

# Antidiabetic drugs

## Notes for Pharmacology I Practicals

**This study material is exclusively for students of general medicine and dentistry in Pharmacology I course. It contains only basic notes of discussed topics, which should be completed with more details and actual information during practical courses to make a complete material for test or exam studies.**

**Thus, without your own notes from the lesson this presentation IS NOT SUFFICIENT for preparation for tests in practicals. This presentation alone can not serve as the only study material for the final exam.**

# Antidiabetic drugs

- Insulins
- Drugs used in T2DM

# Diabetes mellitus

chronic multifactorial endocrine and  
metabolic disease

DM I. type (IDDM) absolute deficiency in insulin (10 - 15 %)

- infections or toxic effect on pancreas
- autoimmune

DM II. type (INDDM) relative deficiency in insulin (85 - 90 %)

# Diabetes Mellitus

- = Chronic, metabolic, etiopathogenetically incompatible disease, the underlying feature of hyperglycemia
- Due to the insufficient effect of insulin on its absolute or relative deficiency
- The genetic predisposition of both forms of DM

# Statistics

Over the past 20 years, the number of diabetics has doubled in the Czech Republic

Incidence - about 80.000 / year, 7.6 new cases per 1000 inhabitants

Comprehensive treatment of patients with type 2 diabetes accounts for 5-10% of healthcare expenses

# Types of diabetes

**Type 1 DM** - absolute insulin deficiency (10-15%) - peak in 13-15 years

A-autoimmune type - leads to destruction of Langerhans islets of beta cells

- antibodies detected in the blood

B-idiopathic type – Ab not detectable - genetic predisposition ?

# Types of diabetes

## Type 2 DM (85-90%)

Relative insulin deficiency

Impaired insulin secretion in pancreatic beta cells

Resistance to insulin in target tissues

Both deviations are mutually reinforcing, it is not clear which is the primary one

Genetic and exogenous factors - obesity, stress, low physical activity, diet, toxins, changes in immune responses

The peak occurrence between 45-65 years, 60-90% with obesity

# Types of diabetes

## Secondary DM

DM accompanying pancreatic disease (including tumors)

DM induced drugs - glucocorticoids, thiazide diuretics  
toxins (streptozotocin)

## Gestational DM

- Up to 17% of pregnant women  
develops in the 2nd trimester (24-28.t.t.) - antiinzulinary action  
of placental hormones ?
- risk for the fetus - diabetic fetopathy - large organs, post-partum  
hypoglycaemia, hyperbilirubinemia, hypokalaemia, weight over 4  
kg

-



# Rare subtypes of diabetes

**LADA** - latent autoimmune diabetes of adults  
DM I.type manifesting in adults > 35 yrs.  
normal weight

**MODY** - maturity onset diabetes of the young  
DM II.type, < 25 yrs, more than 5 yrs treated  
without insulin

## Clinical picture

Polyuria, polydipsy, nighttime urination, weight loss in normal appetite, physical weakness, fatigue, blurred vision, coma (children)

Randomly detected glycemia above 11.1 mmol / L

Fasting glycaemia above 7.0 mmol / L

T1DM - symptoms are more pronounced, develop quickly (weeks)

T2DM - less noticeable symptoms, evolving from months to years

- other - related to organ complications - itchy skin, visual disturbances, pain and tingling, neuralgia, badly healing wounds, skin affections, tooth decay, potency disorders, libido ...

# Clinical management of compensation

Table 6.2—Summary of glycemic recommendations for many nonpregnant adults with diabetes

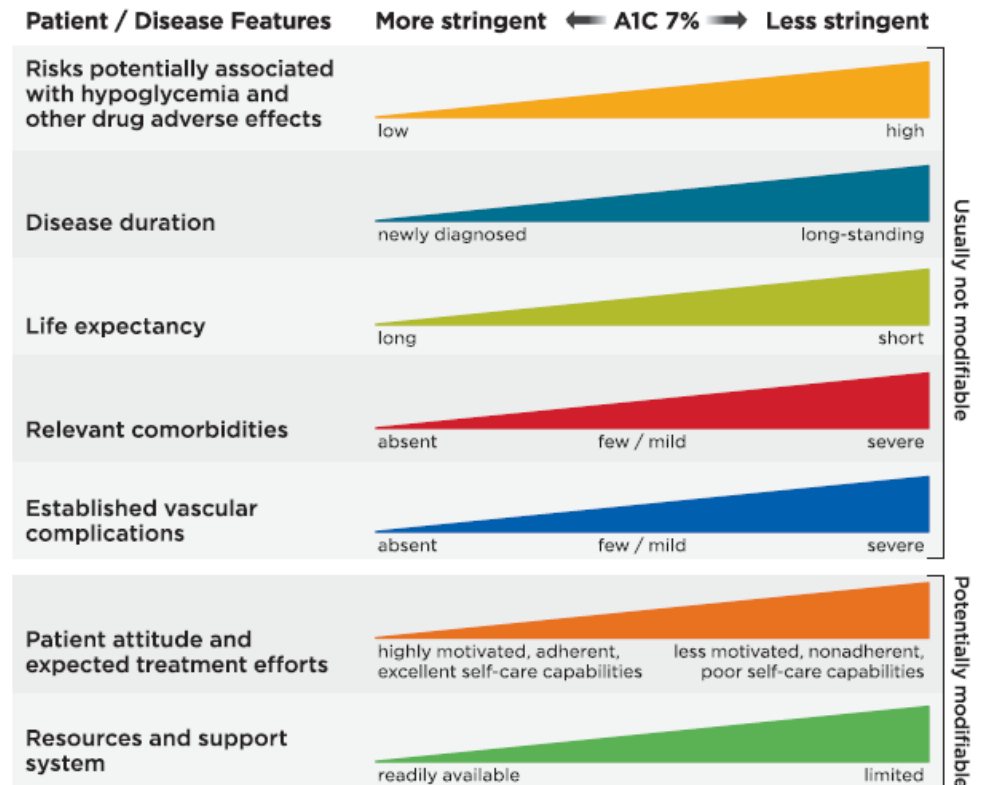
A1C	<7.0% (53 mmol/mol)*
Preprandial capillary plasma glucose	80–130 mg/dL* (4.4–7.2 mmol/L)
Peak postprandial capillary plasma glucose†	<180 mg/dL* (10.0 mmol/L)

## Diet and regimens

Diabetic diet (restriction of carbohydrates: 150-300 g / day), regular, fiber

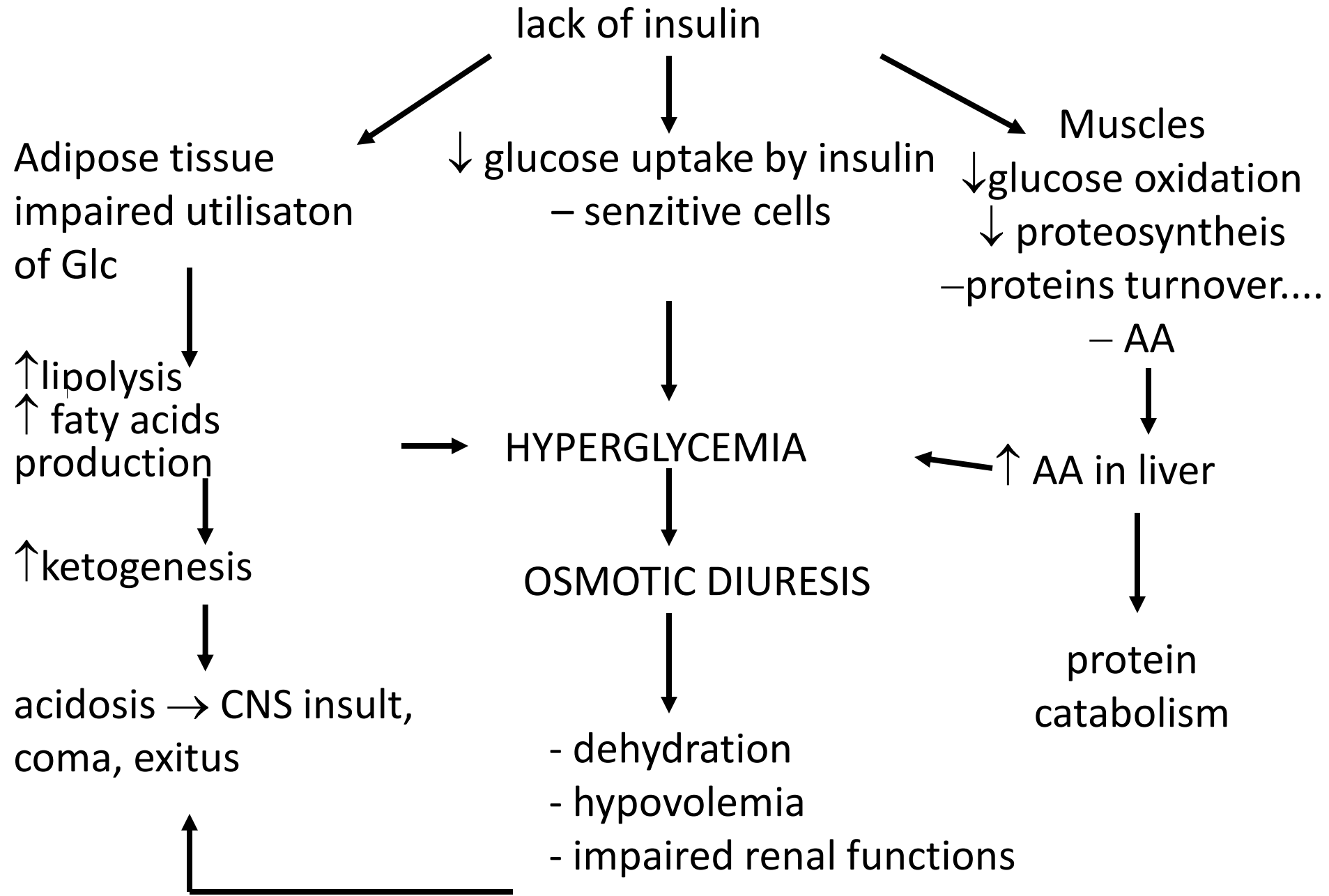
Physical activity (rather aerobic)  
Comorbidity treatment - obesity, dyslipidemia, hypertension, infections, neuropathic pain ...

## Approach to the Management of Hyperglycemia



AMERICAN DIABETES ASSOCIATION STANDARDS OF MEDICAL CARE IN DIABETES—2017,

ADA Guidelines, 2017



# METABOLIC SYNDROME

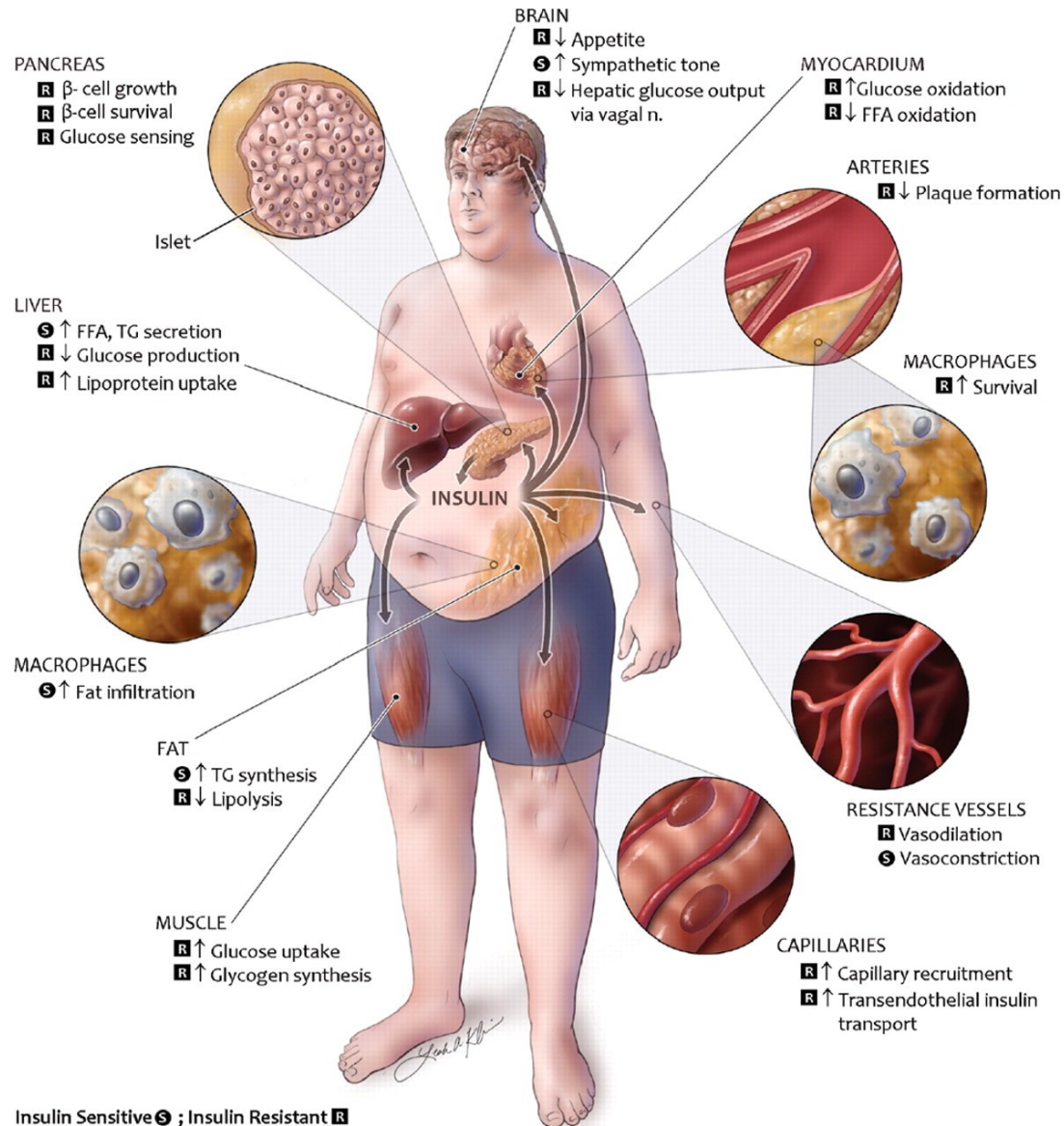
Insulin resistance

Hypertension (high blood pressure)

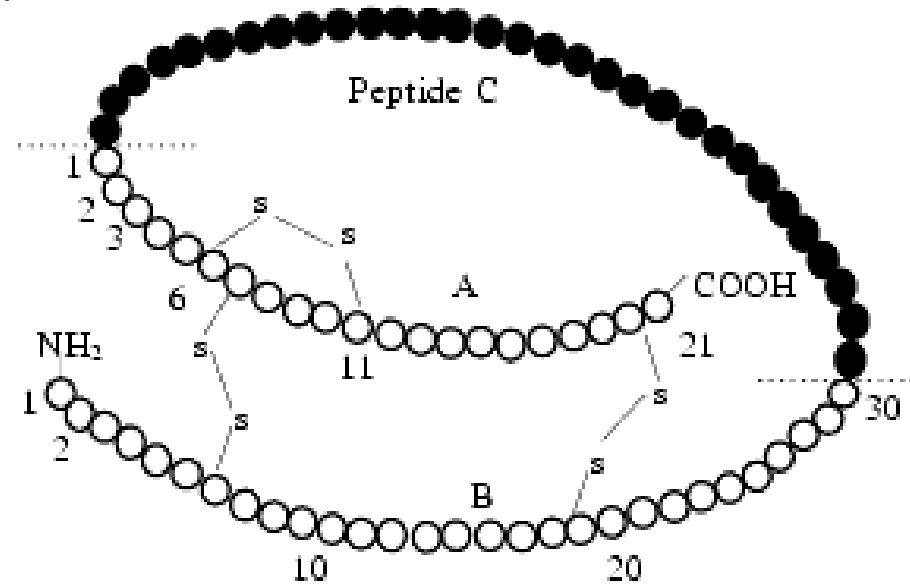
Hypertriglyceridaemia (elevated TAG)

Disorders of glucose tolerance or diabetes

Obesity type of apple (male type of obesity)



**Insulin** = lowmolecular protein, 2 chains  
(A 21 AA, B 30 AA), 2 S-S bonds



Synthesis - preproinsulin (107 AA) →  
→ proinsulin (82 AA, A,B +C-peptide) → insulin

marker of endogenous secretion of insulin  
(is not metabolized by the liver so quickly)

# Pharmacokinetic parameters

- Inter- and intra-individual variability in absorption (25-50 % after *s.c.*, *i.m.*)
  - appl. site, vascularity, temperature, massage, sunbathing, vasodilators
- $T_{1/2}$  7-10 min.

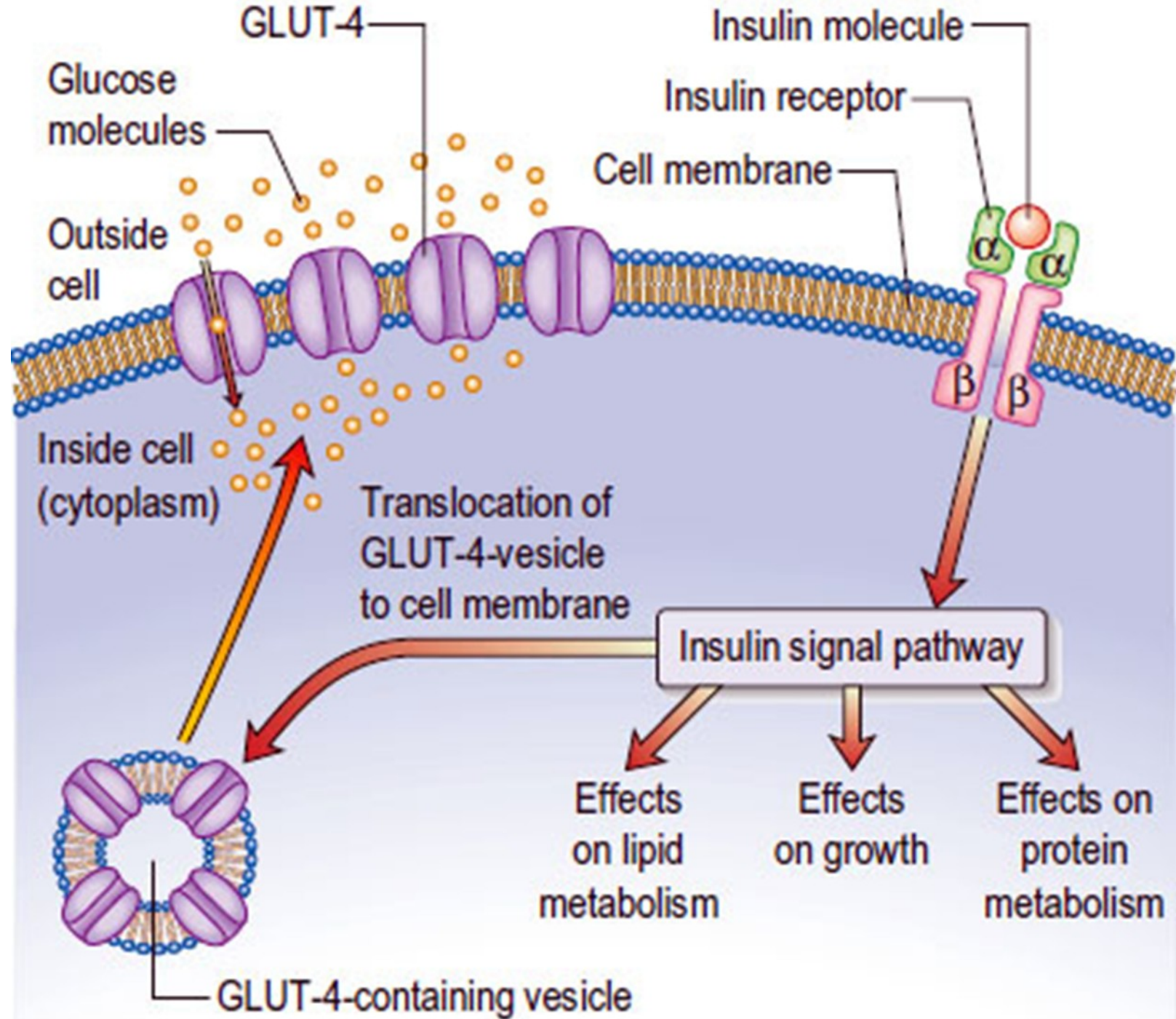
# Factors decreasing insulin secretion

somatostatin

insulin (negative feedback)

$\alpha$  - activation of sympathetic n.s. (adrenalin)





# Species of insulin

**A) Animal insulin** - from pork or beef pancreas, highly pure, monocomponent, today only AUV,

**B) human insulin** - produced biosynthetically (synthetically since the 1960s, biosynthetically from 70 years, commercially since 1982) is called HM

**C) insulin analogues**- biosynthetically prepared, spec.

Properties - length of action (short, prolonged effect)

- the production of antibodies to insulin depends on the purity

# Therapeutical use of insulin

- DM I. Type
- ketosis, ketonuria or ketoacidosis
- patients with serious infection/gangrene
  
- DM II where blood Glc. not normalized with POAD, diet
- DM II patients, use corticosteroids, liver or kidney impairment

# Principles of therapy with insulines

- prevent fluctuation in Glc levels in plasma
- tight glycemic control
- control of glycated hemoglobin (Hb1Ac)
  - indicator of long-term and actual compensation

# Insulin preparations

solutions/suspensions of insulin

suspensions of „zinc-insulin“

suspensions „protamin-zinc-insulin“

$\Sigma$  insulin as a mixture of mono-/di-/tetra-/hexamers

+ pH, stability, isotonicity adjusted

# Insulin preparations

## **Short acting**

A) insulin analogues: insulin lispro, aspart, glulisine

Can be administered intravenously

Start of operation 0-15 min.

Maximum of efficacy 30-45 min after admin.

Effective for 2 - 5 hours.

B) neutral aqueous solutions of insulins

(Crystalline insulin, soluble insulin)

Can be administered intravenously

Start of action 30 min.

Maximum 1 - 3 hours.

Effective for 4 - 6 hours.

## Intermediate acting

NPH (Neutral Protamine Hagedorn)

Protamine insulins or mixtures of amorphous and crystalline forms of insulin in a ratio of 30:70

Start of operation 1 - 2.5 hours

Maximum 4 - 8 hours.

Working time 12 - 24 hours.

Almost no longer used

## Long acting

Crystalline suspensions of large crystals with very slow absorption

Analogs and their conjugates (**glargin, detemir, degludec**)

Onset of effect 2 - 3 hours

Maximum 10-18 h (not apparent in degludec)

Effective for 24 - 36 hours.

Steady state after 3 days (3 doses)

Less hypoglycemia than NPH, less weight gain



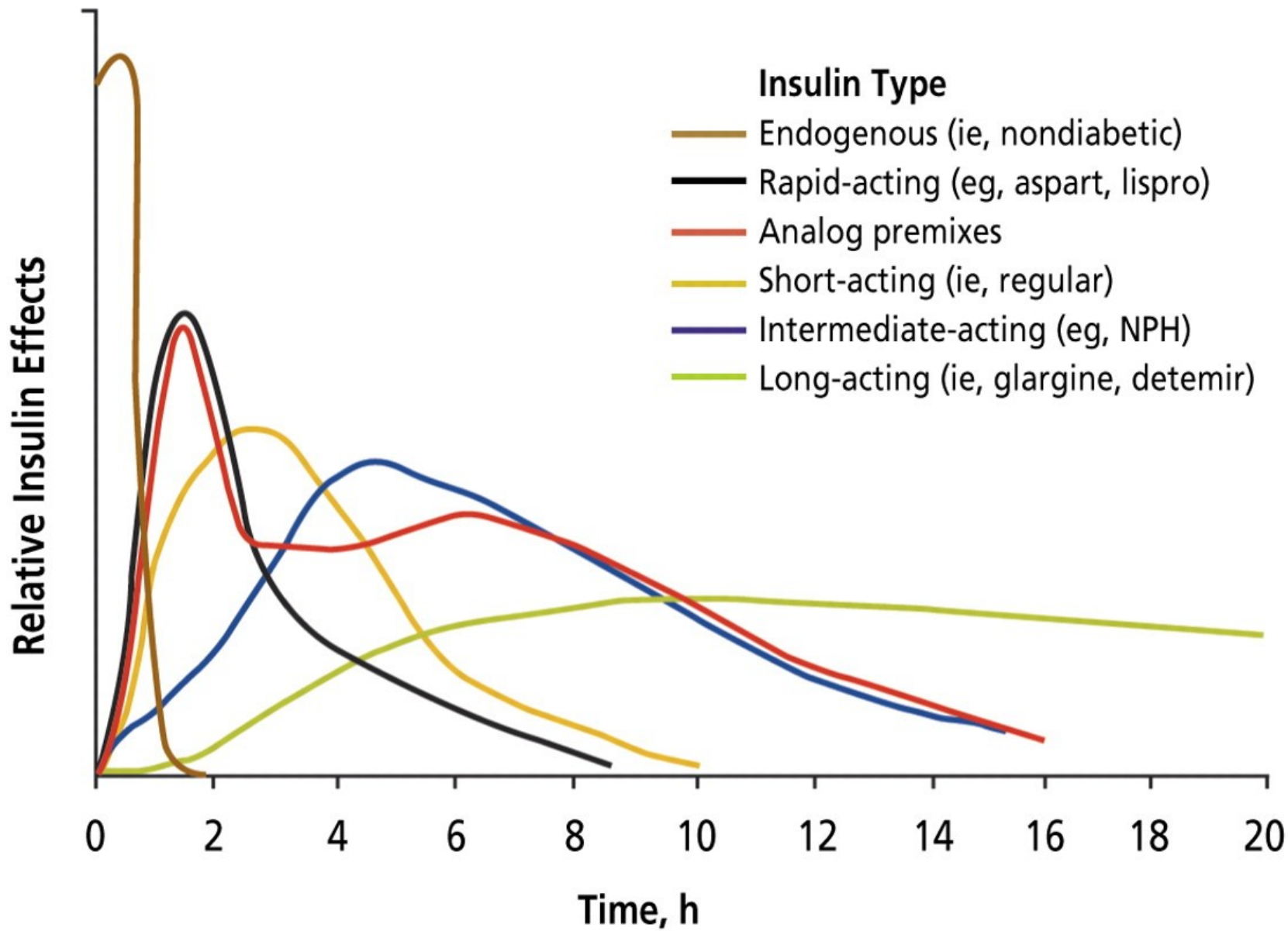
## Long acting insulins

Biosimilars of glargine – **Abasaglar**

**Glargin U300** – slow release from s.c. depo, longer half-life, lower variability, less hypoglycemia during night

**PEG lispro**- long acting insulin (!)

- polyethylenglycol, ↑ hydrodynamic size, slow absorption, degradation



## Complications of insulin therapy

- hypoglycaemia
- allergy
- lipodystrophy

Insulin resistance - spec. antibodies

Weight gain



## Treatment strategies

- the lowest total daily dose

monitoring of glycaemia

more doses, the tighter compensation and the lower total dose

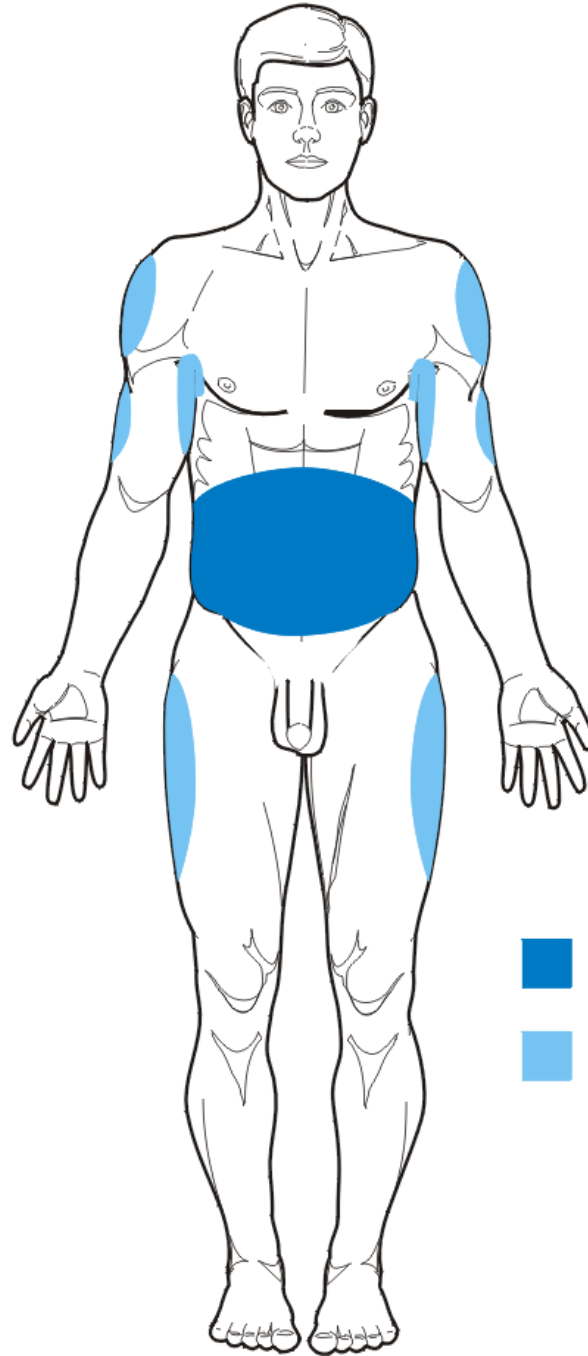
- intensified regimens



Insulin pump

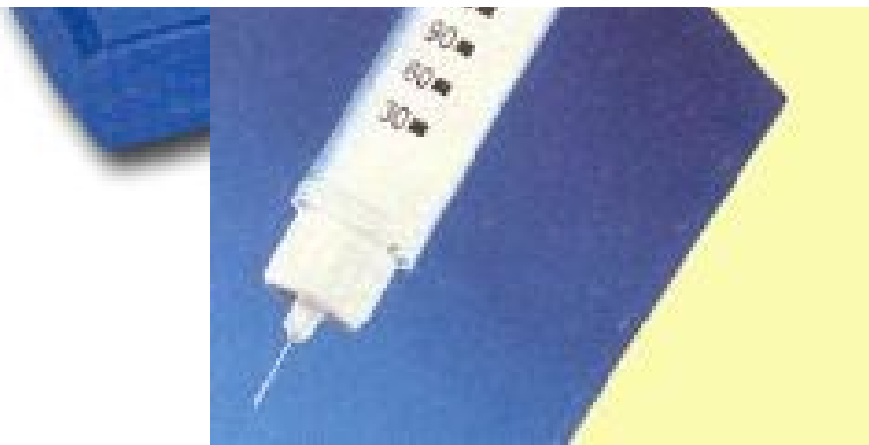
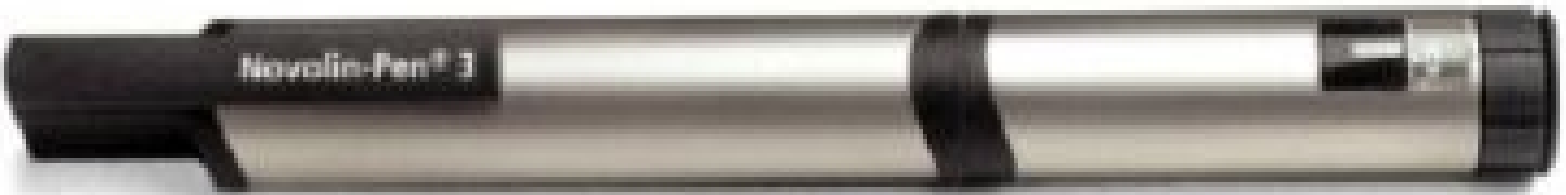
# Delivery systems (self-administration)

- 1) Insulin pen - cartridge with extendable needle; In the form of a fountain pen
- 2) Insulin pumps - continuous infusion s.c. (better compensation, less infectious risk)
- 3) Insulin syringes - with a sealed needle, calibrated per unit
- 4) Inhalation (USA) / transnasal ?

# Insulin administration sites



-  preferred
-  acceptable





# Hypoglycaemia - below 2.8 mmol / l

Causes : - overdose with insulin - delayed food intake, vomiting, diarrhea - excessive physical load (delayed hypoglycaemia)

In the elderly, liver, kidney, cardiac insufficiency

Rapid onset of symptoms: nervousness, tremor, palpitations, restlessness, hunger, sweating, consciousness disorders, changes in EEG, coma, exitus

Therapy: Saccharide / glucose delivery p.o./i.v. (40% glucose, 30-50 ml or more)

Glucagon, followed by glucose



# Glucagon

effects - increases glycemia

- positive inotropic (beta rcp. stimulation)
- positive chronotropic effect

decreases

- gastric and pancreatic secretion
- smooth muscle relaxation (cAMP)

Clinical use - limited

- severe hypoglycemia
- endocrine dg - insulinoma, medullary carcinoma
- beta adrenergic blocker - poisoning - reversal cardiac effect

# **Antidiabetics**

# **Criteria for initiation of pharmacotherapy of DM II type and suitable selection of drug**

- OAD do not replace regimen (diet)
- age, weight, blood insulin level
- glycemia (fasting and postprandial)
- comorbidities, metabolic syndrome

# (Oral) antidiabetics

The effect is linked to the ability of insulin secretion

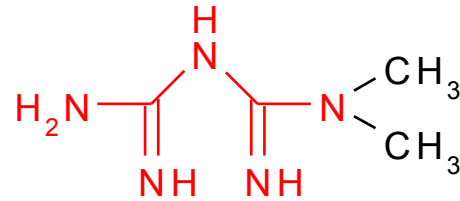
Most OAD are contraindicated in pregnancy (metformin may be used)

- indication:
- T2DM - if not properly compensated with diet
- T1DM with a high insulin resistance, when insulin does not lead to a sufficient decrease in blood glucose

# Antidiabetics

- biguanides
- sulfonylurea derivatives (SU)
- thiazolidindiones
- alpha-glucosidase inhibitors
- meglitinides
- GLP1 analogues
- Inhibitors of DPP IV
- SGLT2 (sodium-glucose cotransporter) inhibitors

# Biguanides



**metformin**

fenformin

buformin

## Mechanism of action

- increase sensitivity of peripheral tissues to insulin
- increase insulin binding to its receptor
- reduce hepatic gluconeogenesis
- decrease glucose absorption from GIT

**Do not affect insulin secretion, function of B cells**

**→ no hypoglycemia**

„euglycemic agents“

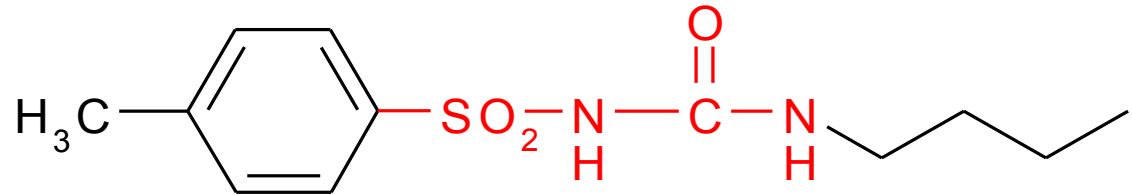
## **Further benefits:**

- Direct stimulation of glycolysis in the periphery
- Reduce hepatic gluconeogenesis
- Delay Glc absorption from GIT
- Decrease plasma glucagon levels
- Increase the proportion of HDL Chol. → improve lipid profile
- Improve rheological properties of blood
- Are not metabolized, low protein binding

## **Side effects**

- Lactic acidosis
- Nausea, GIT problems about 20% of people (diarrhea)
- Reduced absorption vit. B12
- Weight loose
- disulfiram effect

# sulfonylurea derivatives (SU)



Tolbutamide

mechanism of action

- 1) pancreatic – release of I. from beta - cell
- 2) extrapancreatic

- potentiation of endogenous I effect on the target tissue
- reduction of hepatal glucose production
- reduction of hepatal Insulin degradation
- reduction of serum glucagon levels



## SU derivatives

- I. Generation - chlorpropamide  
tolbutamide
- II. Generation - **glibenclamide (gliburide)**  
**glipizide**  
**gliclazide**  
**gliquidone**
- III. Generation - **glimepiride**

**Therapeutic use:** not drugs of choice, 2nd line treatment

## Adverse effects

- increased appetite
- metal taste in mouth
- **Hypoglycemia**
- headaches, nausea (5 %)
- fluids retention
- allergy, fotosensitivity

## Contraindications

DM Type 1 monotherapy, hypoglycemia,  
ketoacidosis, kidney or liver failure  
pregnancy, hypersensitivity

# Thiazolidinediones

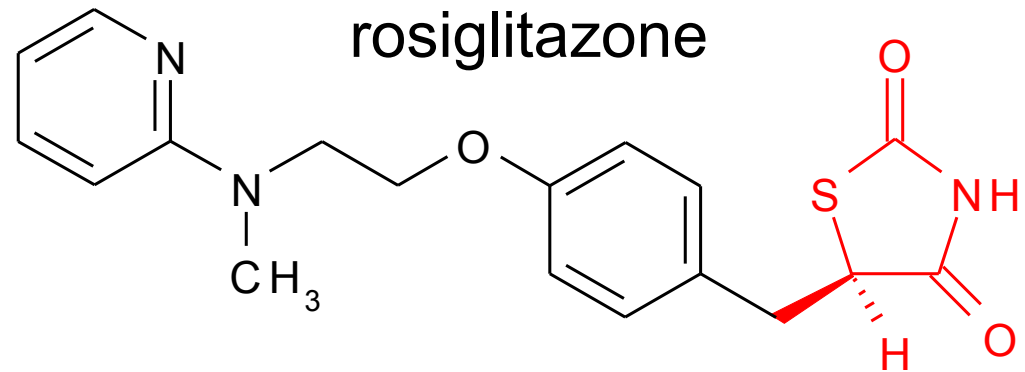
rosiglitazon

pioglitazon

troglitazon

## Mechanism of action

- increase the sensitivity of periphery to insulin
- ligands of PPAR $\gamma$  (part of the steroid and thyroid superfamily of nuclear receptors) modulate the expression of the genes involved in the metabolism of lipids and glucose



# Thiazolidindiones

- Lowering blood glucose by the primary effect on insulin resistance - in diabetic and pre-diabetic patients
- Does not cause hypoglycemia, scavengers
- Increase glycogen synthesis and glycolysis in muscles
- Stimulating glucose oxidation and lipogenesis in adipose tissue and reducing gluconeogenesis in the liver ... optimal metabolic effects

2010 referral – rosiglitazone withdrawn from registration - CVS AE

## **Therapeutic use**

Sensitizers of insulin receptors

The onset of effect in 4 weeks

## **Side effects**

Hepatotoxicity

Fluid retention

Increase TAG

## **Contraindications**

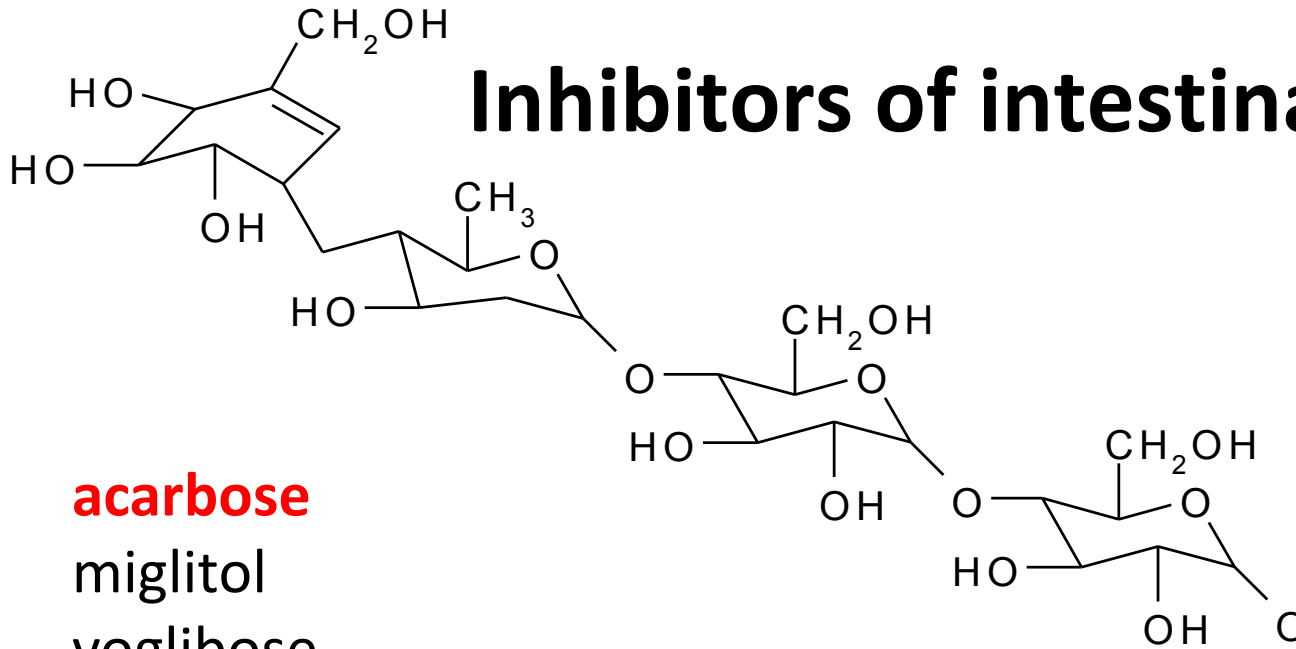
Hypersensitivity

Predisposition to heart failure

Liver damage

Pregnancy, lactation

# Inhibitors of intestinal glucosidase



**acarbose**  
miglitol  
voglibose

## Mechanism of the action

- reduce sacharides absorption from GIT
  - competitive inhibition of the gut  $\alpha$  - glucosidases
- (inhibits the cleavage of the polysacharides from the meal)

# Inhibitors of intestinal glucosidase

- decrease postprandial glycemia
- do not affect monosacharides absorption
- acarbosis do not reach the systemic blood, miglitol does
- „educative drugs“- consequences in bad compliance

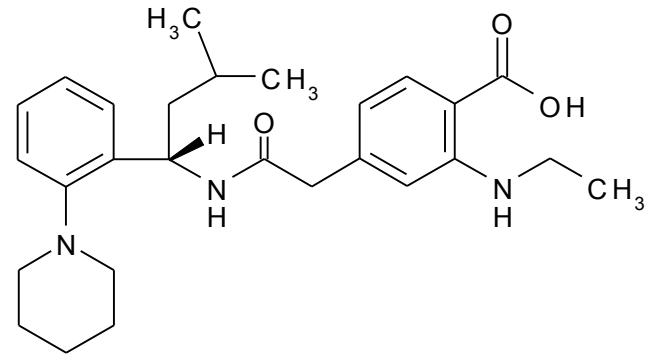
In hypoglycemia and the simultaneous treatment with other POADs can not be administered sucrose (monosacharide necessary - Glu, Fru) or Glucagon

# Meglitinides

repaglinid

nateglinid

meglitinid



repaglinide

## Mechanism of the action

similar to SU-derivatives:

block ATP- sensitive K<sup>+</sup> channel in membrane of beta-cells,  
depolarisation of membrane, activation of voltage-gated  
Ca<sup>2+</sup> channel, influx Ca<sup>2+</sup> , insulin release

through different receptor at K<sup>+</sup> channel



# Meglitinides

repaglinid

nateglinid

meglitinide

## Pharmacokinetics:

- good bioavailability
- extensive protein binding (up to 98 %)
- metabolized - inactive compounds
- excreted mainly in faeces

## Clinical use

- combined with metformin - esp. if patient not sufficiently compensated
- alternative of the SU medication in patients with renal impairment (excreted in bile)

## Contraindications:

- hypersensitivity
- DM I. type
- diabetic ketoacidosis
- pregnancy, lactation

## AE:

Hypoglycemia Nausea, diarrhea, joint pain

# GLP1 – Glucagon-like peptide 1 + analogues „EXENDIN, EXENATIDE“

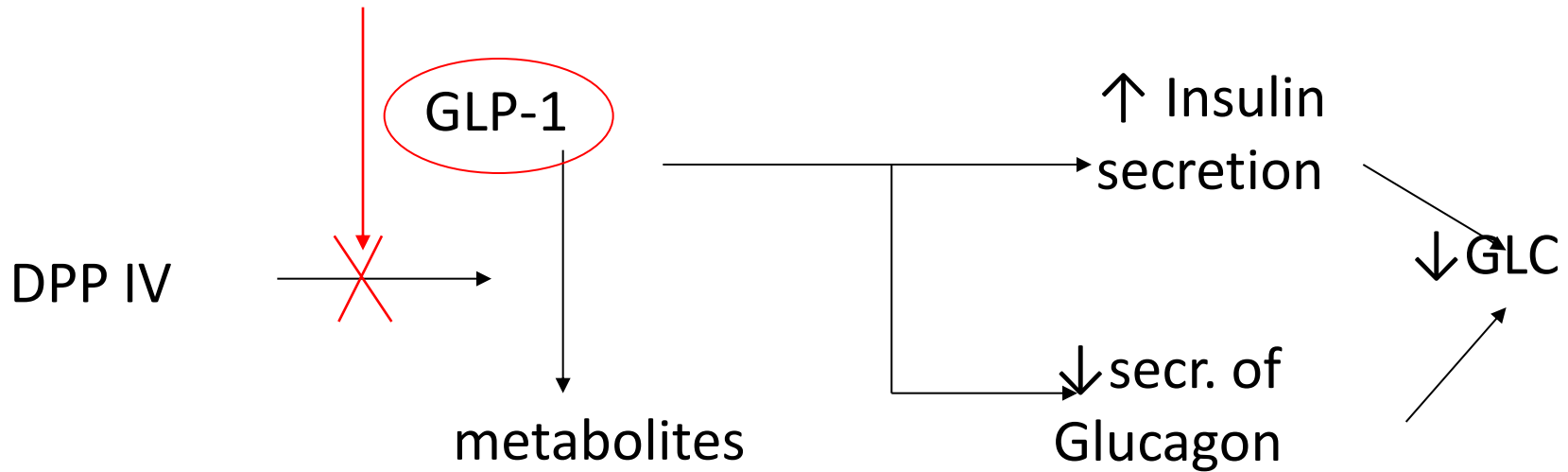
*Heloderma suspectum; Gila Monster*

- exenatide, liraglutide
- lixisenatid, albiglutide
- s.c. administration



- GLP1-physiologically secreted postprandially, in DM II insufficiently
- stimulate insulin secretion (dependent on glycemia) inhibit glucagon secretion, prolong stomach content evacuation

# i DPP IV : inhibitors of dipeptidyl peptidase 4; *syn. „Gliptins“*



- **Advantages:** no hypoglycemia, stops progressin of illness
- Nowadays: in combinatin with others (POADs)  
better glycemc control than conventional drugs

# i DPP IV : inhibitors of dipeptidyl peptidase 4; *syn. „Gliptins“*

- Sitagliptin Launched in the US in 2006, in the Czech Republic 2008
- 24-hour effect - 2-3-fold increase in GLP-1 concentrations
- Protects B cells
- fixed combinations (eg with metformin)
- **Saxagliptin, linagliptin, vildagliptin, allogliptin**, gemigliptin
- For the treatment of T2DM fixed combination with metformin/SU  
glitazone/statin

# SGLT2 (sodium-glucose cotransporter) Inhibitors

- Increased reabsorption in kidney in DM2
- Inhibition SGLT2 = controlled glucosuria
- Dapagliflozin, kanagliflozin, empagliflozin
- Hb1Ac decrease by 0.8%
- BMI decrease (negative energy Balance)

AE: thirst, hypoglycemia, genital infections

CI: over 75 years, concurrent loop diuretics, pioglitazone

# DM - Complications

## 1) hypoglycemia - ( $< 3,5$ mmol/l)

*consciousness* - sweet (sacharide) drink,  
meal

*unconsciousness* - i.v. Glu 20-40%

- u DM I. type *i.v.* glucagon

# DM - Complications

- 2) **allergy** (hypersensitivity IgE) - corticosteroids, adrenalin i.v.
- 3) **insulin resistance** - IgG against insulin (animal insulins), change insulin preparation, POAD
- 4) **lipodystrophy** - change application (scheme), esthetic surgery





# DM - Complications

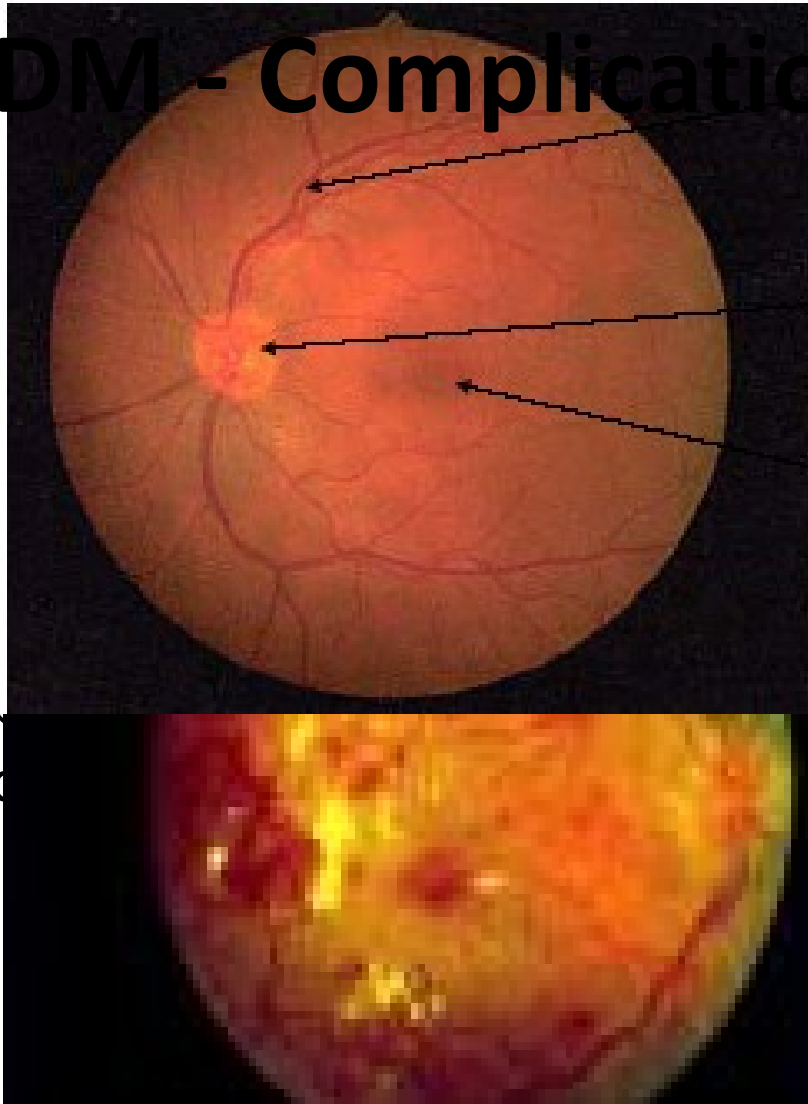
**Diabetic nephropathy** - hypertrophy, hyperfiltration; → nephropathy, ↑blood pressure (ACEi), microalbuminuria, insufficiency

**Diabetic neuropathy** – gabapentin, pregabalin, carbamazepine, TCA, duloxetine

**Hyperlipoproteinemia** - diet, statins, fibrates, probucol, nicotinic acid..

# DM - Complications

D  
CC  
L  
a  
v  
L  
C



proliferation, small vessels

microvascular impairments,

retinopathy, dry, proliferative, complicated  
macular oedema

neuropathies

gangrene



# DM - Complications

Relapse of infections, mycosis  
hypertension

