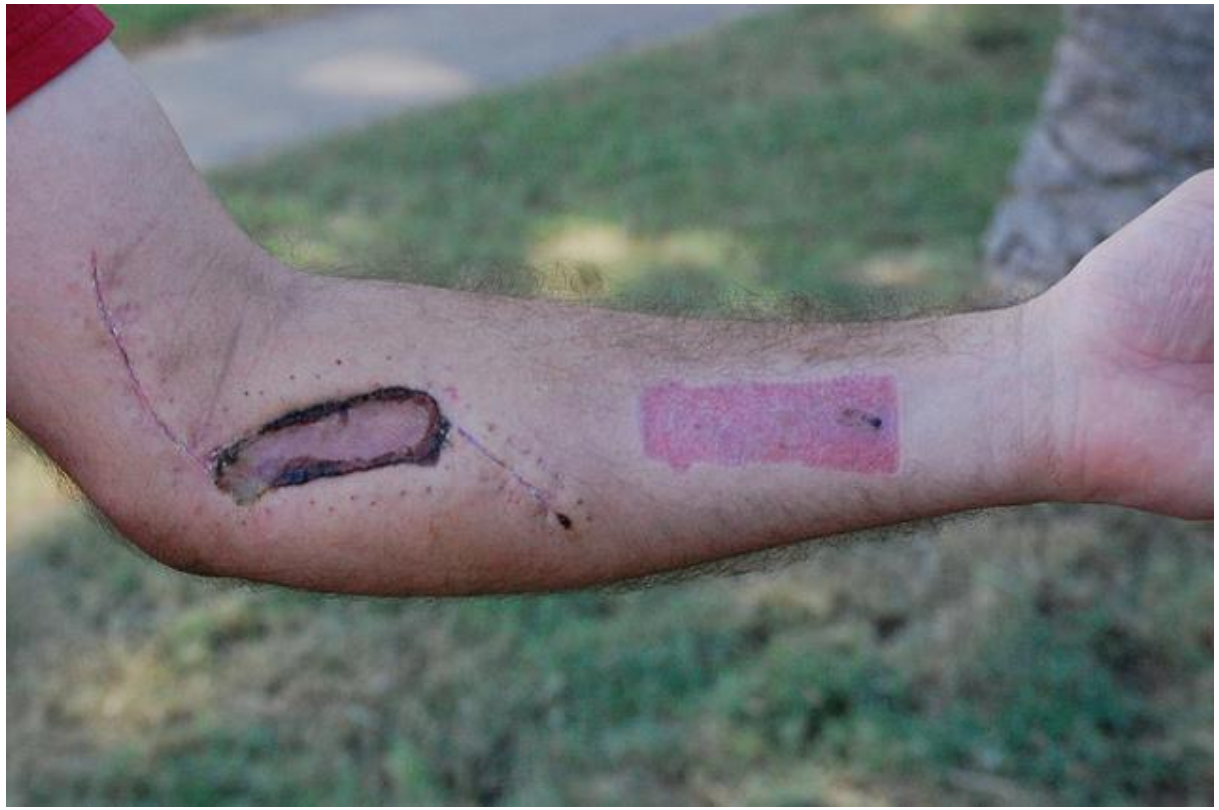
Gila monster



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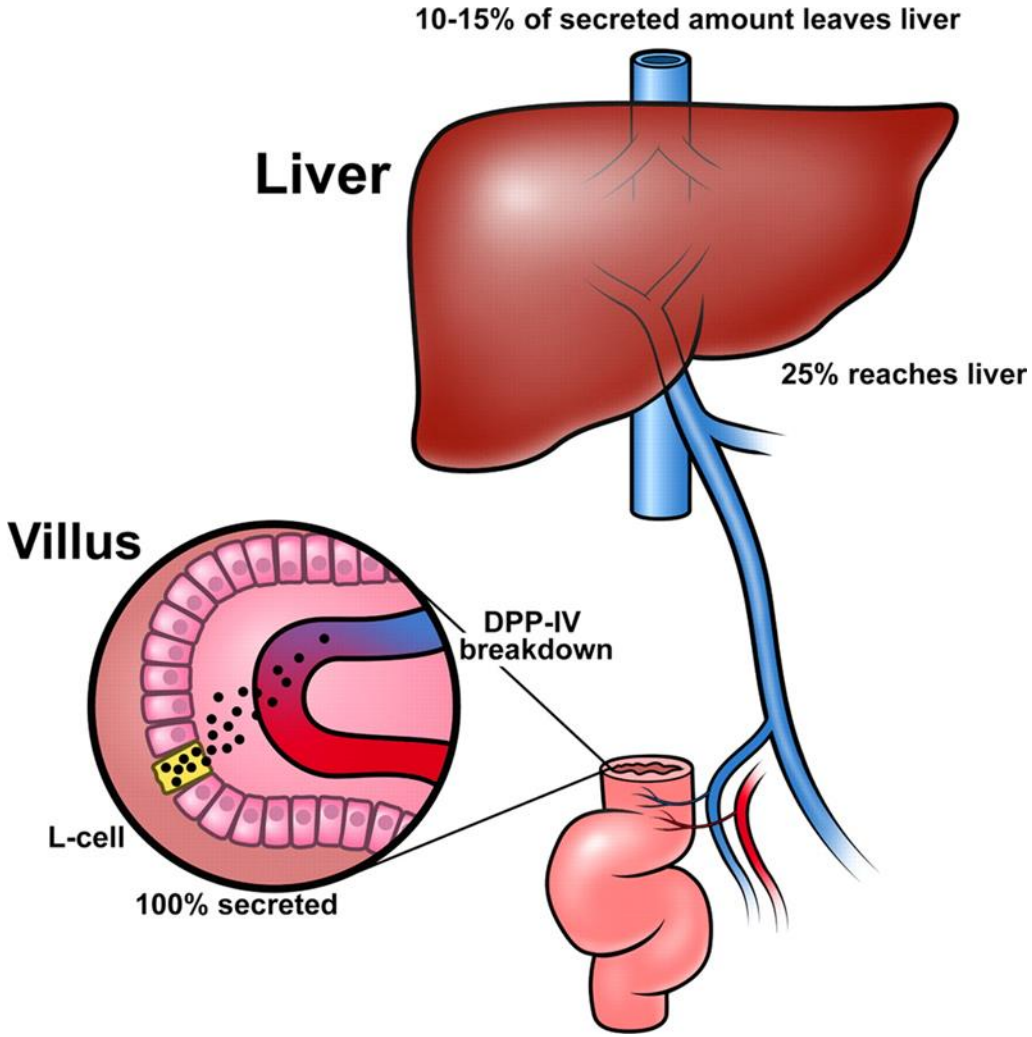
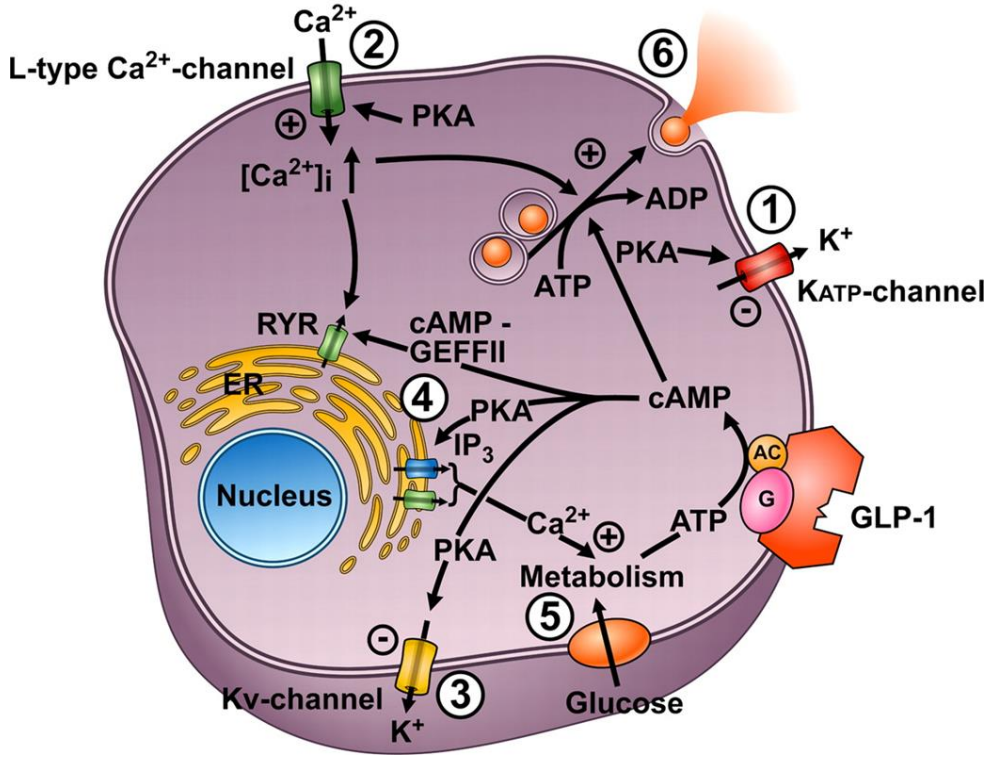
Effect of GLP-1 – anticipation of need to rise insulin





Jens Juul Holst Physiol Rev 2007;87:1409-1439

Physiological Reviews

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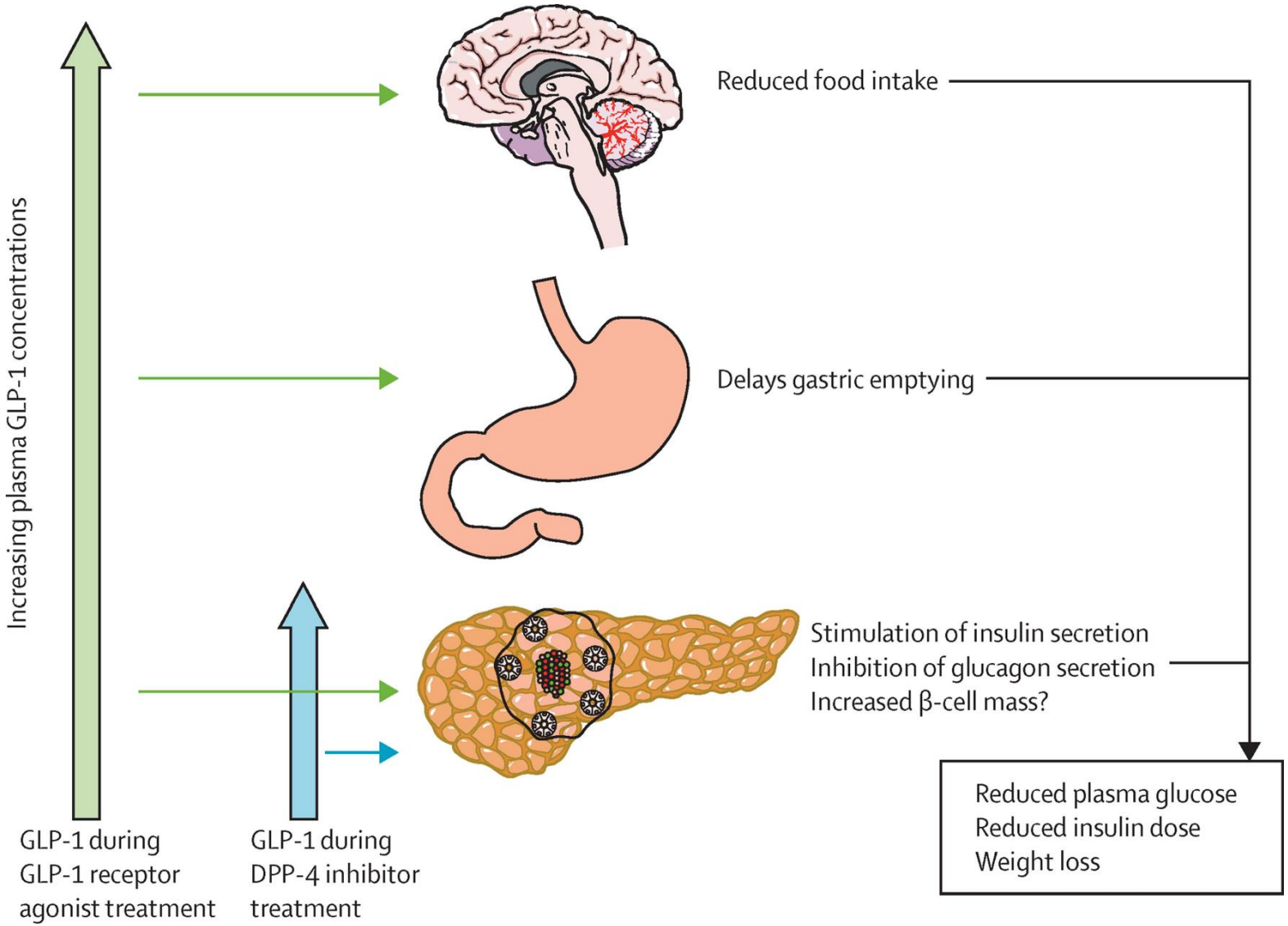
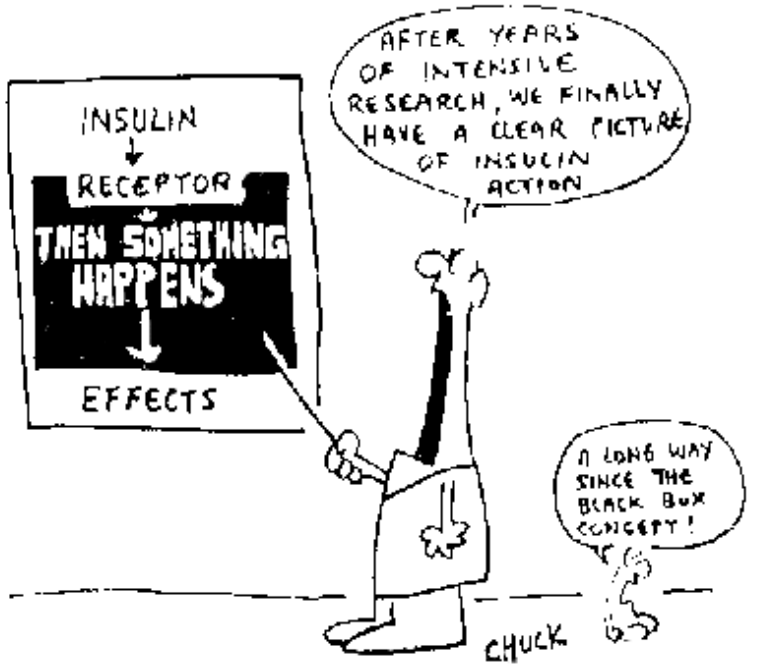
Incretins have systemic effects too





INSULIN SIGNALLING

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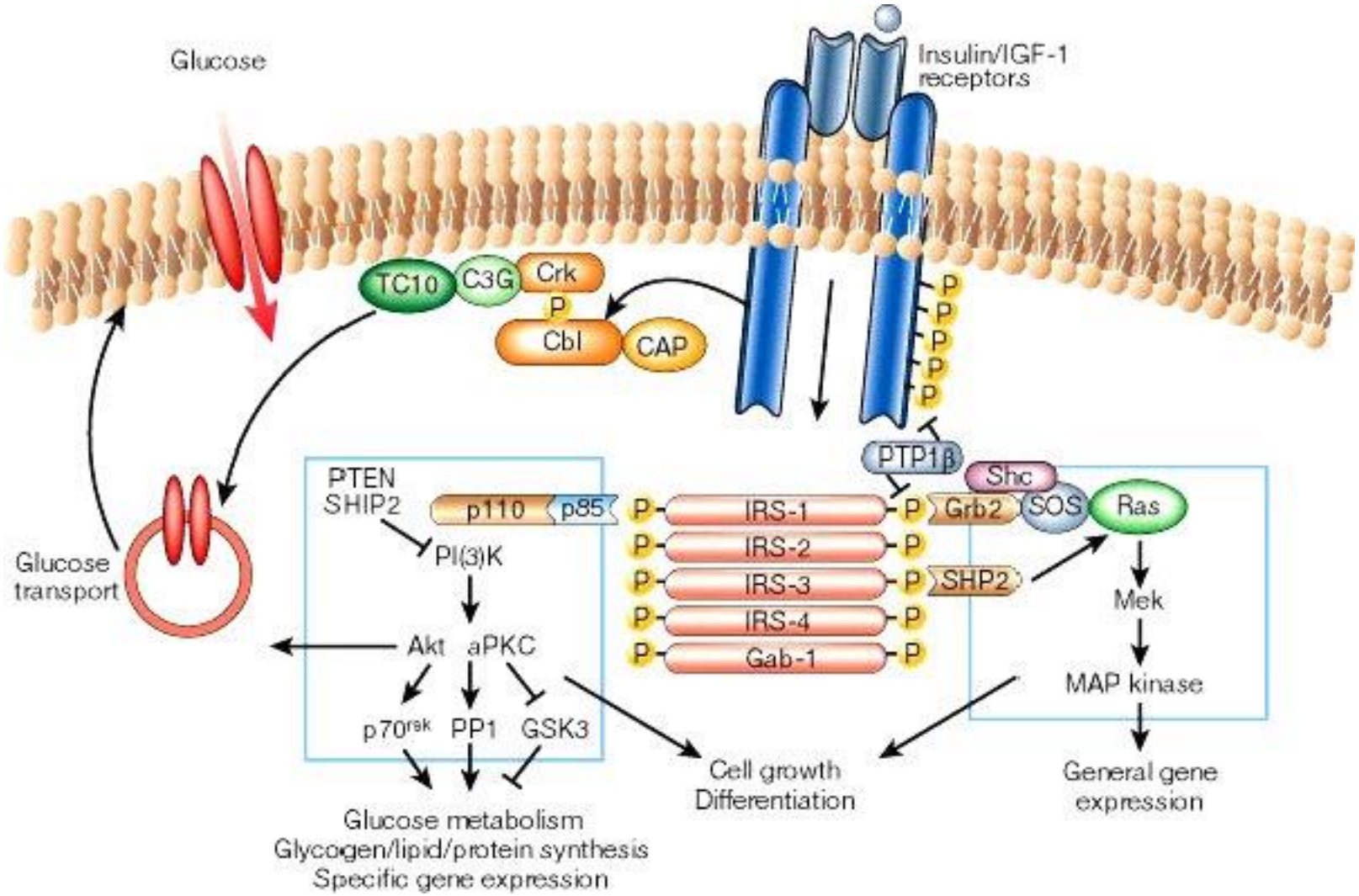
Insulin receptor



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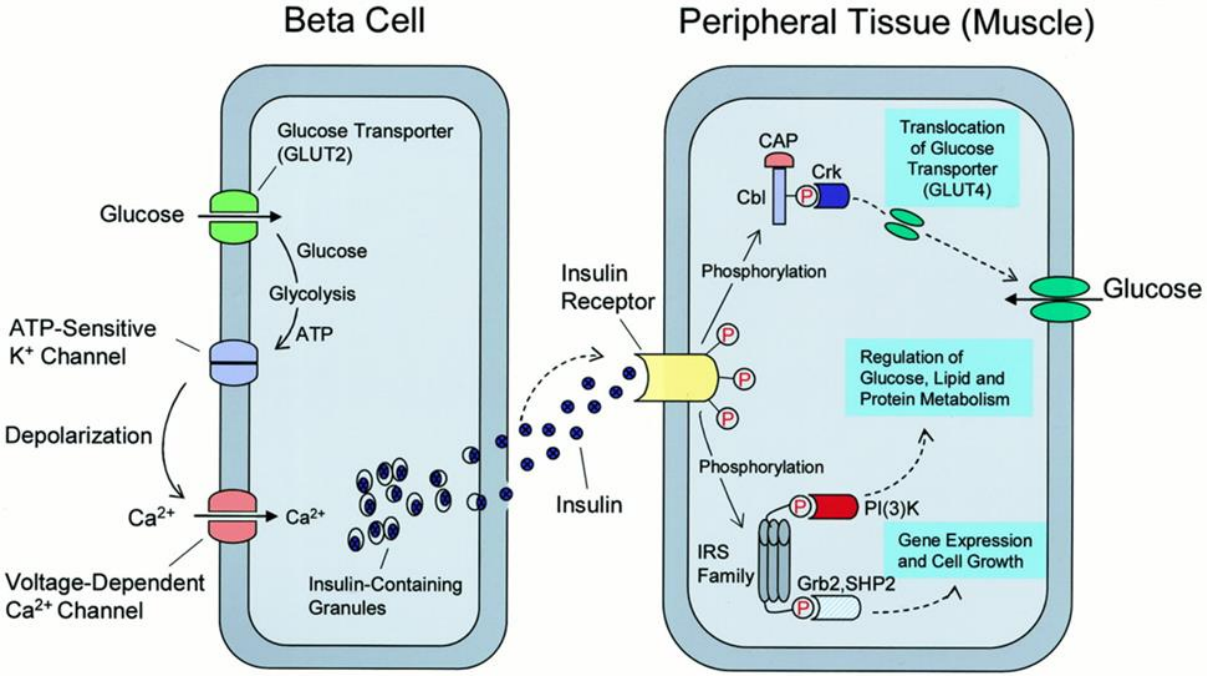
Insulin receptor made simple



- insulin receptor is a **tyrosinkinase** type (2 α and 2 β subunits) receptor
- signal transduction consists of series of phosphorylation events
  - intracellular proteins, other kinases and finaly enzymes
    - i.e. their activation or inhibition
      - activation of anabolic pathways (i.e. glycegenogenesis, lipogenesis)
      - inhibition of catabolic pathways (e.g. lipolysis, glycogenolysis) and gluconeogenesis
- two main effects happen in insulin-dependent tissues
  - (1) ↑ glucose uptake
    - by translocation of GLUT4 in sceleatl muscle and adipose tissue
  - (2) metabolic: IRS → PI-3-K → PDK → PKB (=Akt)
    - → GSK (glycogen-synthase-kinase) → ↑ glycogen synthesis
    - → cAMP phosphodiesterase → inhibition of lipolysis
    - ↓ gluconeogenesis
- ubiquitously (3) ↑ gen. expression (mitogenic effect)
  - MAPK → transcription factors

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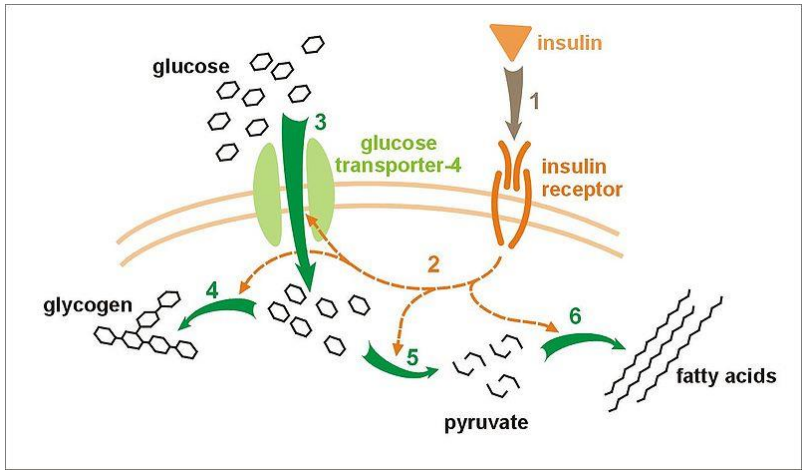
Classification of tissues according to insulin action:

- **insulin-dependent**
  - **skeletal and heart muscle**
  - **adipose tissue**
    - in both glucose uptake facilitated by **GLUT4**, which becomes integrated into cell membrane after insulin receptor activation



  - **liver**
    - metabolic actions

- **insulin-independent**
  - **all others**
    - 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
    - **NOTE skeletal and heart muscle, adipose and liver also express insulin-independent GLUTs**

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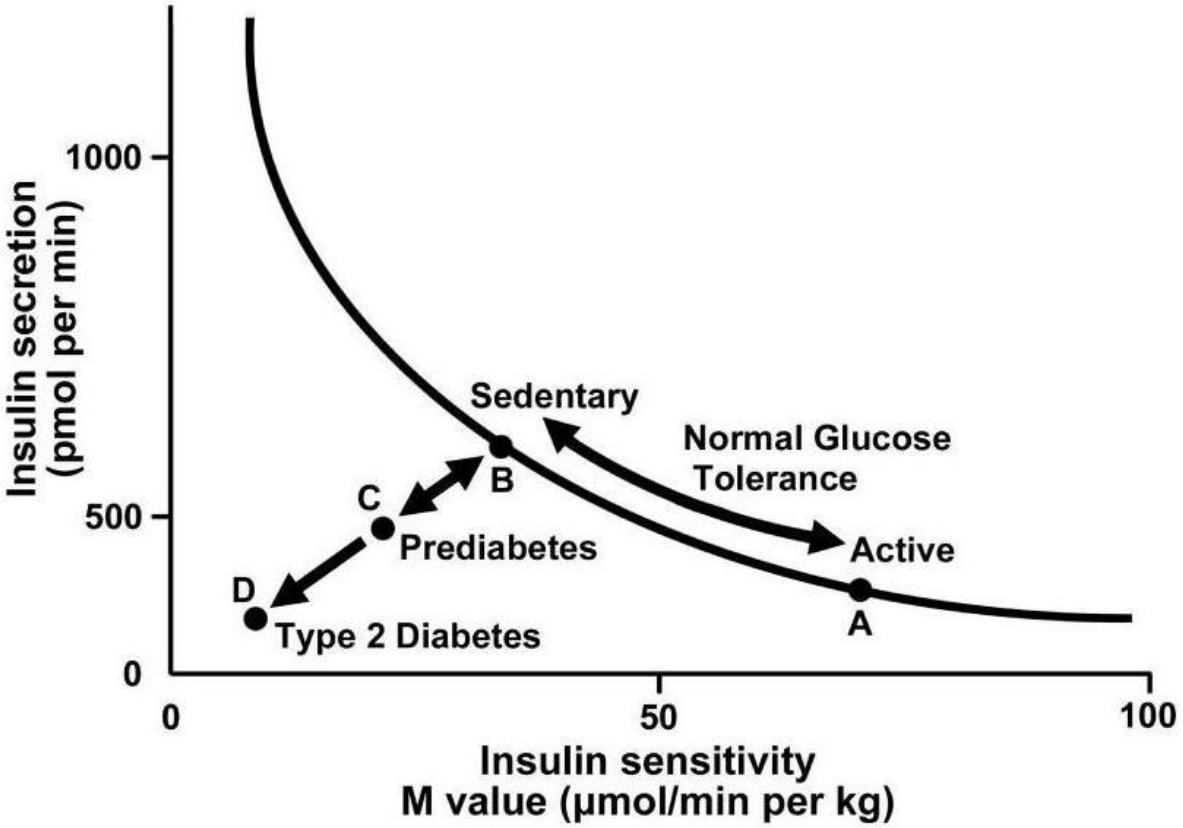
Insulin sensitivity – a hyperbolic relation between i. secretion and sensitivity



- Insulin sensitivity refers to the body's ability to dispose of glucose
  - x-axis represents the amount of glucose cleared at a given insulin dose
- A variety of evidence has shown that active individuals clear greater glucose with lower insulin secretion than sedentary individuals
  - that is, active individuals are more insulin sensitive
  - becoming inactive and or obese makes you insulin resistant
- As sedentary individuals become progressively more insulin resistant, pancreatic beta cells hypertrophy and eventually become unable to secrete sufficient insulin to clear glucose from the blood after a meal
- This end state is referred to as glucose intolerance

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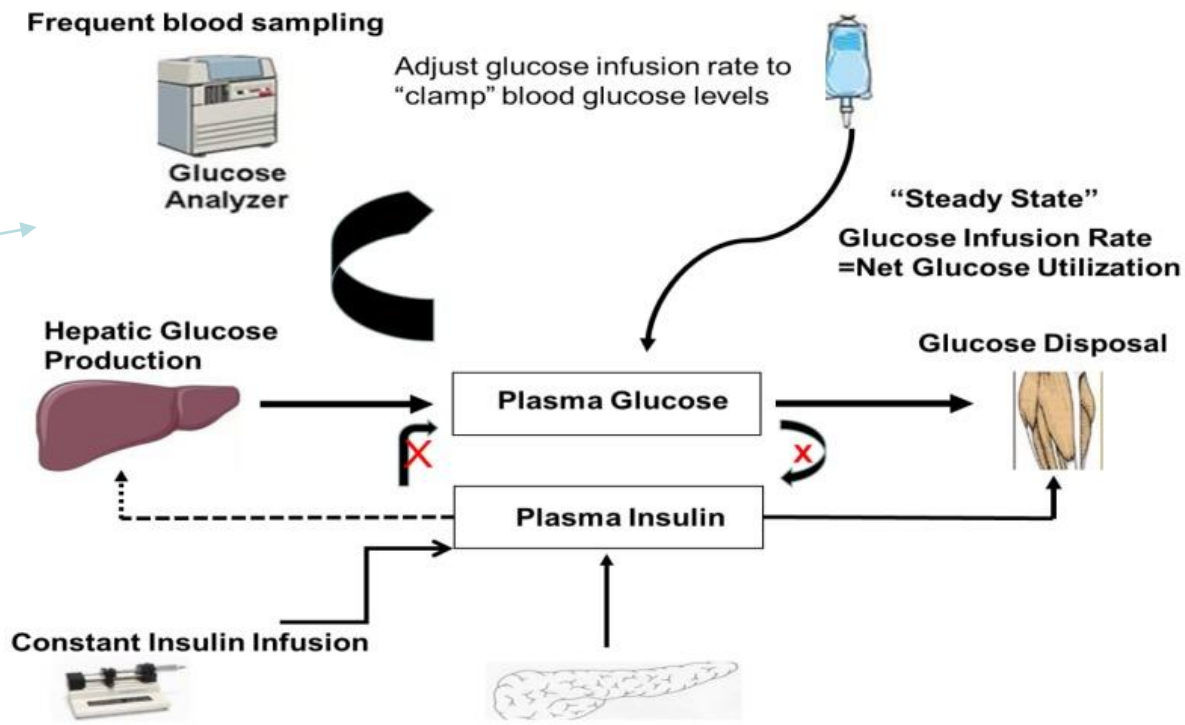
Insulin sensitivity assessment

- insulin sensitivity (= given effect of dose of insulin on individual‘s glycaemia) is a continuous trait
- distinct interindividual variability
- it can be assessed by:
  - hyperinsulinemic euglycemic clamp
  - calculated indexes (based on relationship between glycaemia and insulin during fasting or oGTT)
    - e.g. HOMA, QUICKI, …
- insulin sensitivity changes (= **insulin resistance**) in many situations
  - physiologically in pregnancy
  - pathologically in obesity, inflammation etc.
- **should increasing insulin resistance always lead to compensatory increase of insulin secretion than glycaemia would stay stable**
  - however capacity to compensatory increase secretion of insulin by beta-cells is apparently limited



CLASSIFICATION OF DM, T1DM A T2DM

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Pathophysiology of 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
    - **insulin resistance in peripheral tissues + secondary failure of β-cells of the islets of Langerhans**
      - receptor defect
      - **post-receptor defect**
- prevalence of DM in general population 5%, over the age of 65 already 25%

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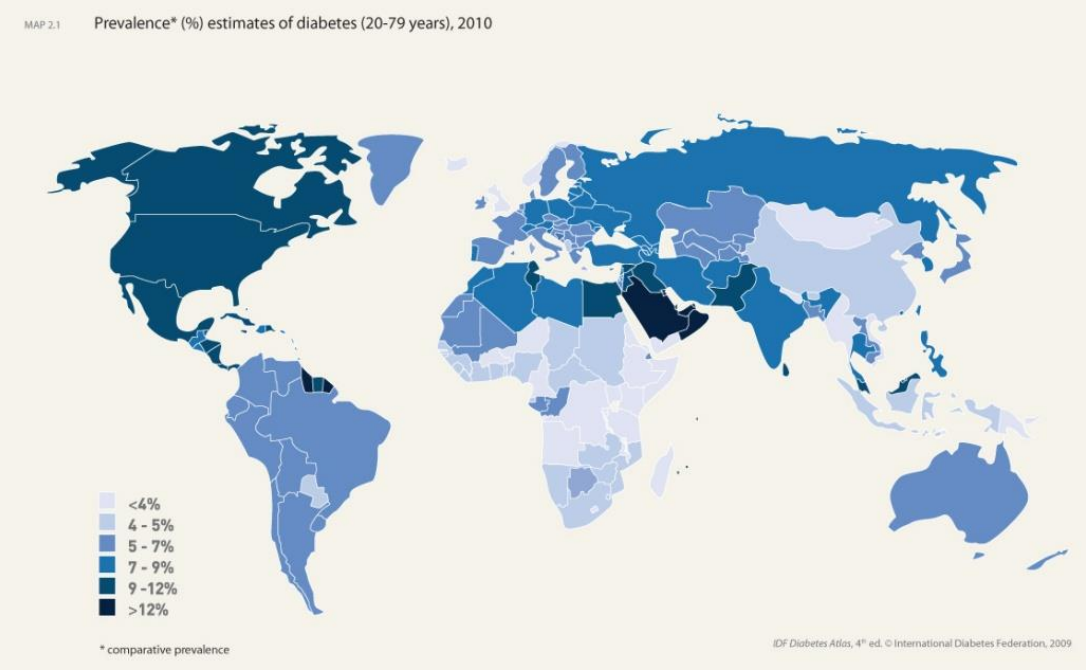
Prevalence (%) of diabetes (population 20-79 years)

2010 – 4.3 bil. (from a total of 7 bil.)

285 mil. diabetics

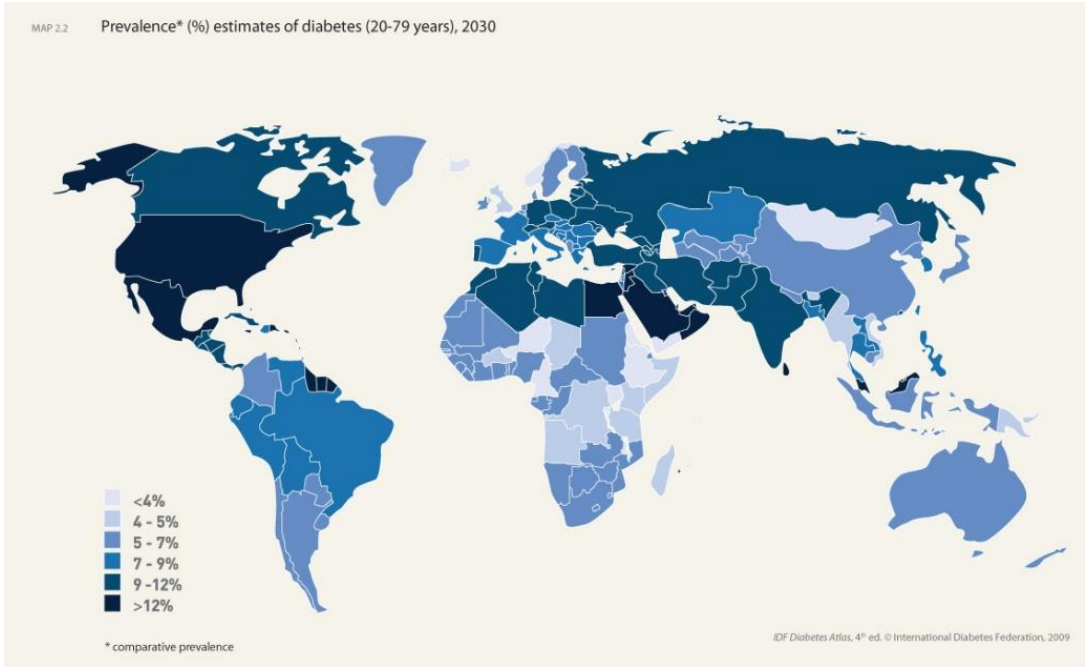
0.75 mil. diabetics in Czech rep.



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]

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Classification of DM

- **Diabetes mellitus type 1 (T1DM) ~5%**
- **Diabetes mellitus type 2 (T2DM) ~90%**
- **Gestational diabetes mellitus (GDM) ~10 - 15% of pregnant women**
- **Monogenic DM ~2%**
  - neonatal
  - MODY (1 - 6)
- **Secondary**
  - diseases of exocrine pancreas
    - chron. pancreatitis, tumor, cystic fibrosis, hemochromatosis
  - endocrine disorders (insulin contra regulation)
  - Cushing syndrome, acromegaly, pheochromocytoma, hyperthyreosis
- **Drug induced** (iatrogenic) DM
  - glucocorticoids and others
- Other forms (syndromic)
  - mutation of mitochondrial DNA
  - genetic defects leading to insulin resistance (type A insulin resistance, leprechaunismus, Rabson-Mendenhal syndrome, lipoatrophic DM)
  - other genetic syndromes associated with DM (m. Down, Klinefelter, Turner)

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T2DM

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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

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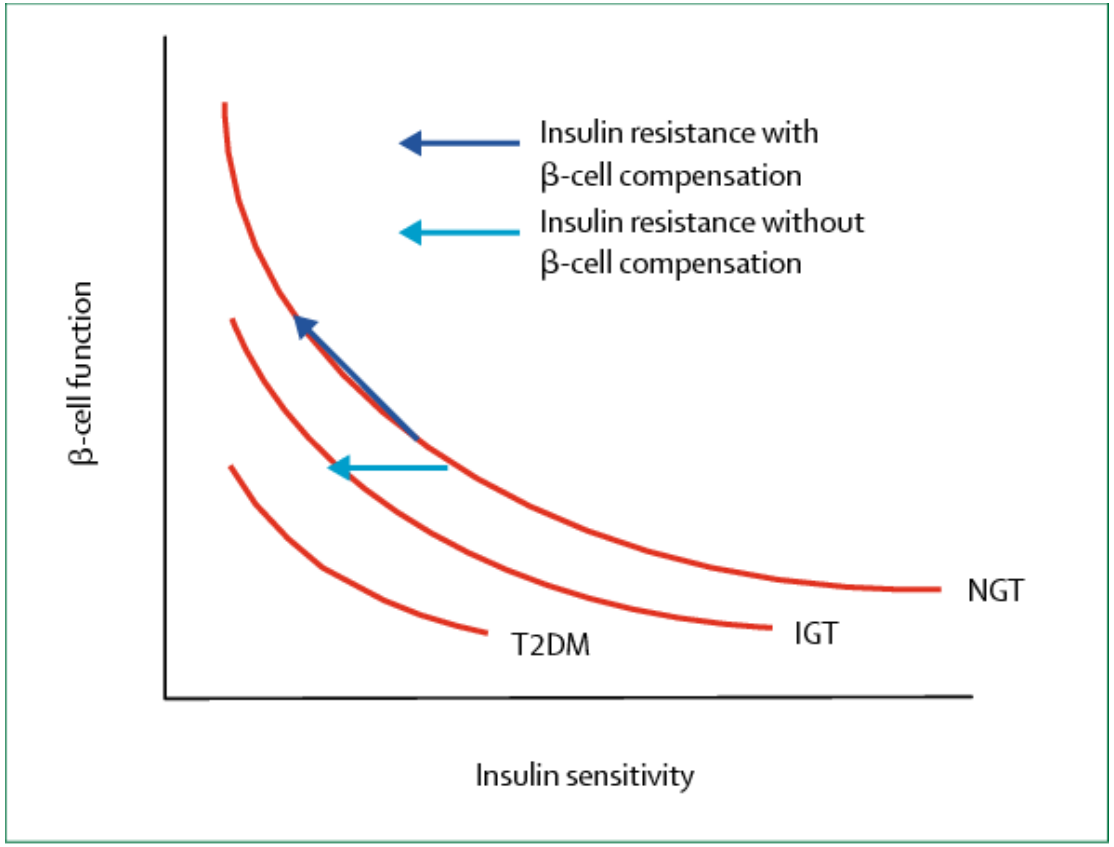
From insulin resistance to T2DM

- insulin sensitivity changes (= **insulin resistance**) in many situations
  - physiologically in pregnancy
  - pathologically in obesity, inflammation etc.
- **should increasing insulin resistance always lead to compensatory increase of insulin secretion than glycaemia would stay stable**
  - however capacity to compensatory increase secretion of insulin by beta-cells is apparently limited
- 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"??**
  - see later T2DM genetics



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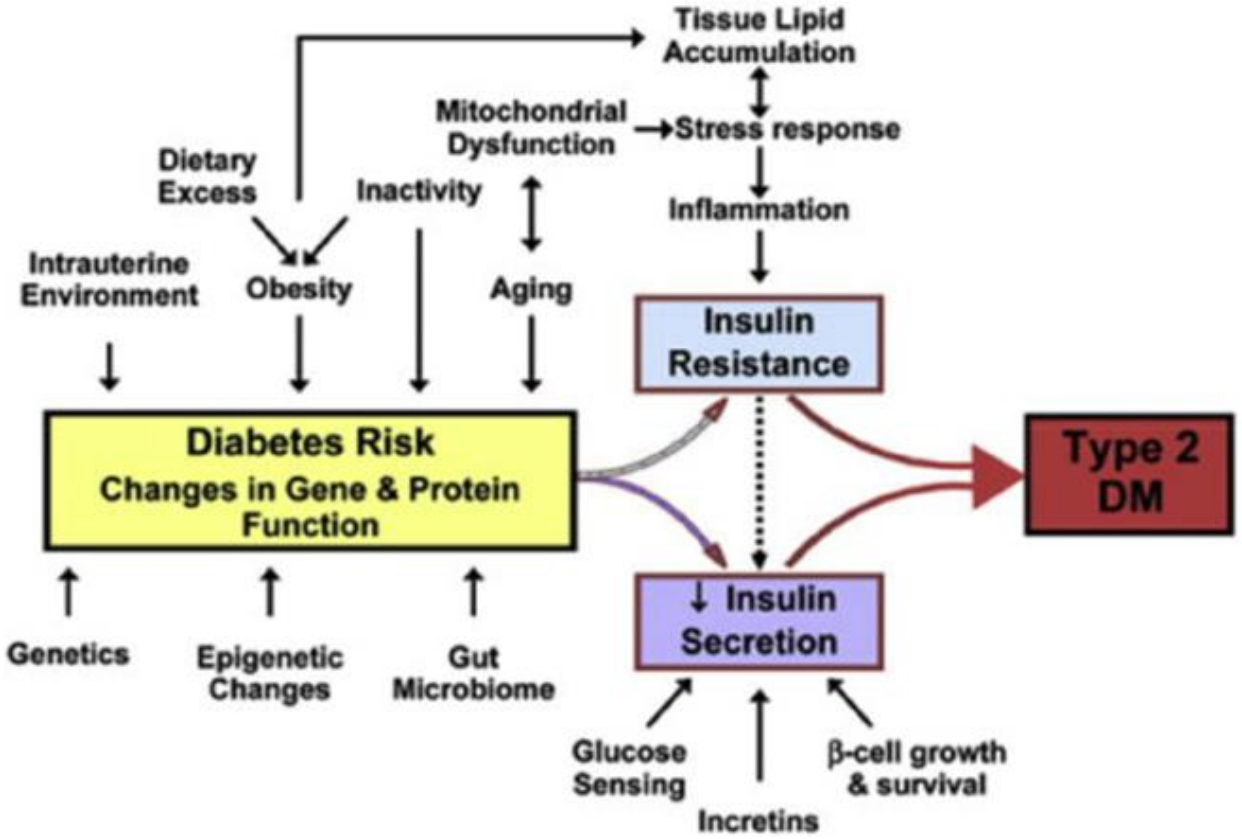
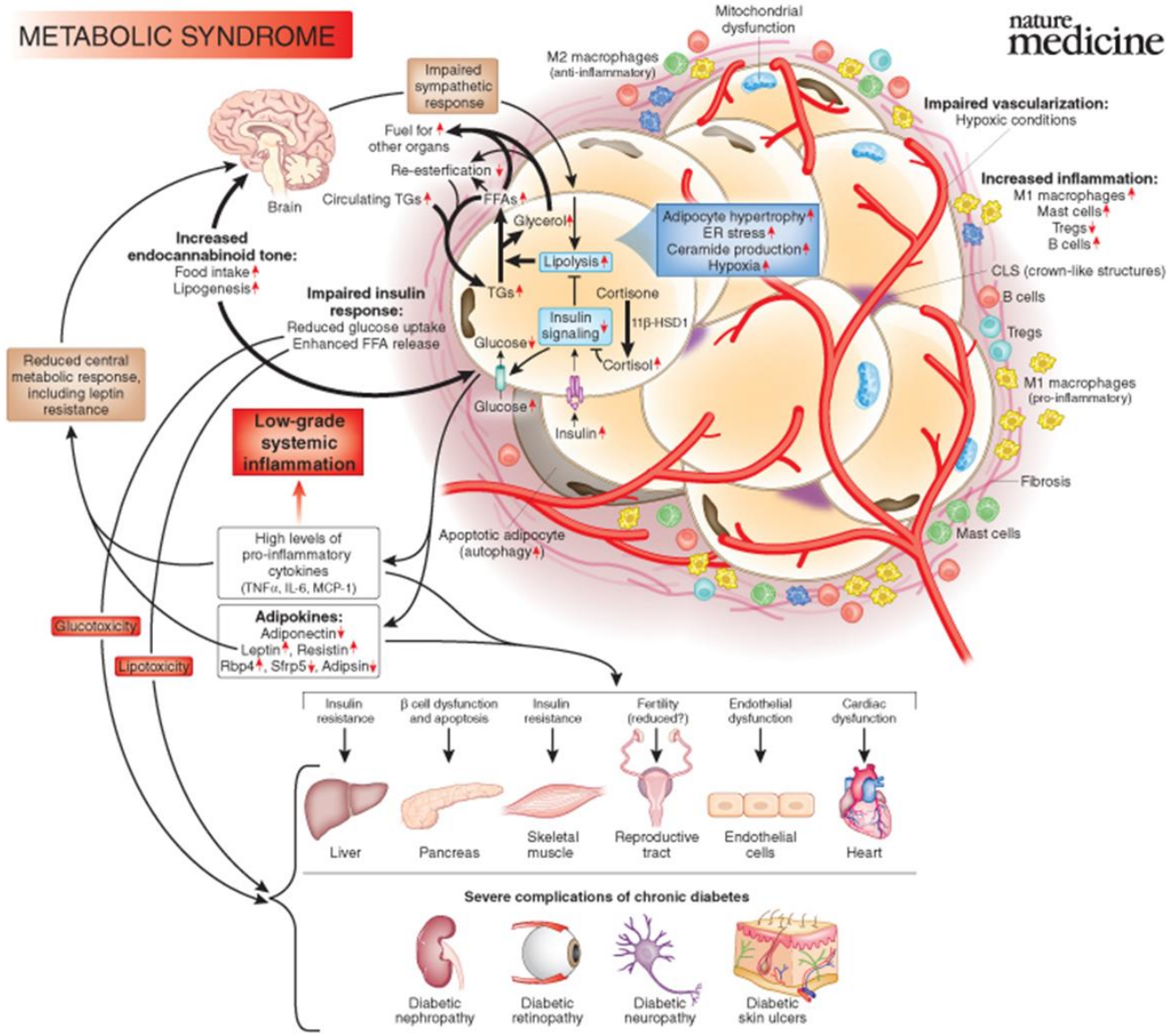
What determines insulin resistance and/or insulin secretion?

- insulin resistance
  - genetic predisposition (polygenic) – thrifty genotype/phenotype
  - acquired factors
    - diet – high fat/low fiber
      - competition of Gls with NEFA!!!
    - **obesity – 90% T2DM are obese**
      - effect of adipokines from adipose tissue (visceral!)
      - low-grade inflammation
      - lipid spillover – competition with Glc
      - several other mechaisms
    - physical inactivity - ↓ mobilization of GLUT4
    - down-regulation of ins. receptor due to hyperinsulinemia
- impairment of insulin secretion
  - inherited factors - genetics
    - fewer B-cells (~20-40%)
    - defect of 1. phase of Ins secretion (~80% reduction)
  - acquired factors
    - – gluco- and lipotoxicity for B-cells



Metabolic syndrome – a unifying effect of obesity



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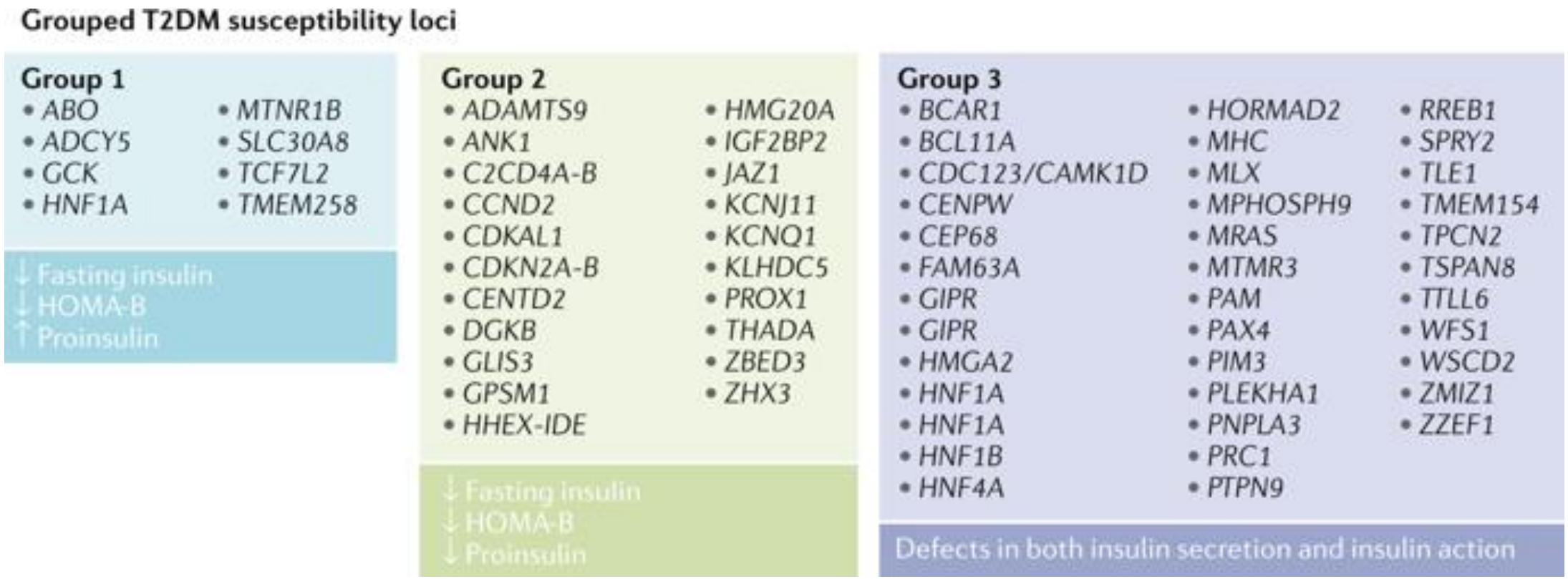
Genetics of T2DM



- Genome-wide association studies (GWAS) have identified over 400 genetic signals that are associated with altered risk of T2DM. Human physiology and epigenomic data support a central role for the pancreatic islet in the pathogenesis of T2DM

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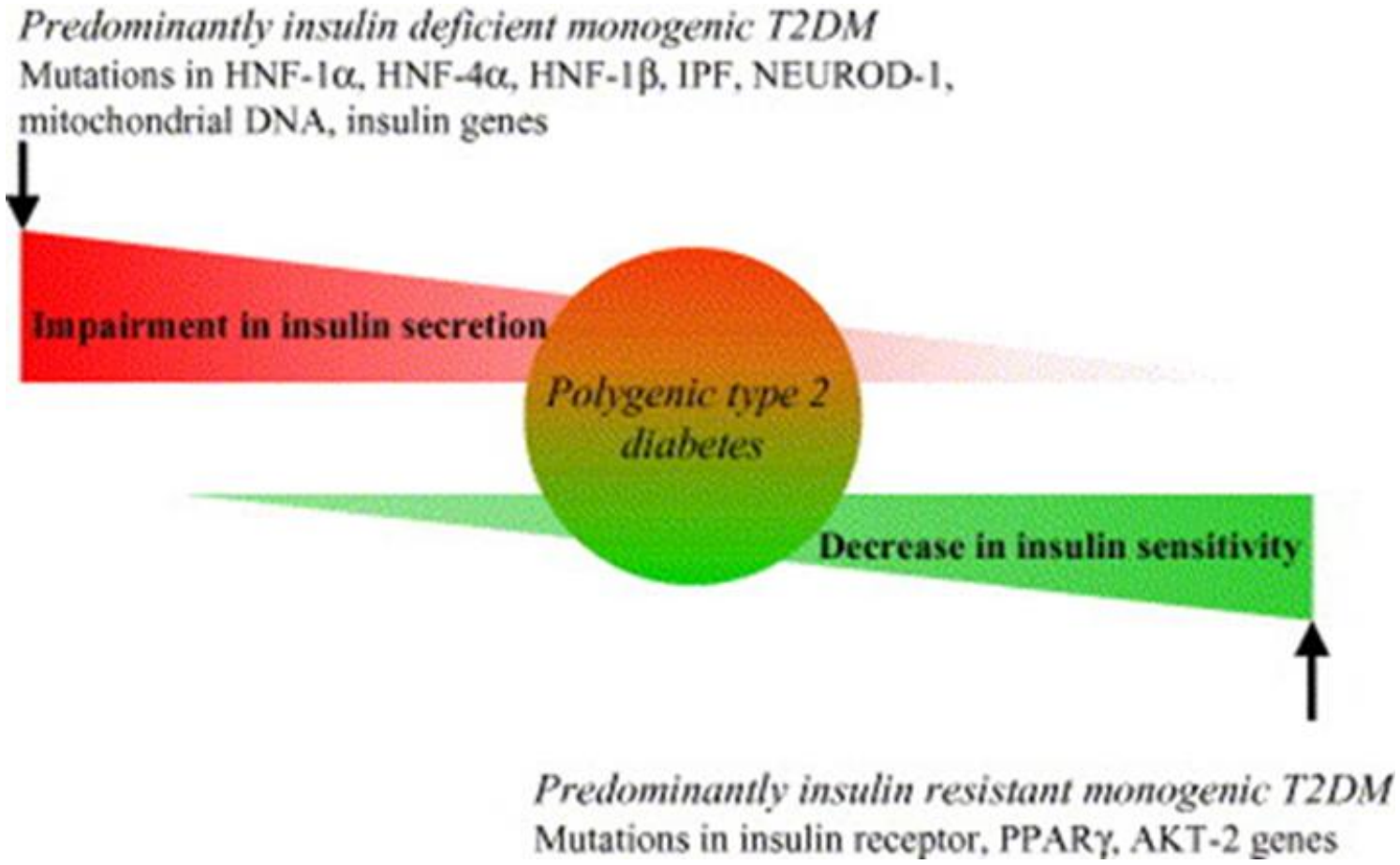
Genetics of T2DM – a spectrum of impairments



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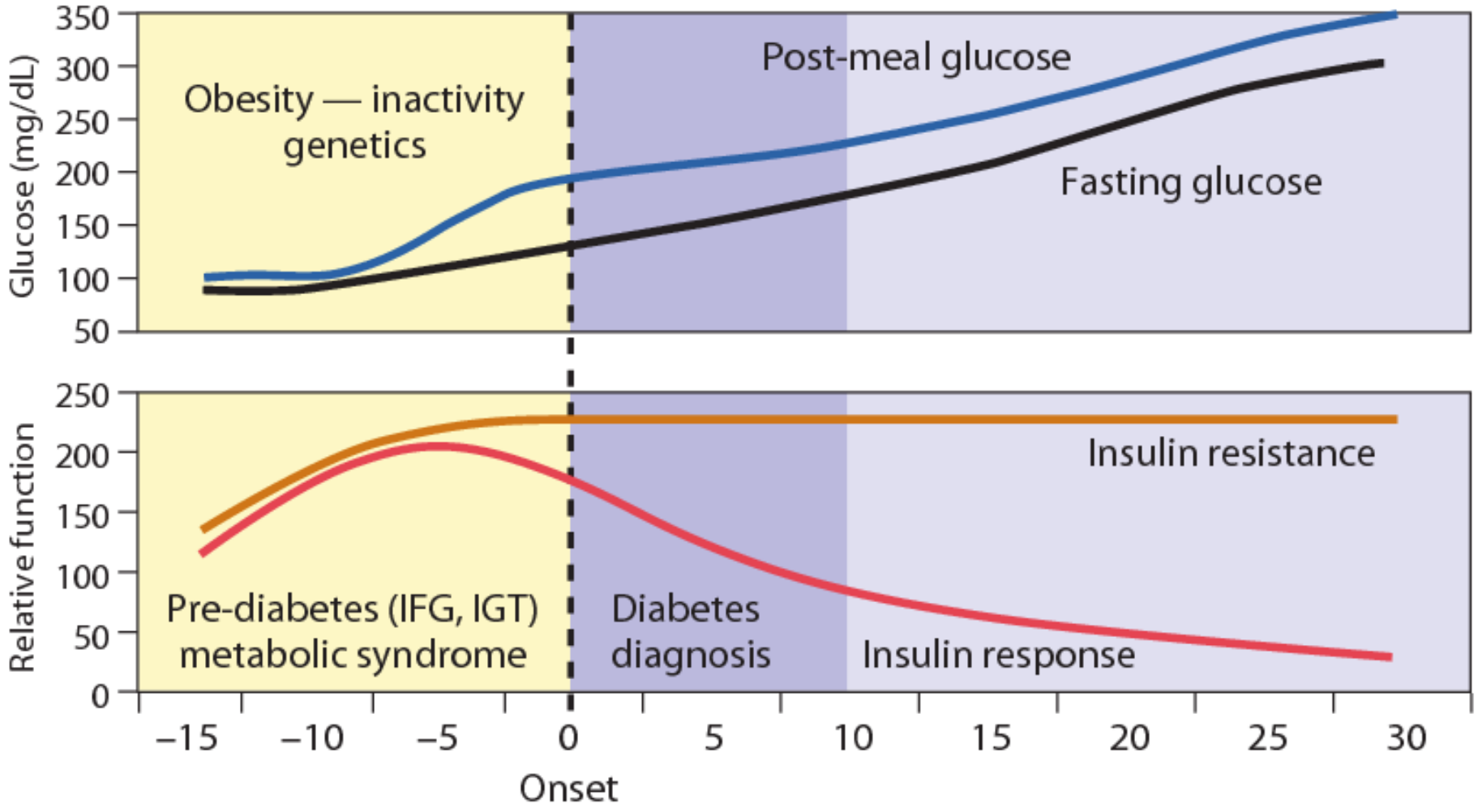
Natural history of T2DM – time course



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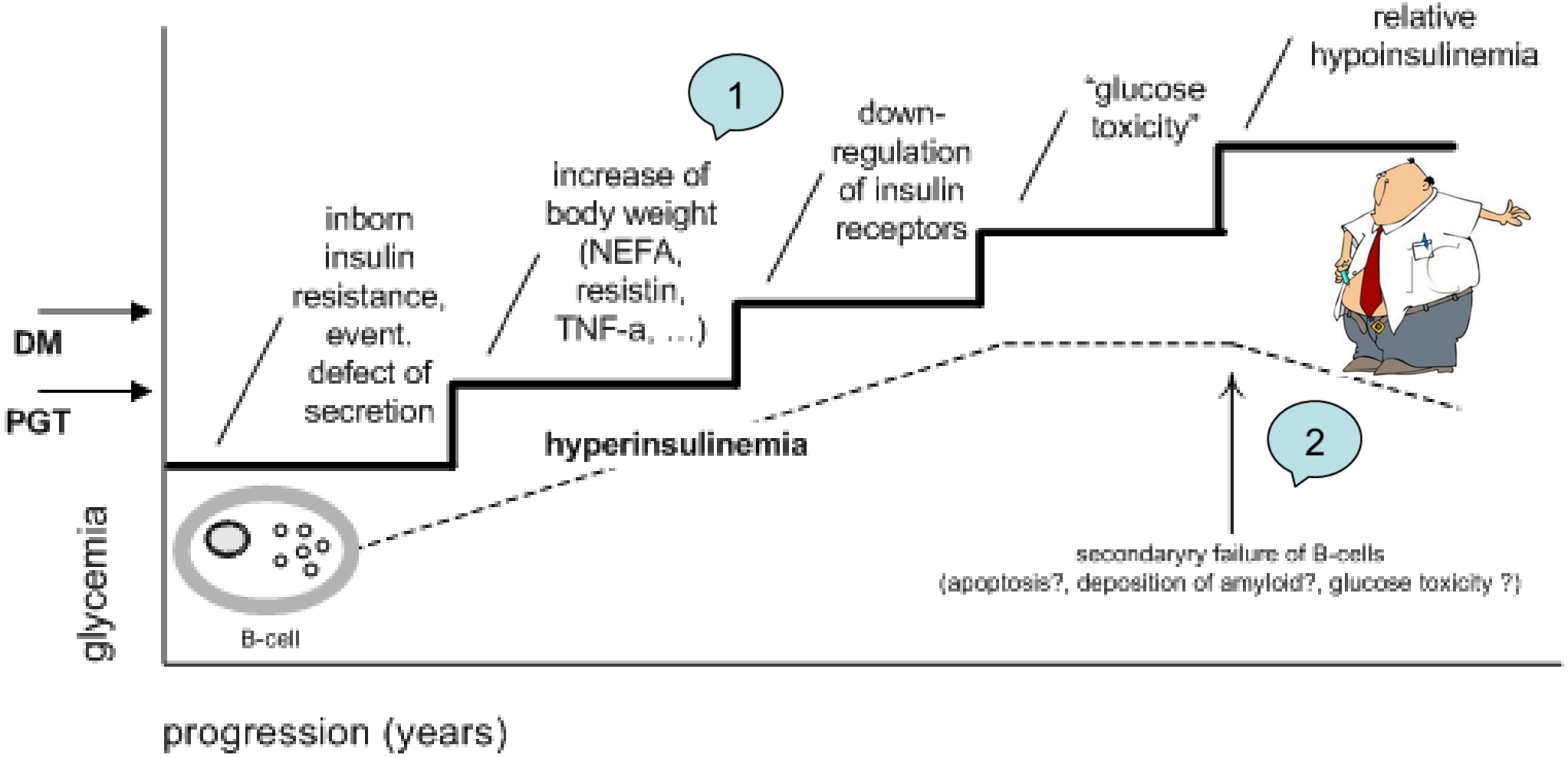
Natural history of T2DM – disease mechanisms



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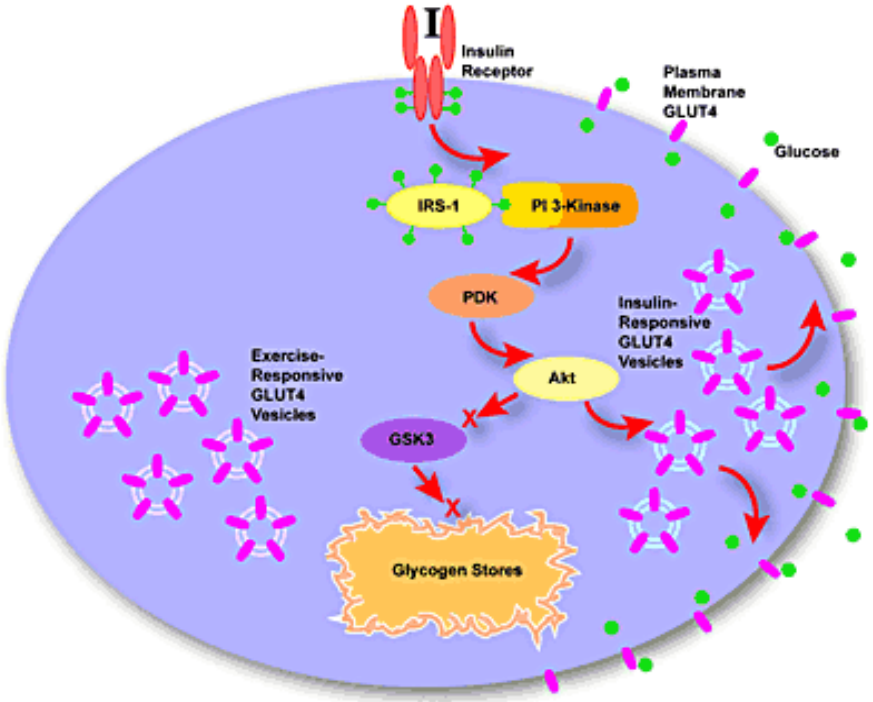
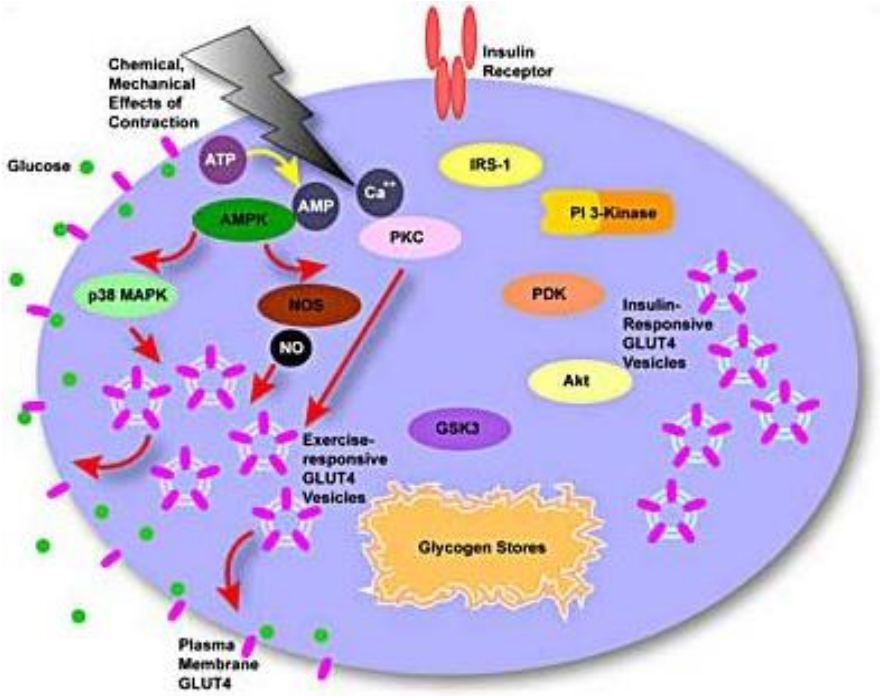
1 Insulin- and “sport”-dependent translocation of GLUT4





- 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

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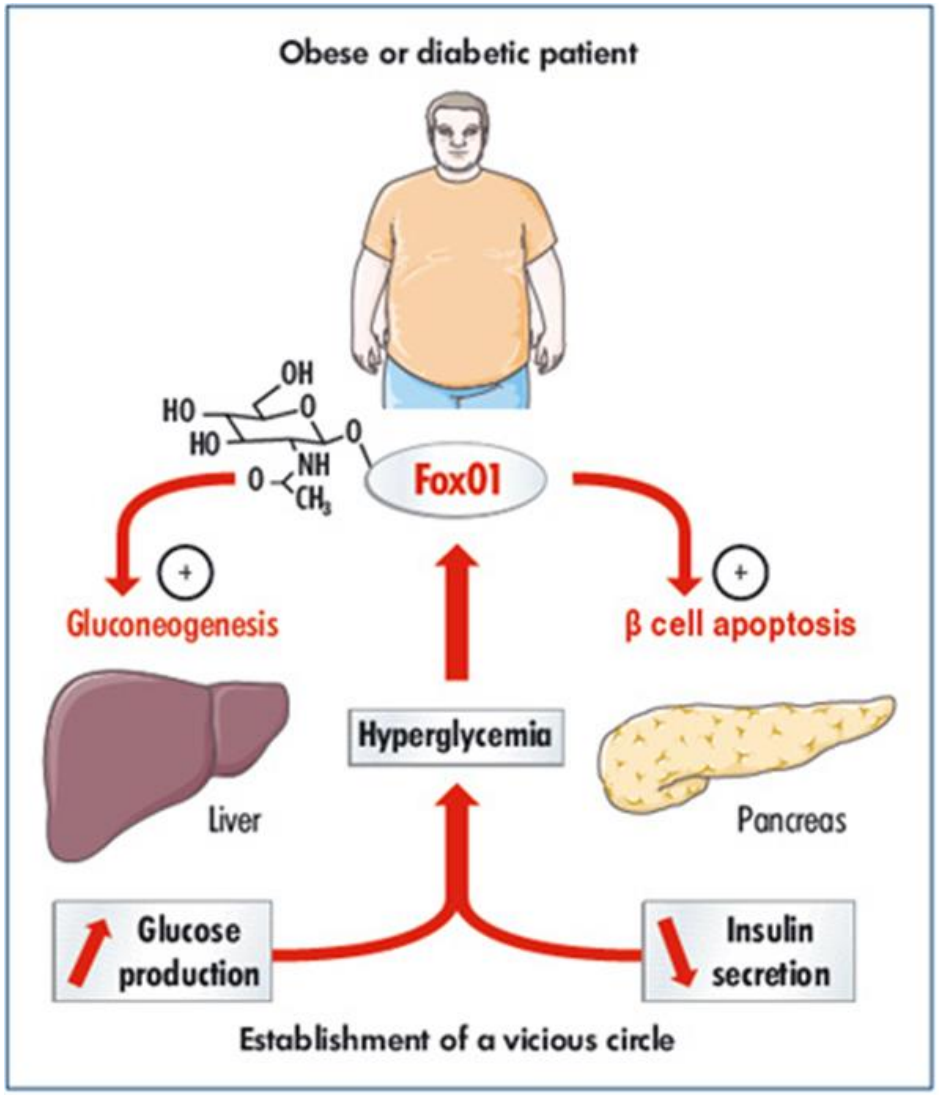
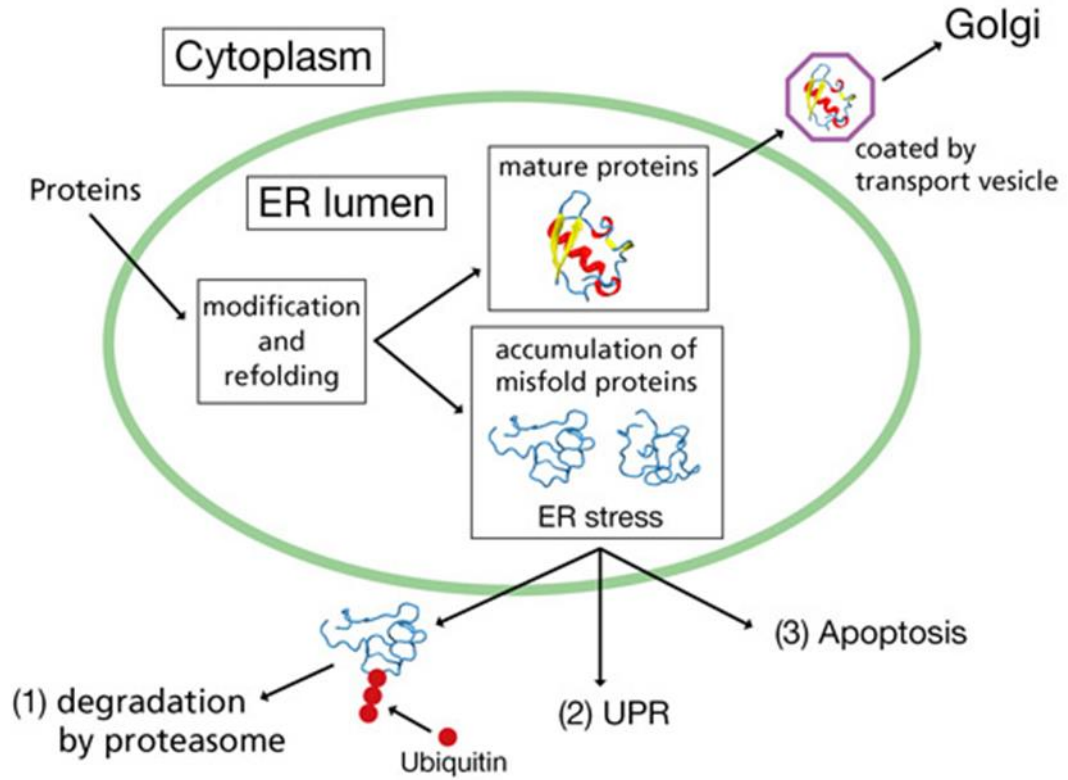
2 Secondary failure of β cells

- hyperglycemia induces:
  - oxidative stress
  - endoplasmic reticulum (ER) stress
- high concentration of NEFA causes lipotoxicity
  - short term increase of NEFA stimulates secretion of insulin
  - long term exposure to NEFA, esp. long-chain saturated (e.g. palmitate), suppress secretion of insulin and damages B-cells
    - ↑ ceramide → **apoptosis**



ER stress → Unfolded protein response

- The unfolded protein response (UPR) is activated in response to an accumulation of unfolded or misfolded proteins in the lumen of ER
  - incl. insulin in β-cells
- UPR has two primary aims:
  - initially to restore normal function of the cell by halting protein translation and activate the signaling pathways that lead to increasing the production of molecular chaperones involved in protein folding
  - if these objectives are not achieved within a certain time lapse or the disruption is prolonged, the UPR aims to apoptosis



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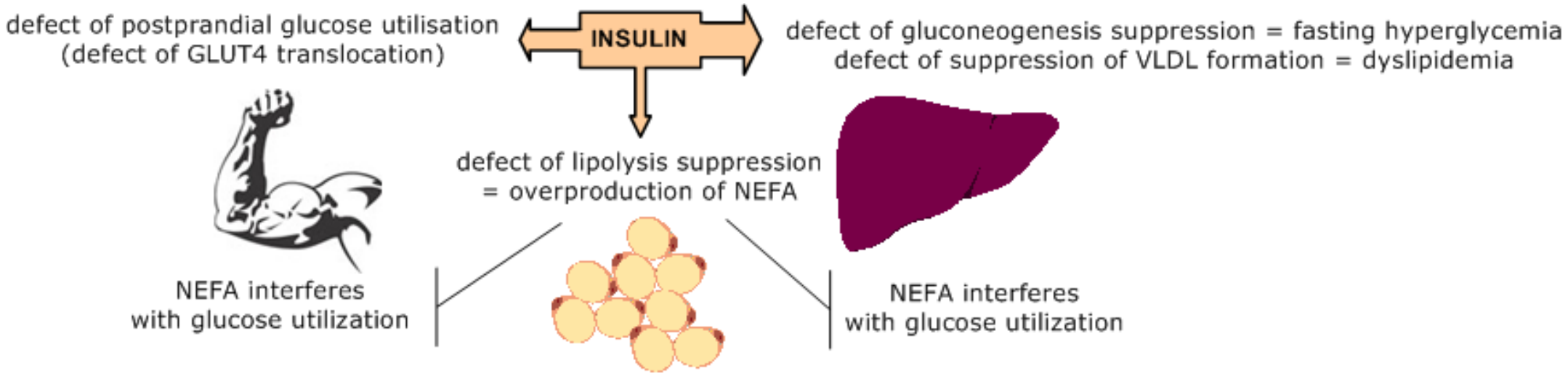
Overt T2DM



- manifest T2DM is characterized by (variable degree of):
  - fasting hyperglycemia (due to gluconeogenesis)
    - **insulin resistance in liver**
  - postprandial hyperglycemia (due to decreased peripheral glucose uptake
    - **insulin resistance in muscle and adipose tissue**
  - mixed dyslipidemia
    - increased plasma NEFA (due to unsuppressed lipolysis)
      - **insulin resistance in adipose tissue**
    - pro-atherogenic dyslipidemia (due to stimulated VLDL production in liver)
      - **substrate effect**

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GESTATIONAL DM (GDM)

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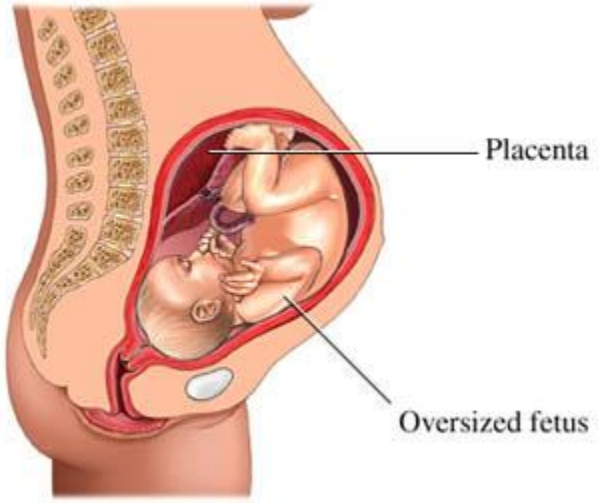
Gestational diabetes mellitus (GDM)

- GDM develops during pregnancy (gestation) and it is one of the most common health problems of pregnancy
  - **up to 10%** of expectant mothers
- GDM is a serious problem because high blood sugar **affect both mother and offspring**
- GDM pathophysiology
  - hormonal changes in physiological pregnancy (i.e. **placental hormones**) cause mild **insulin resistance**
    - this is beneficial for the foetus and baby since glucose is the nutrient and insulin a growth hormone
    - placenta is ready and glucose-screening test is thus performed typically between 24 and 28 weeks
  - this requires additional insulin and normal pancreas can keep up with increased demands
  - if not, blood glucose levels rise too high, resulting in GDM
    - **risk factors**: age, overweight/obesity, susceptibility genes for T2DM, diet
- maternal hyperglycaemia stimulates **baby's pancreas to produce more insulin** to process the extra glucose
  - as a result baby can put on extra weight (**macrosomia**) with subsequent **complications during the birth** (shoulder dystocia, fractured bone or nerve damage)
    - hence the recommendation for early caesarean section
  - additionally, foetal hyperinsulinemia increases the risk of **post-delivery hypoglycaemia**
  - babies who have excessive fat stores as a result of high maternal sugar levels during pregnancy often continue to be overweight in childhood and adulthood (**foetal programming**)
- blood sugar usually returns to normal soon after delivery, however, GDM increases the **risk** for getting it again during the future pregnancy and for developing diabetes (**T2DM**) later in life (up to **50% post-GDM subjects**!!!)



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T1DM

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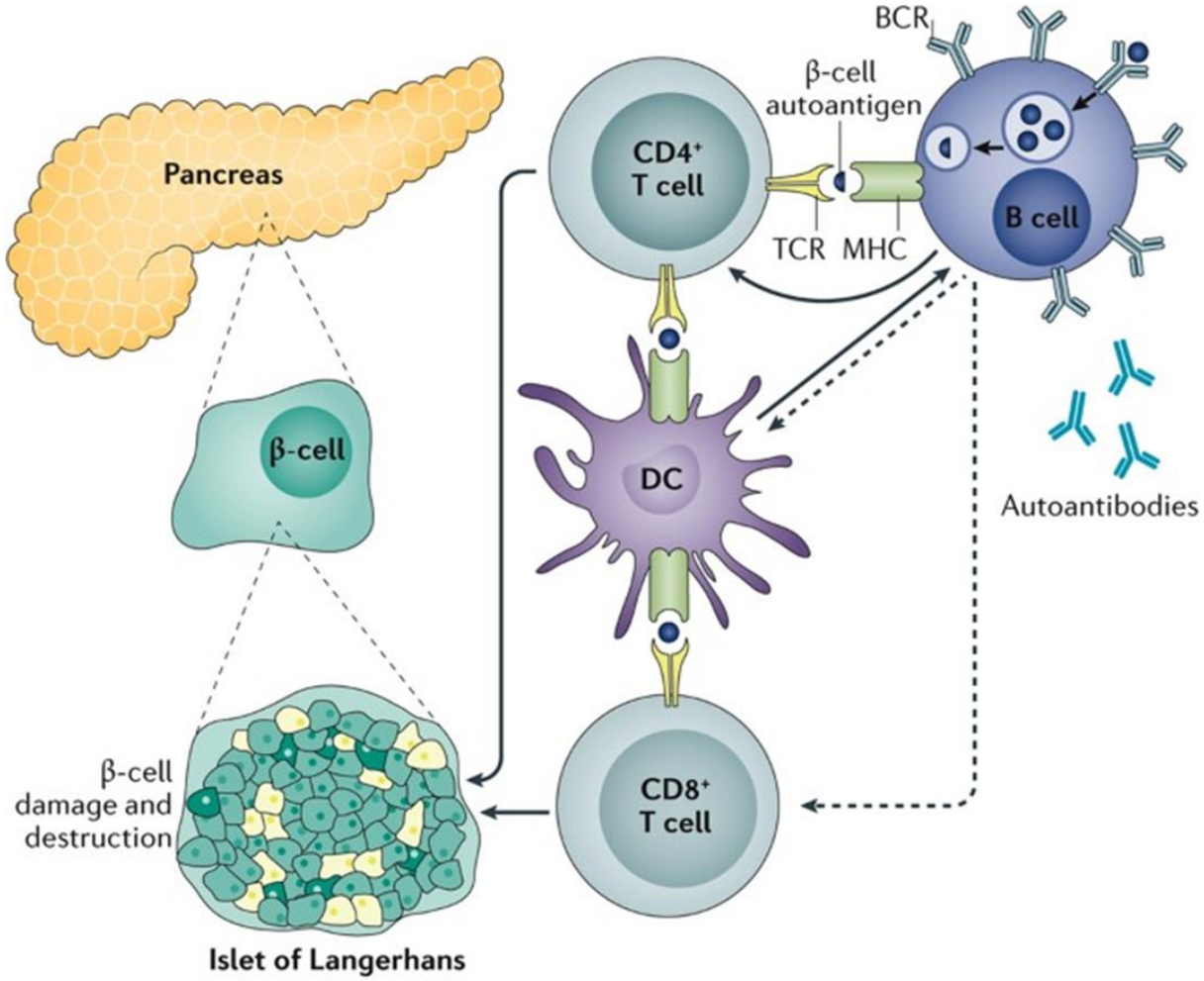
T2DM – key points

- The incidence of T1DM in childhood has increased and the age at diagnosis has decreased due to **environmental changes** during the last half of the twentieth century
- Inherited defects in central and peripheral immune tolerance (**genetic susceptibility**) allow the generation of autoimmune responses directed against pancreatic islets
  - T1DM as a clinical disease is diagnosed at the end of a prodrome of β-cell autoimmunity
- Environmental factors that modify the immune system, such as **microbiome, infections and nutrition**, affect the development and course of the autoimmune response
- T1DM is a heterogeneous disease with multiple different features, but two major pathways can be discerned with either insulin autoantibodies or glutamic acid decarboxylase autoantibodies as the first autoantibody indicating initiation of the autoimmune process
- Multiple trials aiming to prevent development of the disease in different phases of the autoimmune process are ongoing or being planned



Nature Reviews | Disease Primers

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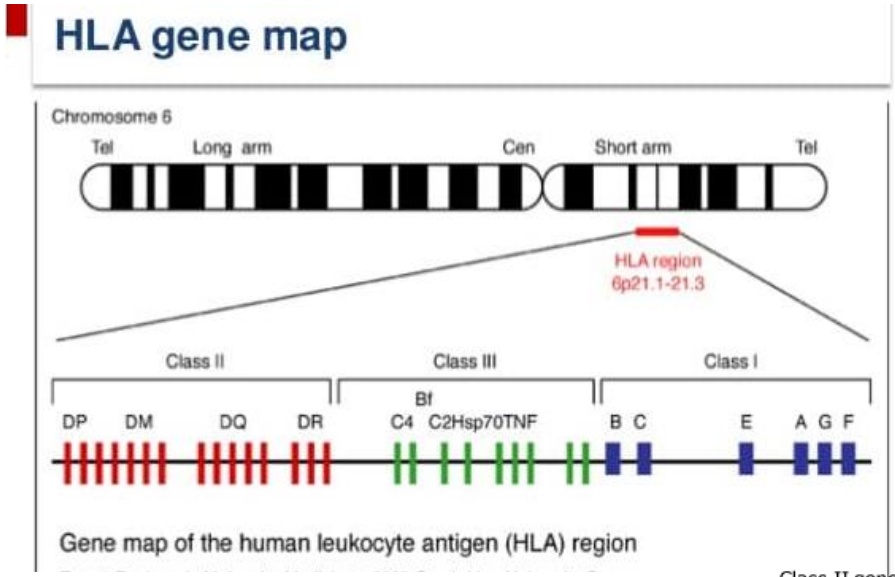
T1DM genetic susceptibility



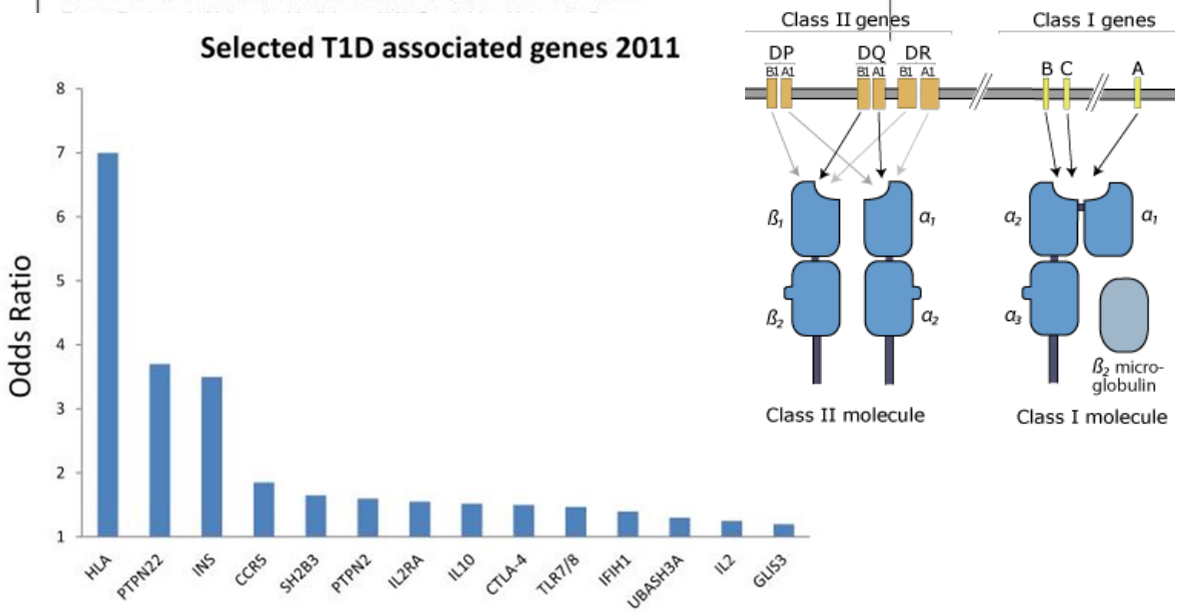


Figure 6: The relative effects of selected T1D associated genes on susceptibility to T1D (adapted from Todd 2010)

- selective autoimmune destruction of β cells in genetically predisposed individuals
  - genetics of T1DM is extremely complicated!!! with many population-specific and age-specific effects
- genetic susceptibility
  - (1) HLA loci – chromosome 6 – MHC class II and I
    - association with HLA-DR3-DQ2 or HLA-DR4-DQ8 haplotypes (or both)
    - DR3-DQ2 and DR4-DQ8
  - (2) non-HLA loci
    - chromosome 11 - insulin gene
      - promotor polymorphism (VNTR) affect insulin expression in the thymus
    - PTPN gene = lymphocyte activity
- some loci can contribute to initiation of autoimmune destruction and others to the rate of progression of the disease
  - T1DM is therefore a clinically heterogeneous disease
- in both cases genetic background leads to insufficient deletion of autoreactive T-lymphocytes in thymus and therefore **suboptimal central immune (auto)tolerance**

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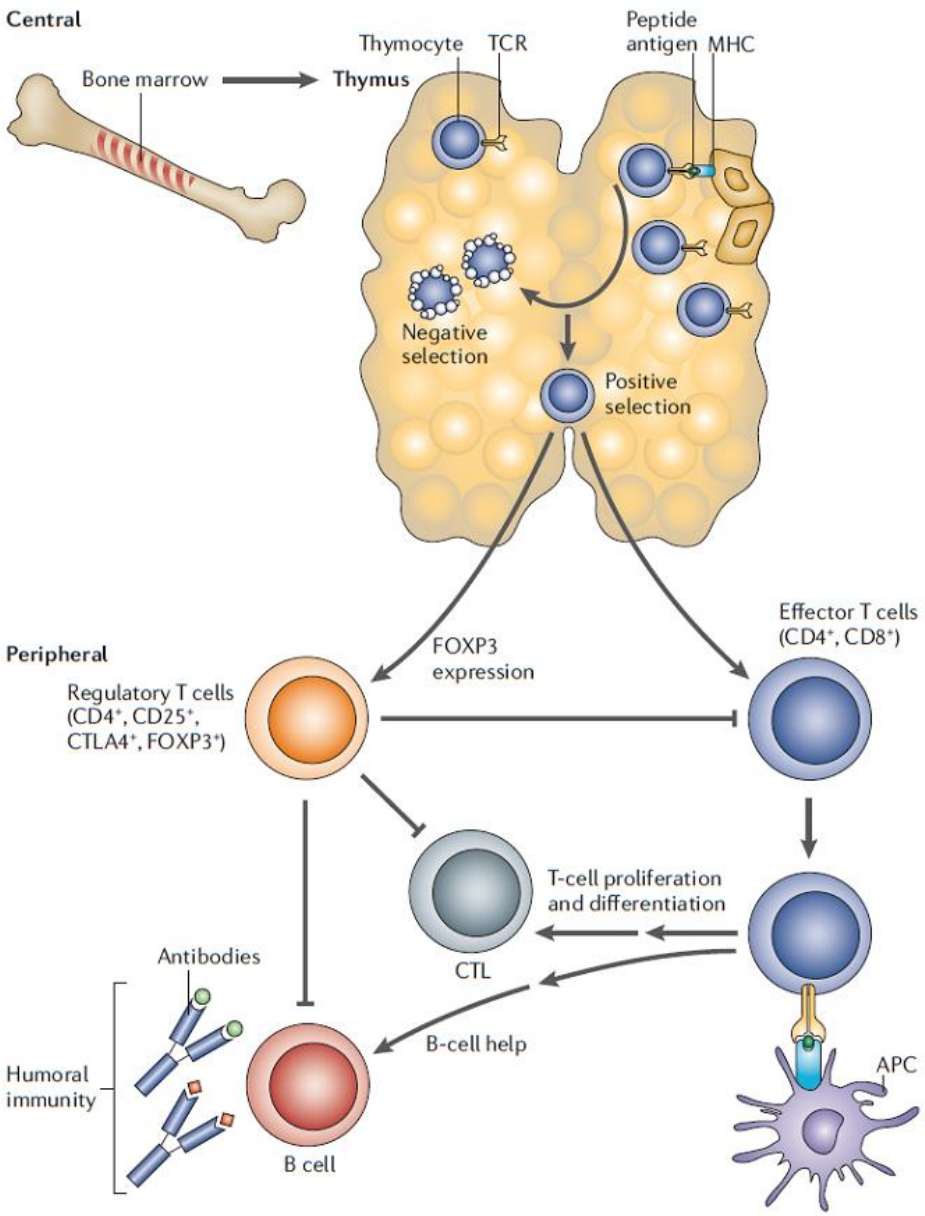
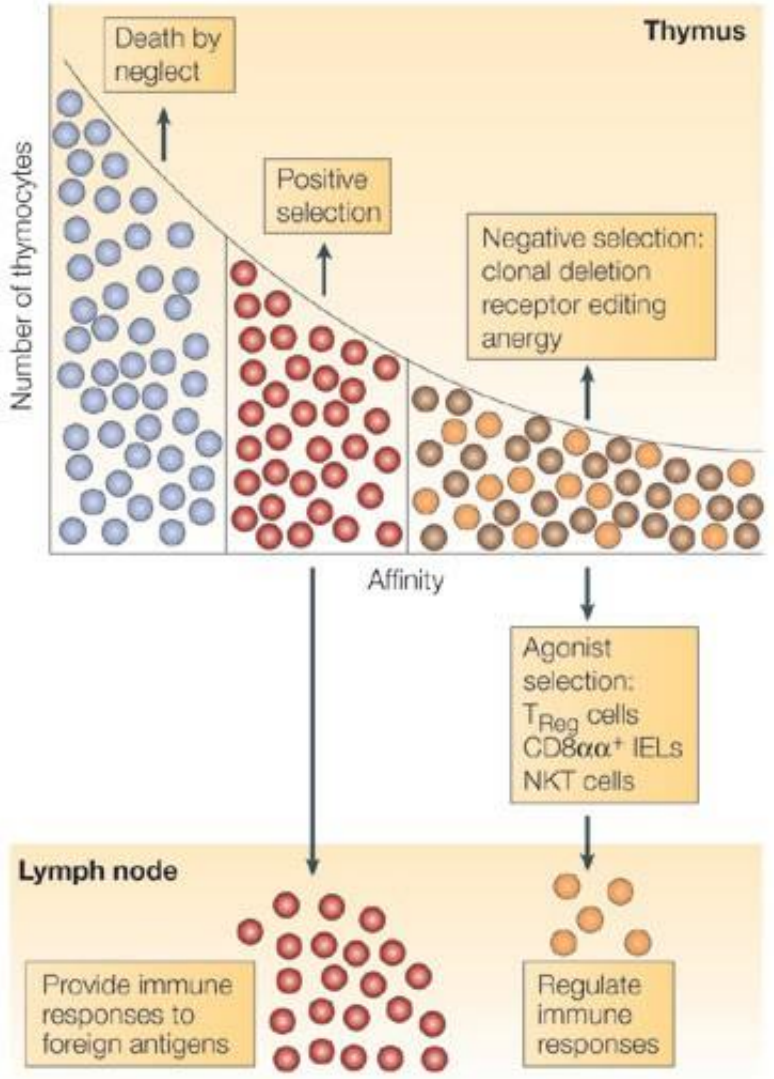
Crucial role of thymus in establishing a central autotolerance





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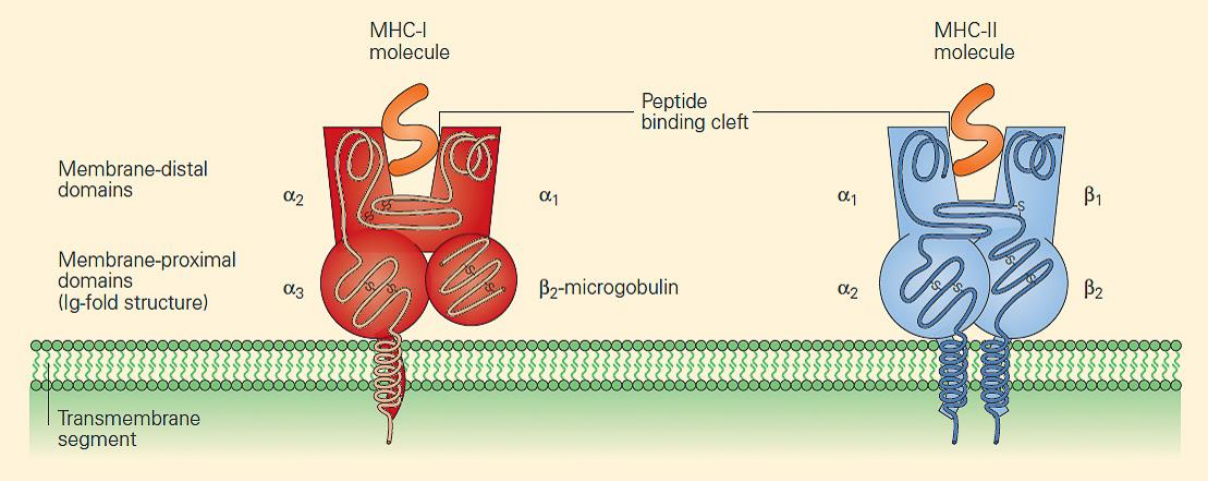
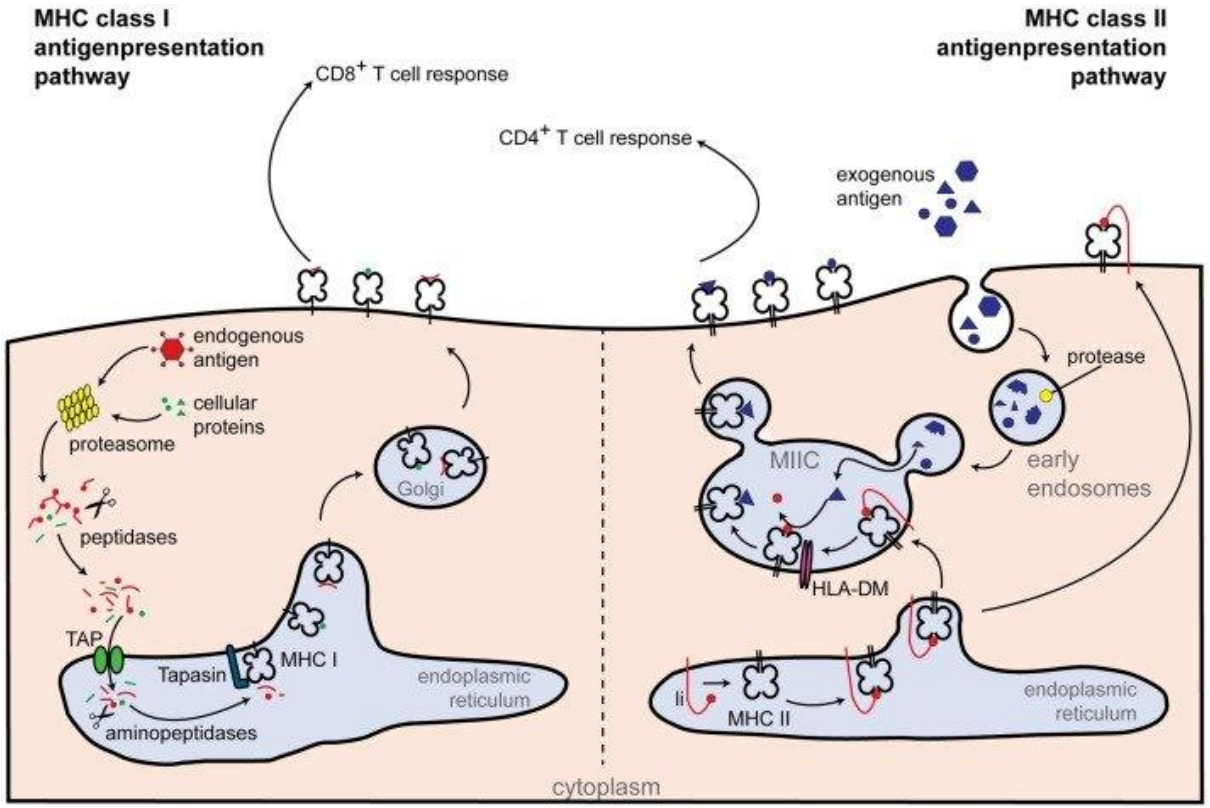
Presentation of peptides by MHC I or II class



- MHC loci on the short arm of chromosome 6 represent a most variable part of human genome
  - this is essential to mount a flexible immune response against ever changing microbial pathogen antigens



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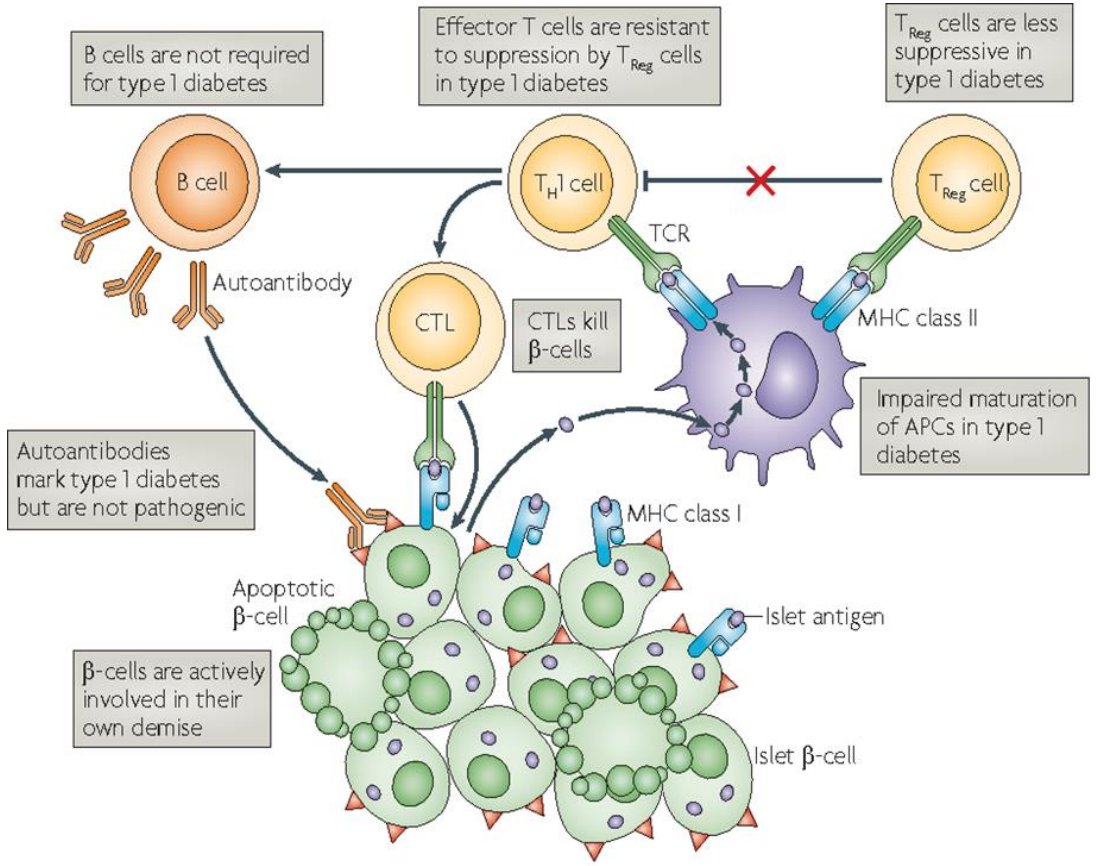
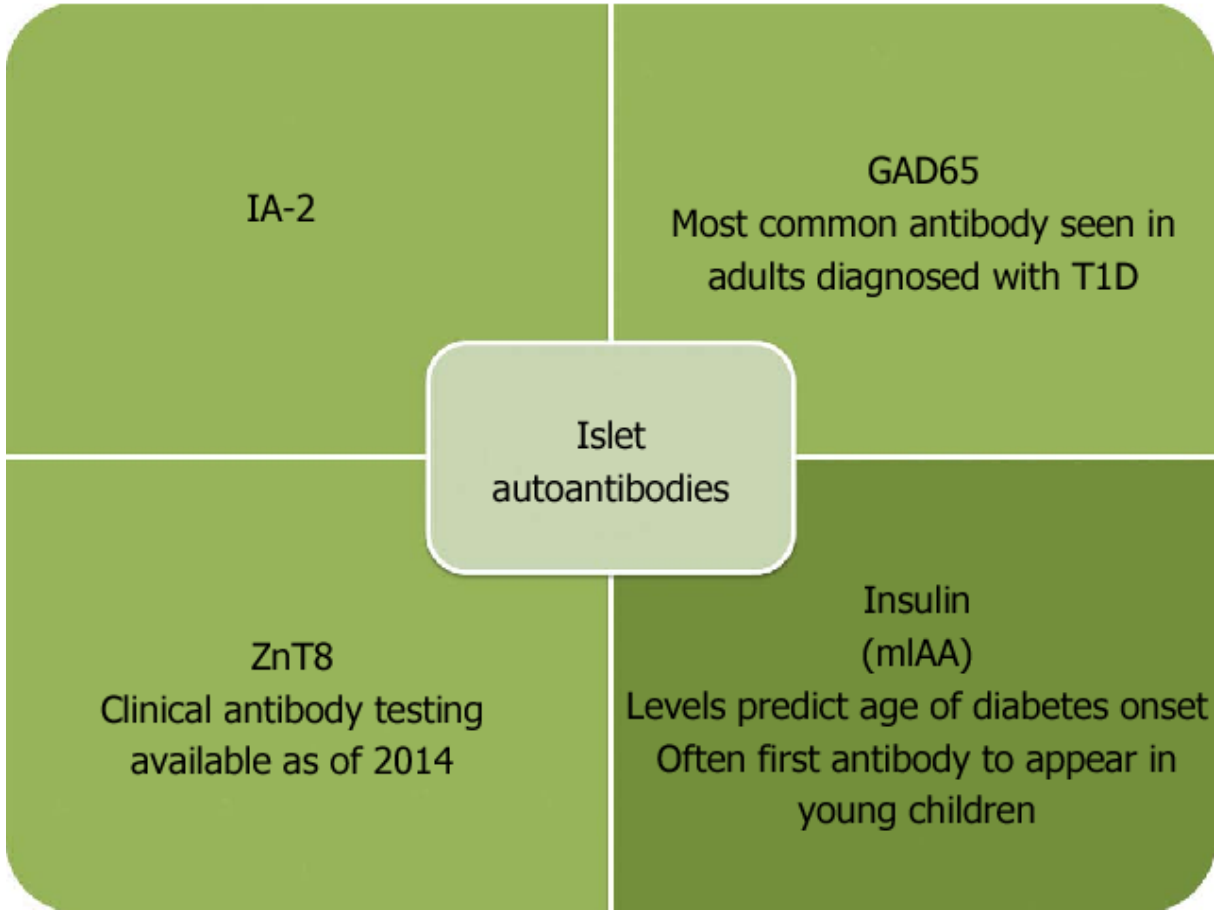
T1DM autoimmunity principles

- **(1)** genetic background conferred by **HLA loci** leads to insufficient deletion of autoreactive T-lymphocytes in thymus and therefore **suboptimal central immune (auto)tolerance**
  - **cytotoxic autoimmunity** mediated by T-lymphocytes is a primary driver of the b-cell destruction
    - **CD8+** present in inflammatory infiltration of the Langerhans islets (i.e. **insulitis**)
    - **CD4+** mediated **B-lymphocyte activation** towards the auto-antibody production
  - **humoral autoimmunity** (antibodies against β cell structures) is a secondary mechanism amplifying the destruction
    - antibodies are diagnostic and prognostic markers of autoimmunity rather than causal agents
  - HLA loci contribute to event. clustering of autoimmune diseases
    - T1DM + celiac disease
    - T1DM + thyreopathy
    - autoimmune polyendocrine syndrome type 2 (APS-2) = T1DM + m. Addison + Hashimoto + event. others
- **(2) non-HLA loci** influence
  - tissue specificity – INS gene
  - the aggressiveness of the autoimmune process – PTPN gene



heterogeneous pattern of antibody panel

- early age by autoantibodies primarily directed against insulin or glutamic acid decarboxylase, or both, but rarely against islet antigen-2. After the initial appearance of one of these autoantibody biomarkers, a second, third, or fourth autoantibody against either islet antigen-2 or the ZnT8 transporter might also appear. The larger the number of β-cell autoantibody types, the greater the risk of rapid progression to clinical onset of diabetes. This association does not necessarily mean that the β-cell autoantibodies are pathogenic, but rather that they represent reproducible biomarkers of the pathogenesis



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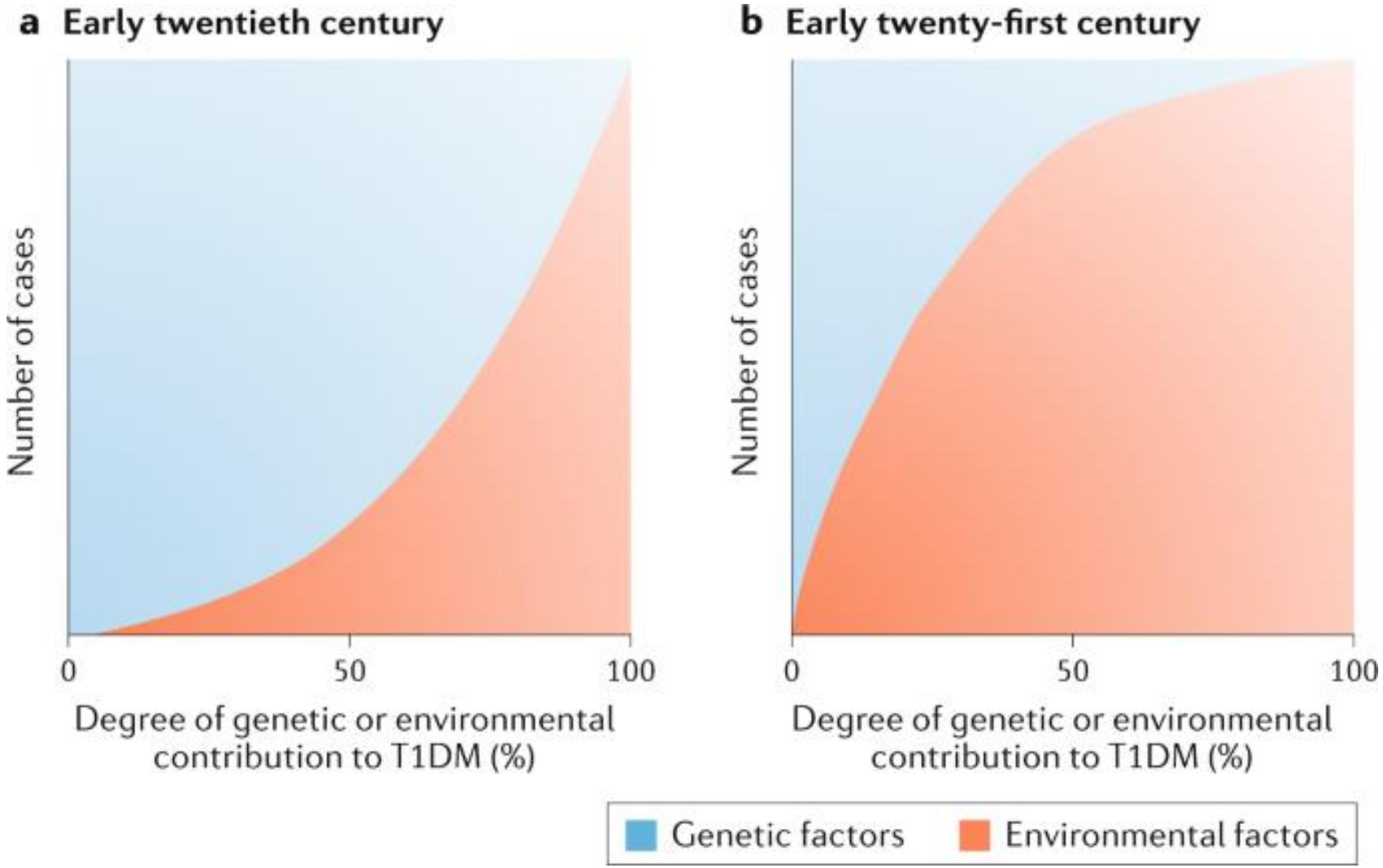
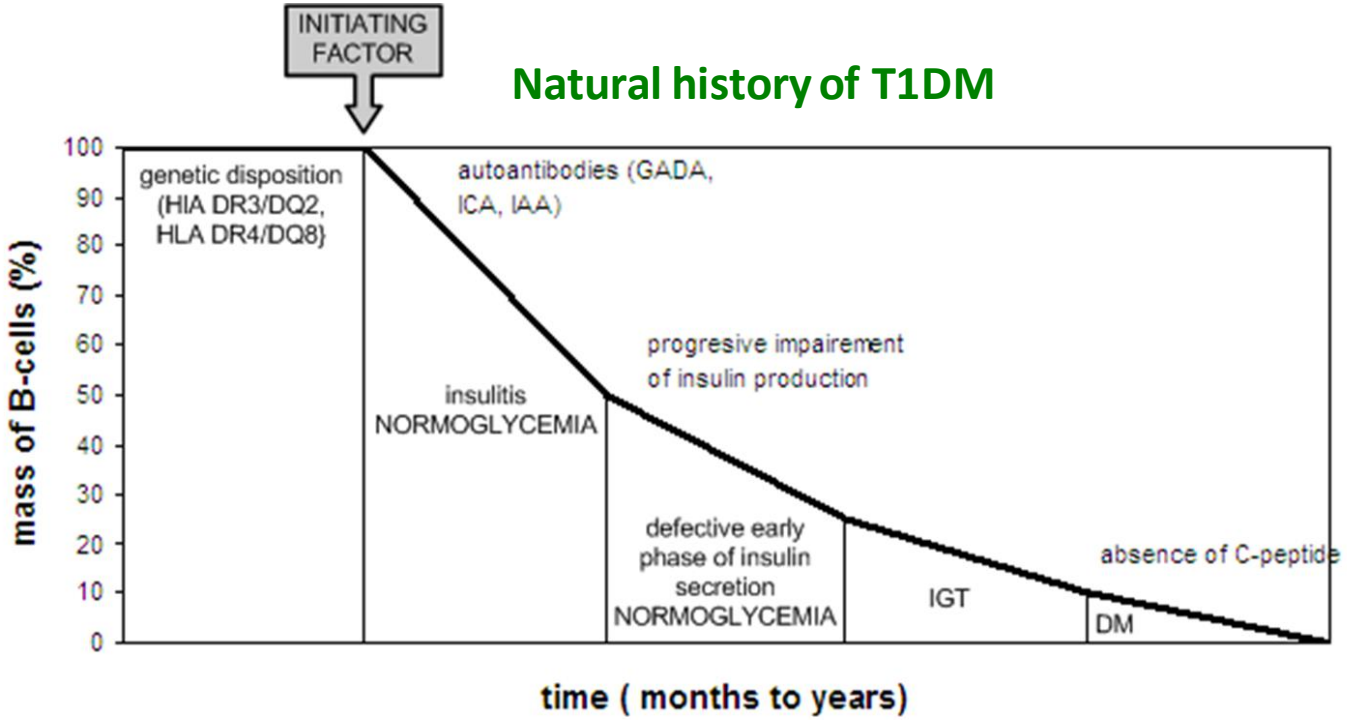
T1DM environmental triggers



T1DM environmental triggers

- autoimmunity has to be triggered by variou environmental factors (according to the epidemiologic evidence)
  - (1) infection
    - viruses
      - rubella, measles, coxsackie B, CMV, EBV, enteroviruses, retro-viruses
    - mechanism is unclear
      - cytolytic (⊗ sequestration of antigens
      - formation of neoantigens
      - molecular mimicry or superantigens
  - (2) diet – early exposition proteins of cow's milk plus short breastfeeding
    - bovine insulin
  - (3) vitamin D
    - deficiency correlates with northern-southern geographical gradient?
  - toxins (diet, water, bacteria)
  - gluten???
- manifestation typically in childhood
- absolute dependence on exogenous supplementation by insulin



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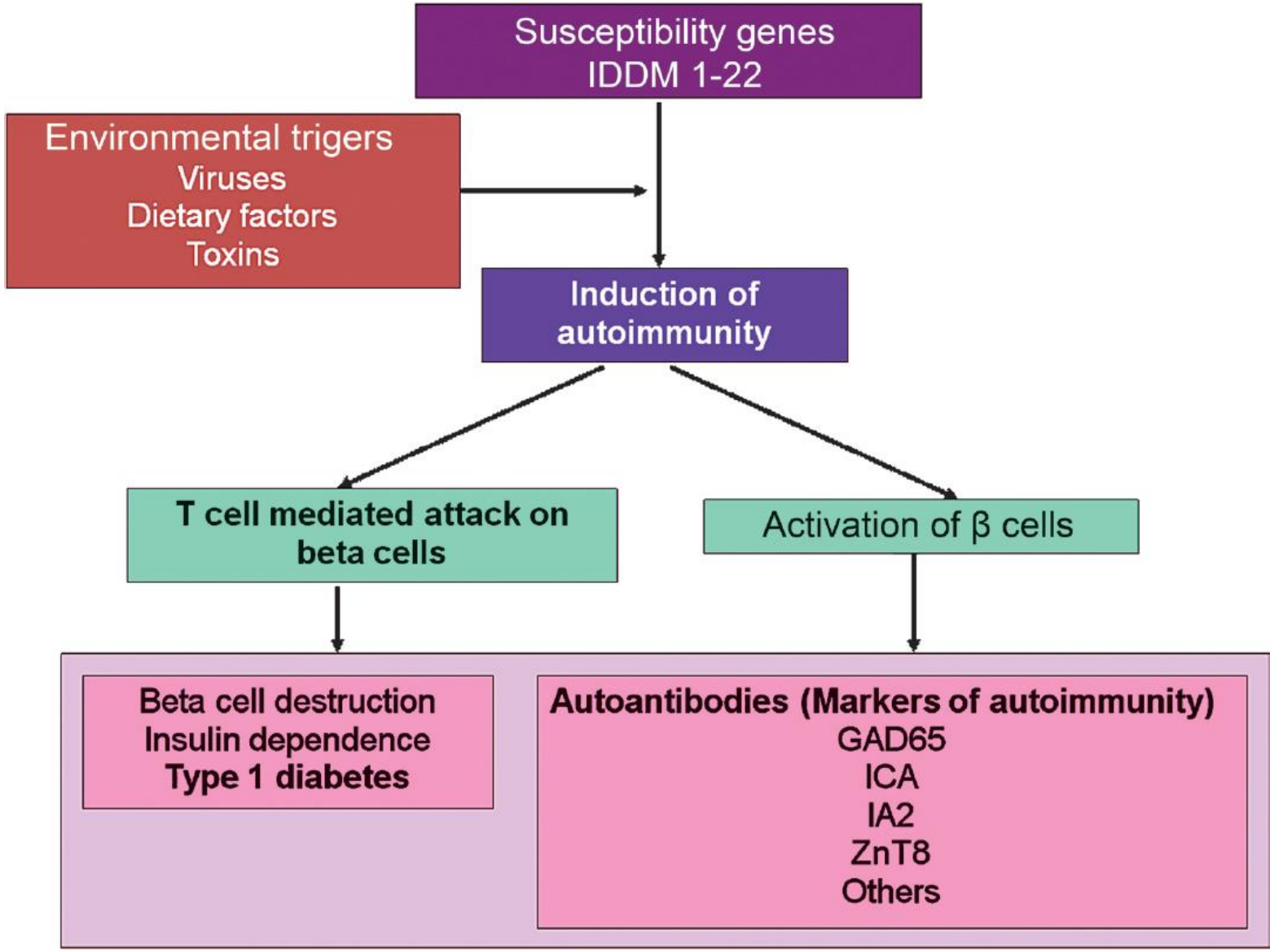
Summary of T1DM etiopathogenesis



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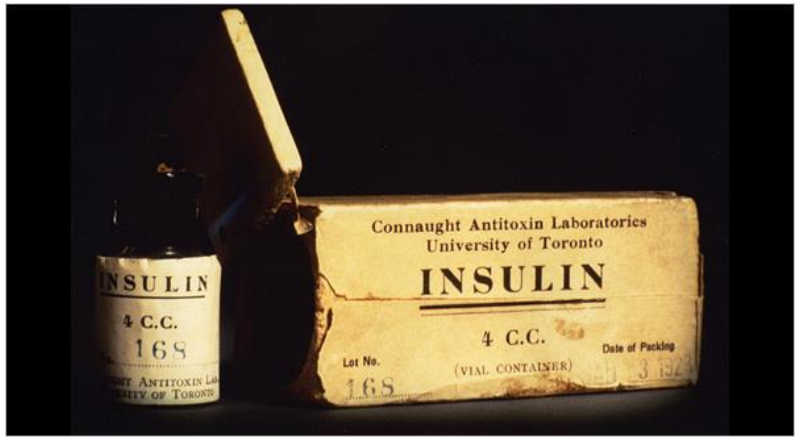
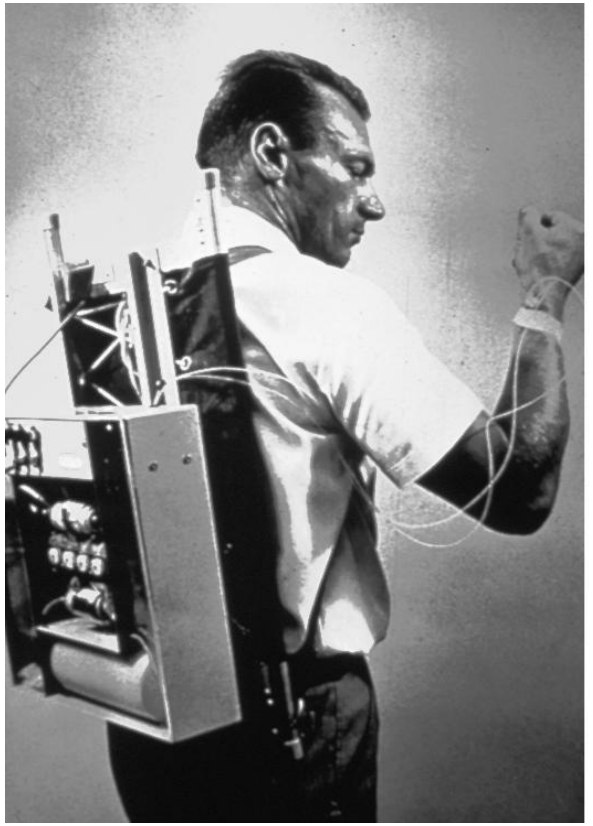
Insulin treatment historically





2 tuny prasečích slinivek ⇒ cca 100g inzulinu

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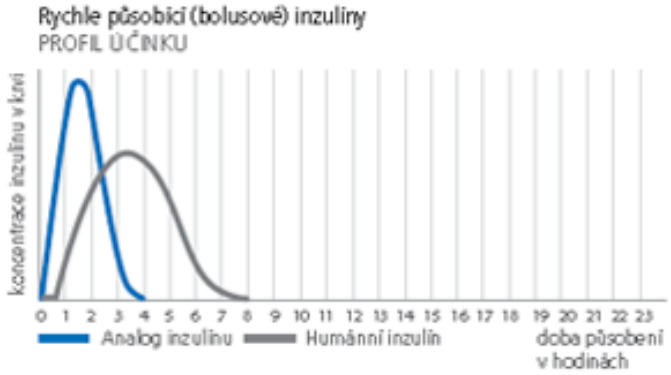
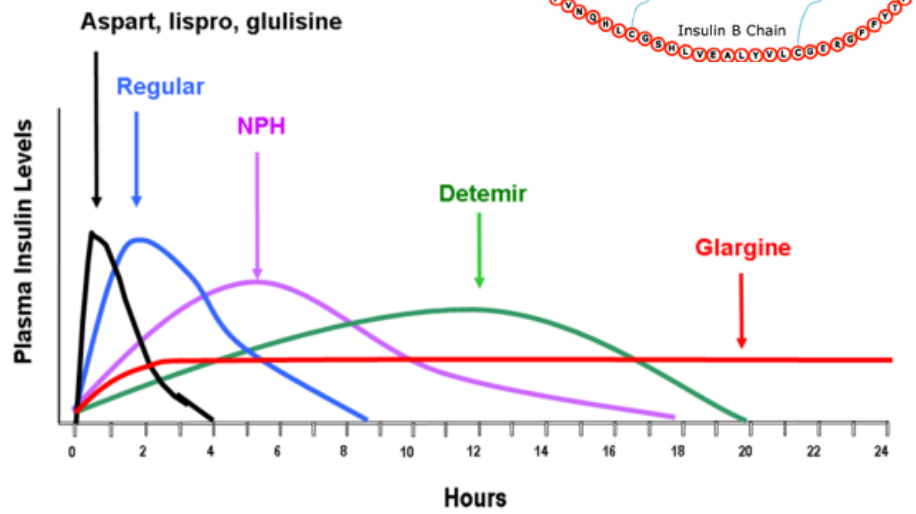
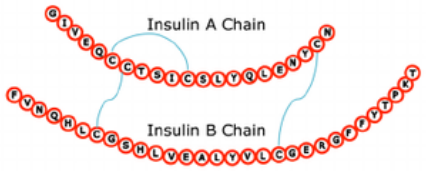
Insulin treatment nowadays (analogues)

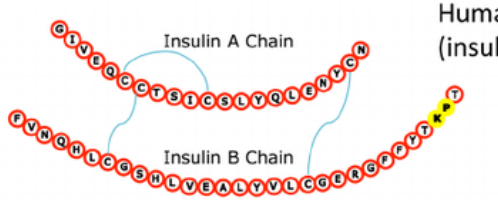




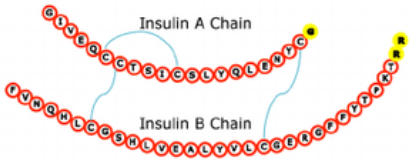
Human Insulin
MW 5808



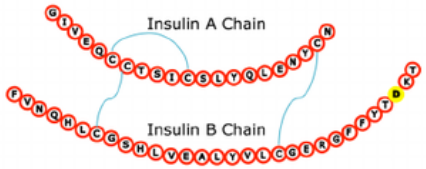
Humalog
(insulin lispro)



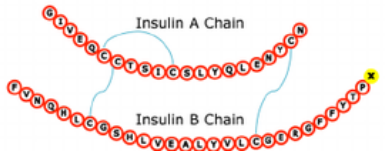
Insulin glargine
(Lantus®)
Avg MW 6063



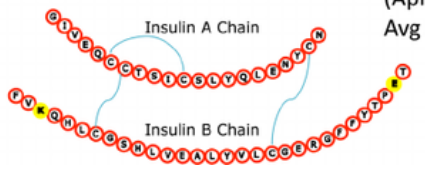
Insulin aspart
(Novalog®)
Avg MW 5826



Insulin detemir
(Levemir®)
Avg MW 5917



Insulin glulisine
(Apidra®)
Avg MW 5823



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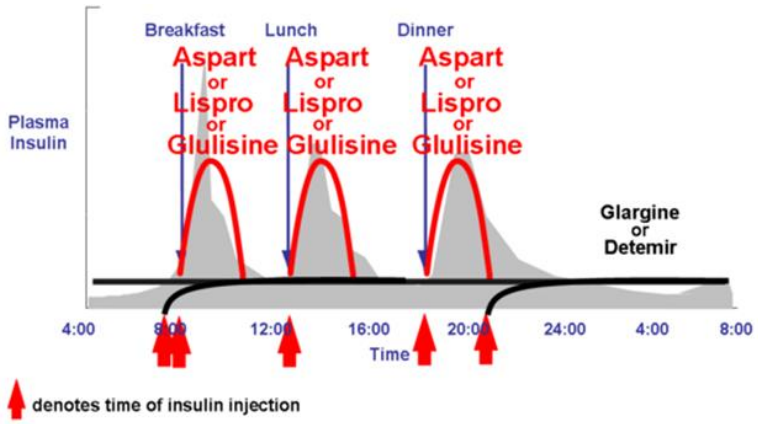
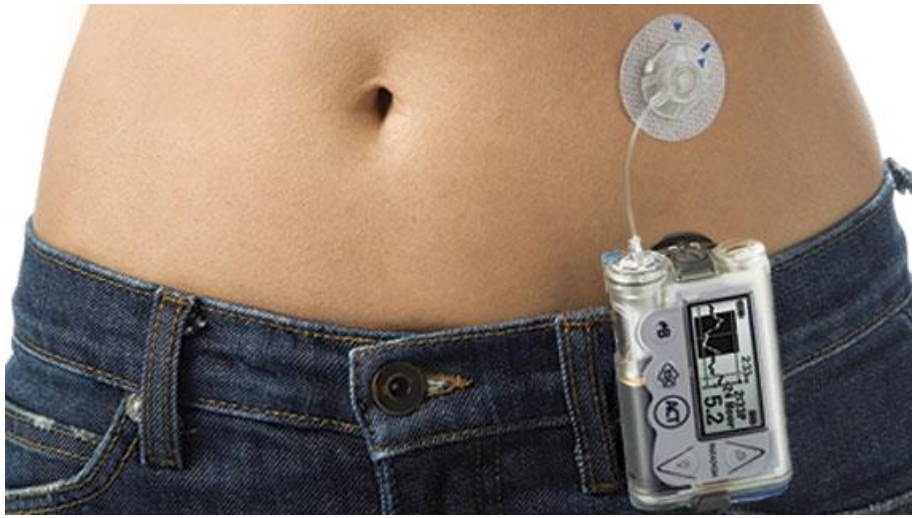
Insulin treatment nowadays (analogues)





Rare forms of DM

- **LADA** (Latent Autoimmune Diabetes in Adults) = **slow-onset T1DM**
  - diagnosis in > 30yrs of age, clinically similar to T2DM (slow onset)
  - initially on diet and pills, no ketoacidosis
  - later insulin dependent (during months – 1 year)
  - positive antibodies (= autoimmunity), low or no C-peptide
  - negative family history of T2DM
- **MODY** (Maturity-onset diabetes of the young) – cca 5% T2DM
  - **monogenic** diabetes with familiar clustering and well defined (Mendelian) inheritance (usually AD), early manifestation (childhood or adolescence) and without obesity
  - 6 types (MODY1-6)
  - pathophysiology: genetically conditioned **dysfunction of β-cells** but long-term measurable C-peptide without the signs of autoimmunity
    - MODY due to **glucokinase** mutations (MODY2)
      - glucokinase = "glucose sensor" (impaired insulin secretion)
      - milder form without the complication risk
    - MODY due to **transcription factor** mutations (other 5 types)
      - severe defects of β-cells progressively leading to diabetes with complications
      - impairment of glucose-stimulated insulin secretion and proliferation and differentiation of β-cells

MODY	lokus	gen	produkt	prim. defekt	závaž	[illegible]
1	20q	*HNF4A*	hepatocyte nuclear factor-4α	pankreas	vysoká	časté
2	7p	*GCK*	glukokináza	pancreas/játra	mírná	vzácně
3	12q	*TCF1 (HNF1A)*	hepatocyte nuclear factor-1α	pancreas/ledviny	vysoká	časté
4	13q	*IPF1*	insulin promoter factor-1	pancreas	vysoká	?
5	17q	*TCF2 (HNF4B)*	hepatocyte nuclear factor-1β	pancreas/ledviny	vysoká	renální
6	2q32	*NEUROD1*	NEUROD1	pankreas	vysoká	?

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Main characteristics – comparison of T1DM, T2DM and MODY



	T1DM	T2DM	MODY
onset	childhood (≤30 yrs)	adults (middle to older age)	youth
genetic susceptibility	yes (oligogenic)	yes (polygenic)	yes (monogenic)
clinical manifestation	often acute	mild or none	gradual/often mild
autoimmunity	yes	no	no
insulin resistance	no	yes	no (often problem with secretion)
dependence on insulin	yes	no (only in late stages)	no
obesity	no	yes	no

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Acute manifestation and long-term consequences (complications) of diabetes

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Q2: Effect of rising plasma glucose ???

OSMOLARITA = 2 Na^+ + urea + glukóza

275 - 295 = 2 x 140 + 2.5 + 5

> 300 = 2 x 140 + 2.5 + **35**

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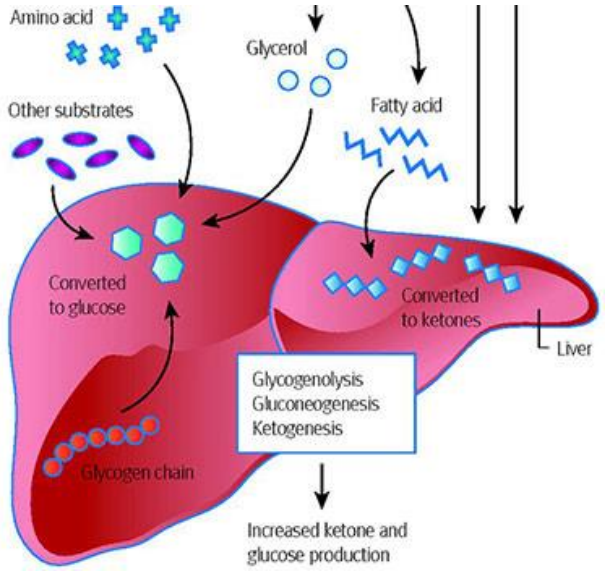
Clinical presentation of DM

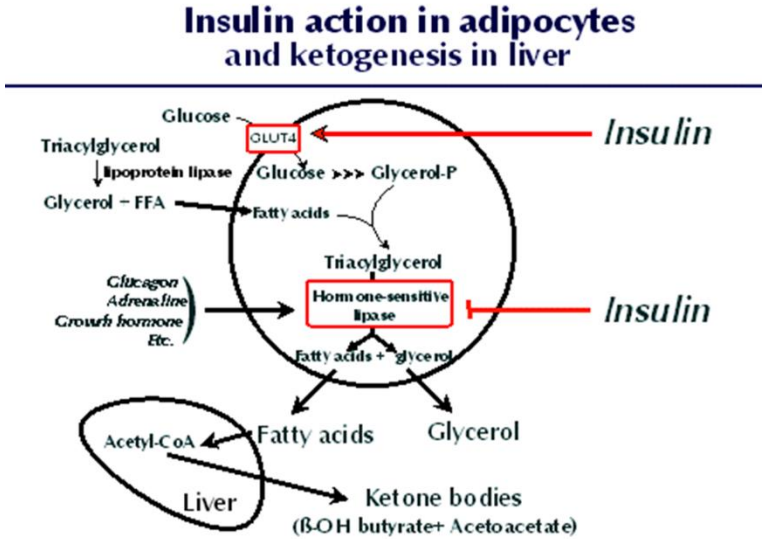
- due to the mild increase of blood osmolarity, osmotic diuresis and dehydratation
  - classical
    - polyuria, thirst, polydipsia
    - tiredness
    - temporary impairment of vision
  - others
    - recurrent infections
    - perio-/parodontitis

- extreme hyperglycemia (>40 mmol/l, osmolarity >350 mosmol/l)
  - **ketoacidosis/coma**
    - ↑ ketone bodies, metabolic acidosis an d hyperglycemia
  - **non-ketoticidotic hyperglycemic coma**
    - hyperglycemia, dehydration and pre-renal uremia
  - **lactic acidosis/coma**
    - either complication of therapy (biguanides / type of peroral antidiabetics)
    - associated with hypoxic states (sepsis, shock, heart failure, …)

Diabetic ketoacidosis

- Excessive thirst
- Frequent urination
- Nausea and vomiting
- Abdominal pain
- Weakness or fatigue
- Shortness of breath
- Fruity-scented breath
- Confusion





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Late complications of DM

- microvascular
  - diabetic retinopathy
  - diabetic nephropathy
    - diabetic kidney disease (DKD)
  - 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

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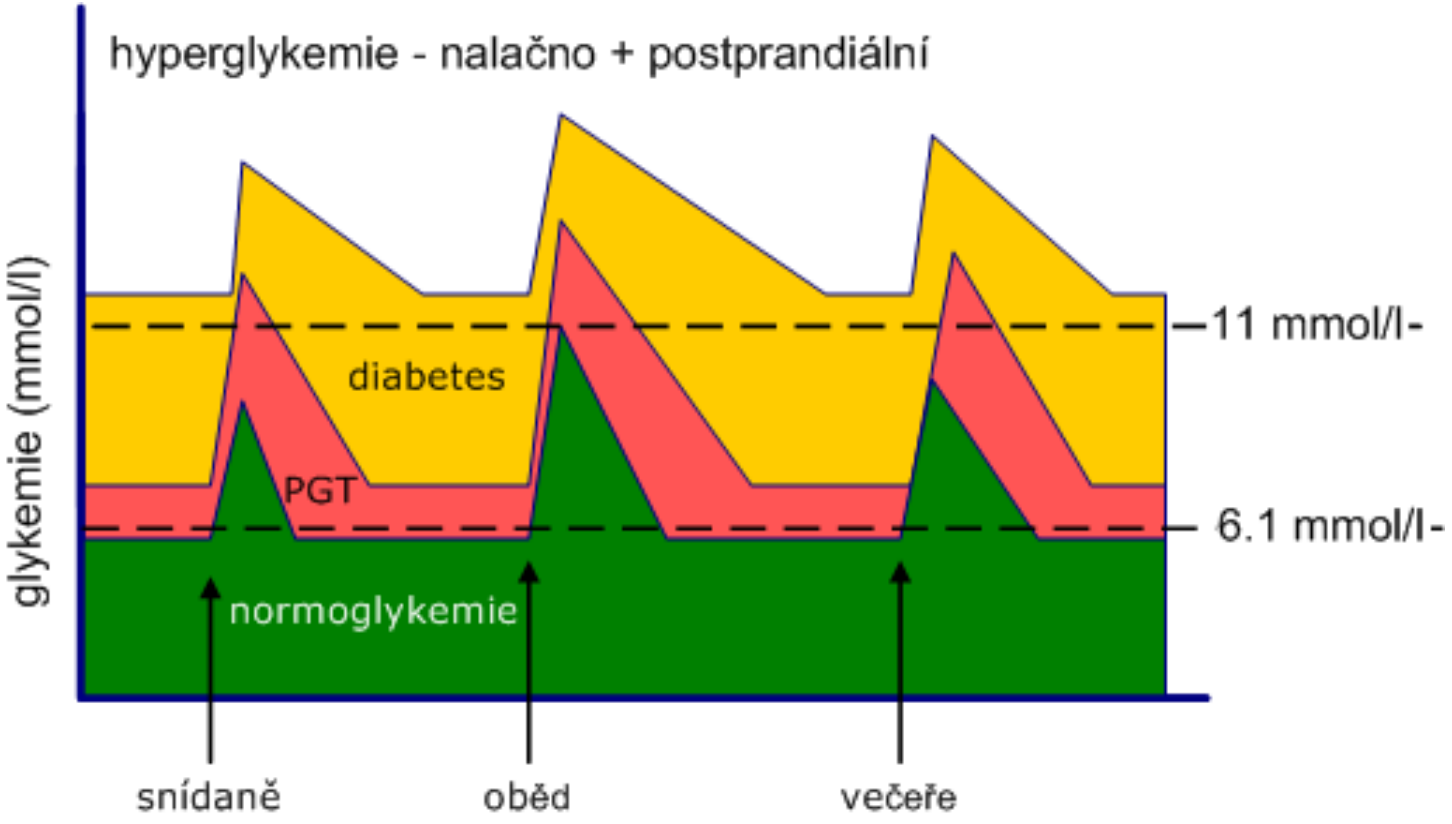
Chronic hyperglycemia



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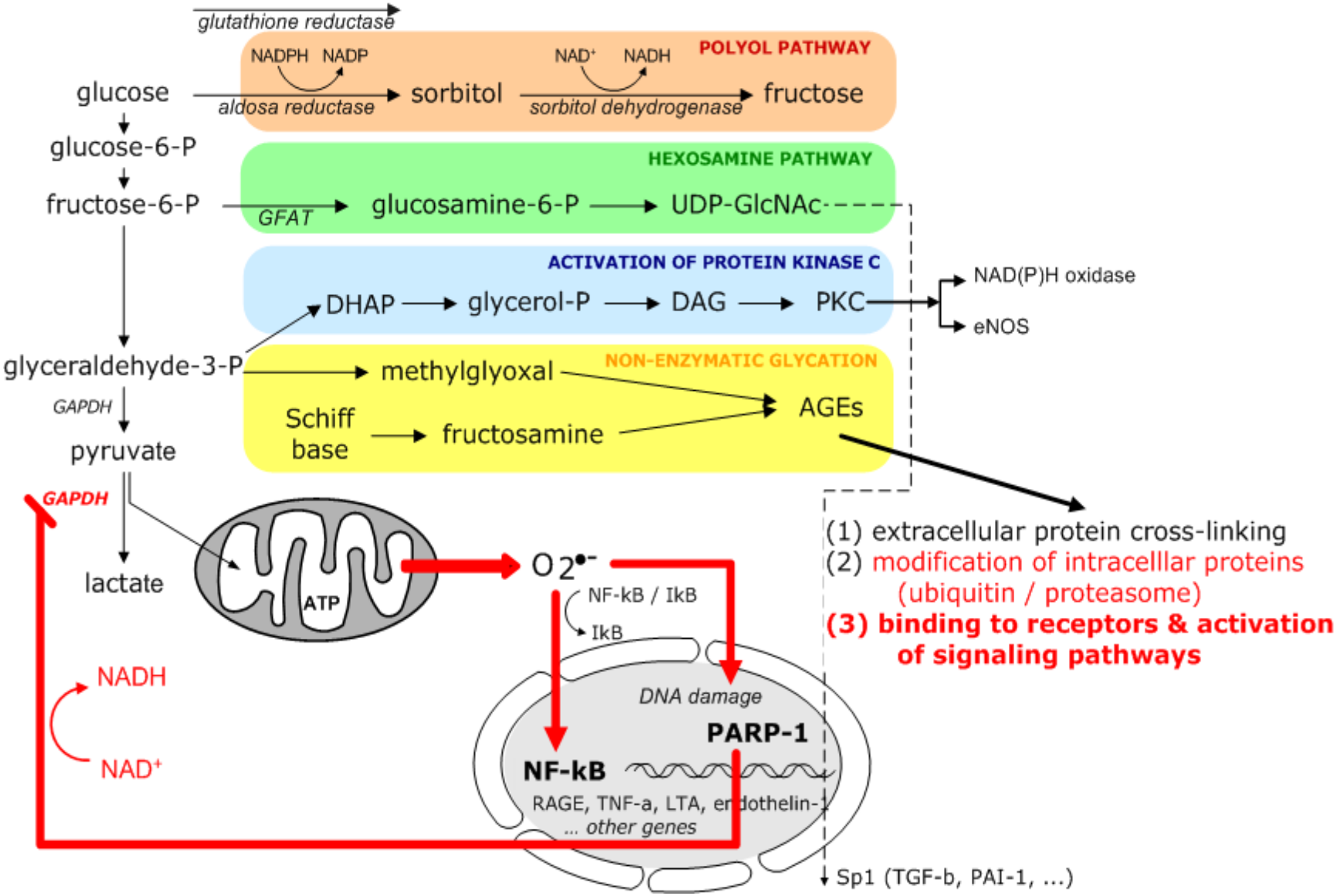
Pathogenesis of complications



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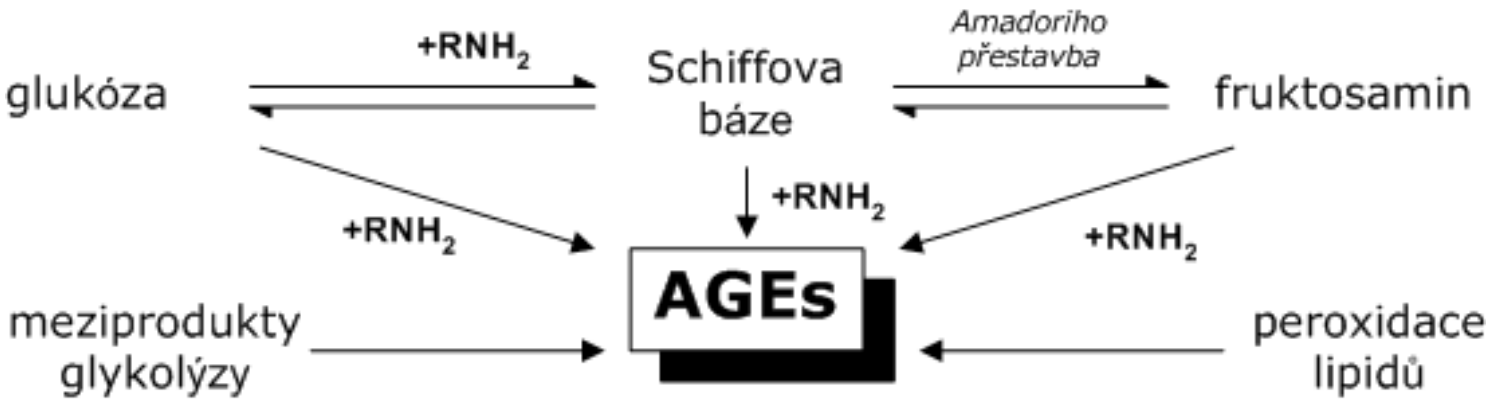
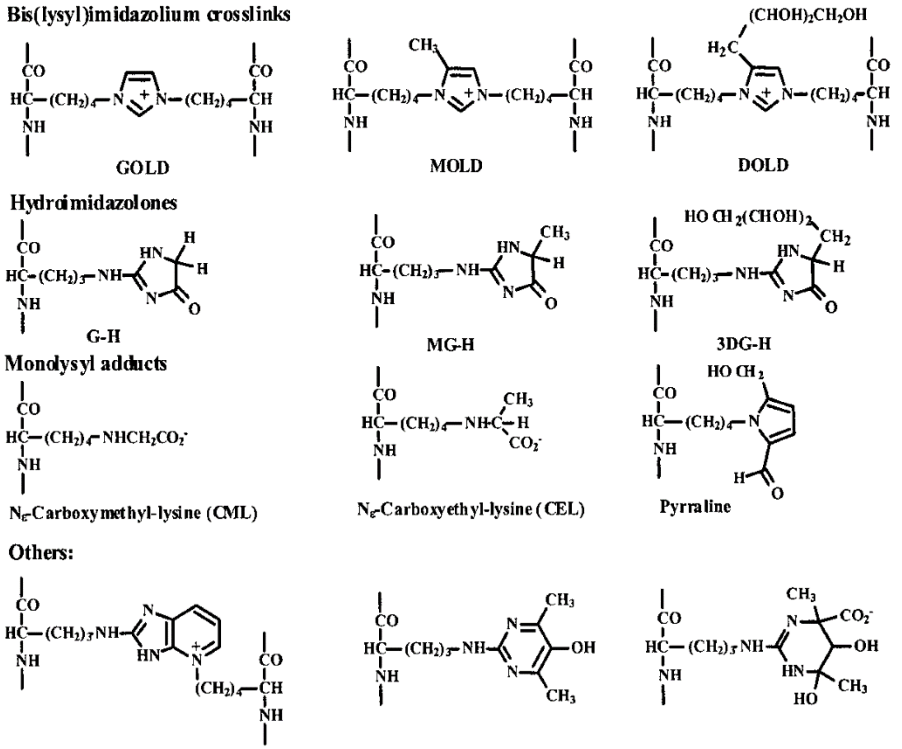
Advanced glycation end products (AGEs)





- cross-linking of extracellular proteins
- modification of intracellular proteins and DNA
  - ubiquitin/proteasom
- binding to pattern-recognition receptors and activation of signaling pathways

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Maillard reaction in food – AGEs in diet

- AGEs are similar to products of Maillard reaction (MRP) formed during thermal processing of food
  - sugar + protein
- Louis Camille Maillard (1878 - 1936)
  - original description of reactions during cooking (“browning”) leading to formation of MRPs (=AGEs)
    - MRP influence taste and visual characteristics, smell, shelve life
  - biologic properties of MRP
    - positive – antioxidants
      - melanoidins, polyphenols
    - negative – carcinogens
      - acrylamid

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Pathophysiology of DKD

Diabetes

Genetic / Epigenetic factors
- Susceptibility genes

Metabolic Stimulus
- Hyperglycemia
- Insulin resistance
- ROS

Haemodynamic Stimulus
- Hypertension
- Fluid/Salt Balance

Microalbuminuria

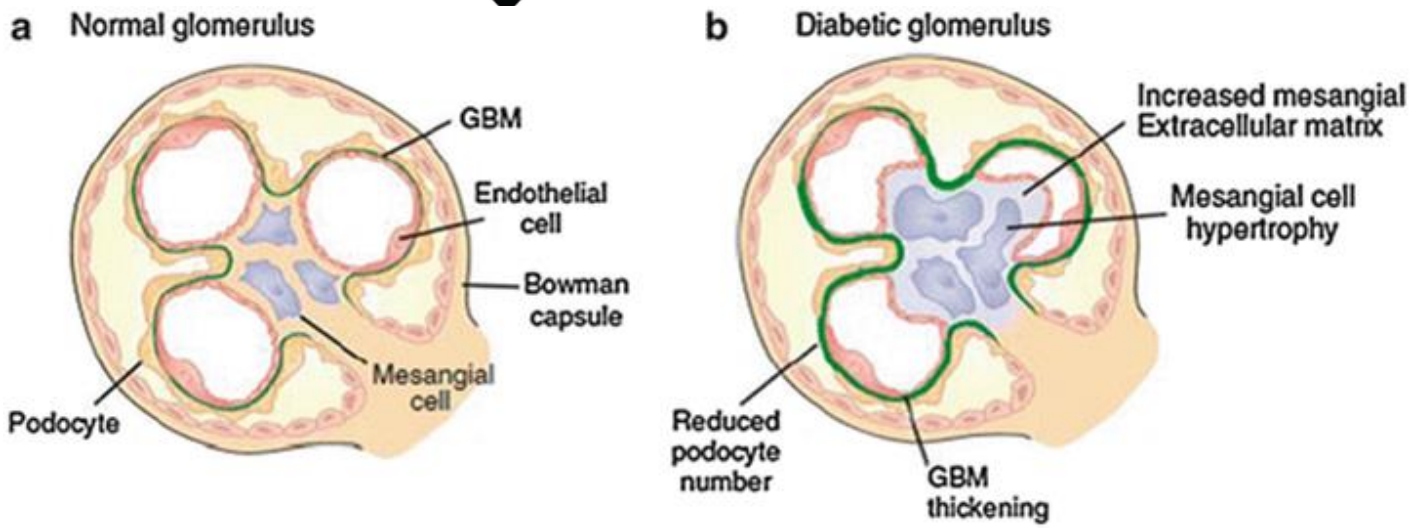
Signalling Pathway activation
- TGFβ1, CTGF, VEGF,
- PKC, Ang II
- AGEs
- NFκB pathway
- miRNA responses

→

Renal consequences
- Infiltrating immune cells
- Matrix accumulation
- Endothelial dysfunction
- Podocyte loss
- Basement membrane thickening
- Proteinuria
- Renal tubule damage

Macroalbuminuria

ESRD



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