Antidiabetic drugs

Jan Jurica

Antidiabetic drugs

- Insulin
- 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

Types of diabetes

Type 2 DM (85-90%)

Relative insulin deficiency

Damaged 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

- Gestational DM = in 20% of non-obese and 60% of obese women with GDM – risk for DM2 in 15yrs, OR = 7

Types of diabetes

OGTT

75 g of glucose in 200 ml of water
2 hours after collection and determination of glycemia in venous plasma

Interpretation:
≤ 7.8 mmol /L DM excluded
7.8 - 11 mmol / L - impaired glucose tolerance.
> 11.1 mmol / L Diabetes mellitus

Rare subtypes of diabetes

LADA - latent autoimunne 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 by OAD/non-insulin

Regulation of blood glucose

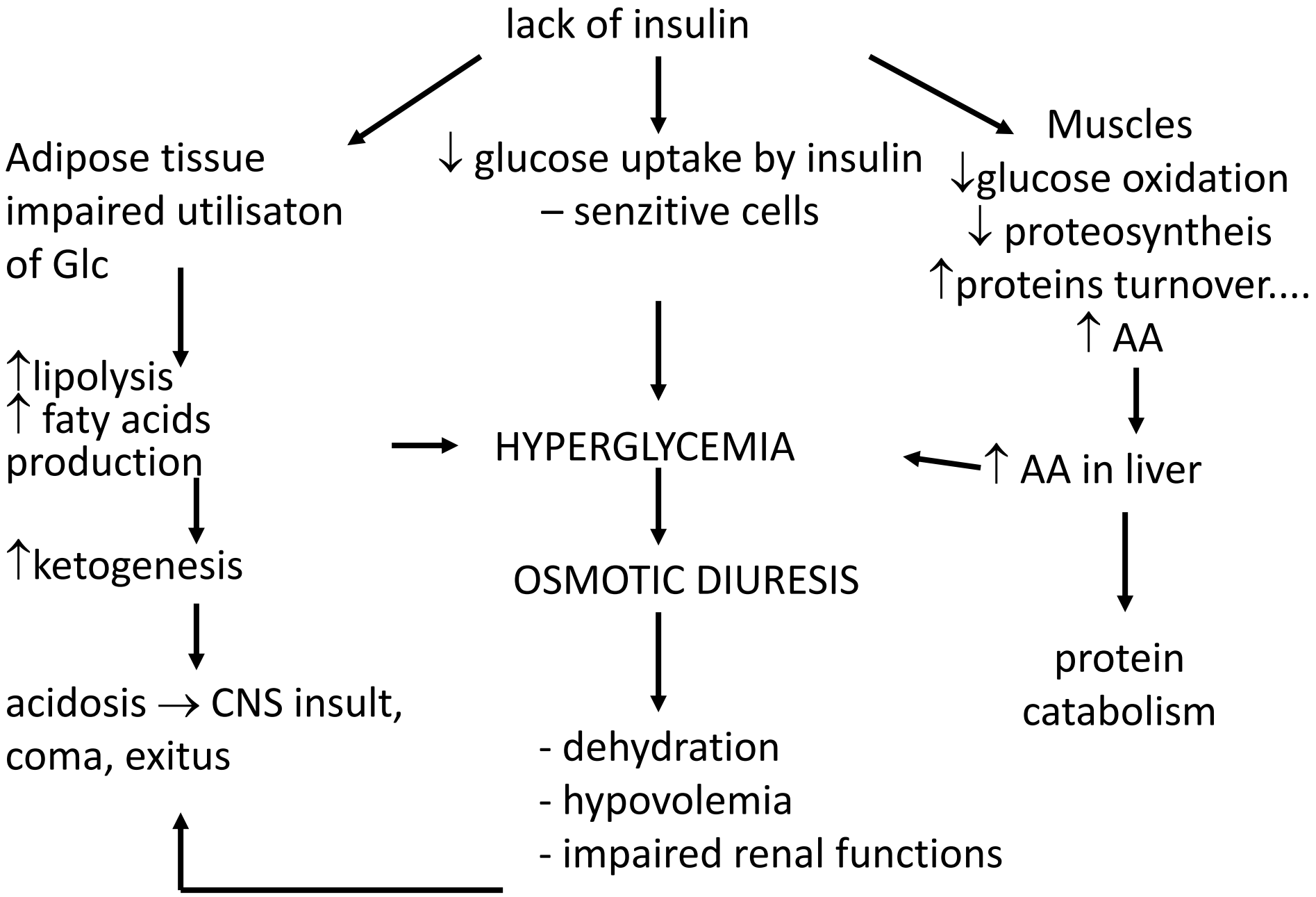
1. hormonal - antagonism with glucagon in the liver, cortisol muscle tissue, aldosterone and growth hormone

2. autoregulation - glycaemia works back to secretion – Glc penetrates into B cells and opens Ca channel, signal for insulin release

3. nervous system - PS has a hypoglycemizing effect, S hyper.

Insulin is produced at a dose of 20-40 IU / day - 1/2 continuous, 1/2 pulse

👁 Insulin is rapidly metabolised by proteases and glutathione insulin transhydrogenases (plasma half-life of 3-5 min)


lack of insulin
Adipose tissue
impaired utilisaton
of Glc
↓ glucose uptake by insulin
– senzitive cells
Muscles
↓glucose oxidation
↓ proteosyntheis
↑proteins turnover....
↑ AA
↑lipolysis
↑ faty acids
production
HYPERGLYCEMIA
↑ AA in liver
↑ketogenesis
OSMOTIC DIURESIS
protein
catabolism
acidosis → CNS insult,
coma, exitus
- dehydration
- hypovolemia
- impaired renal functions

METABOLIC SYNDROME

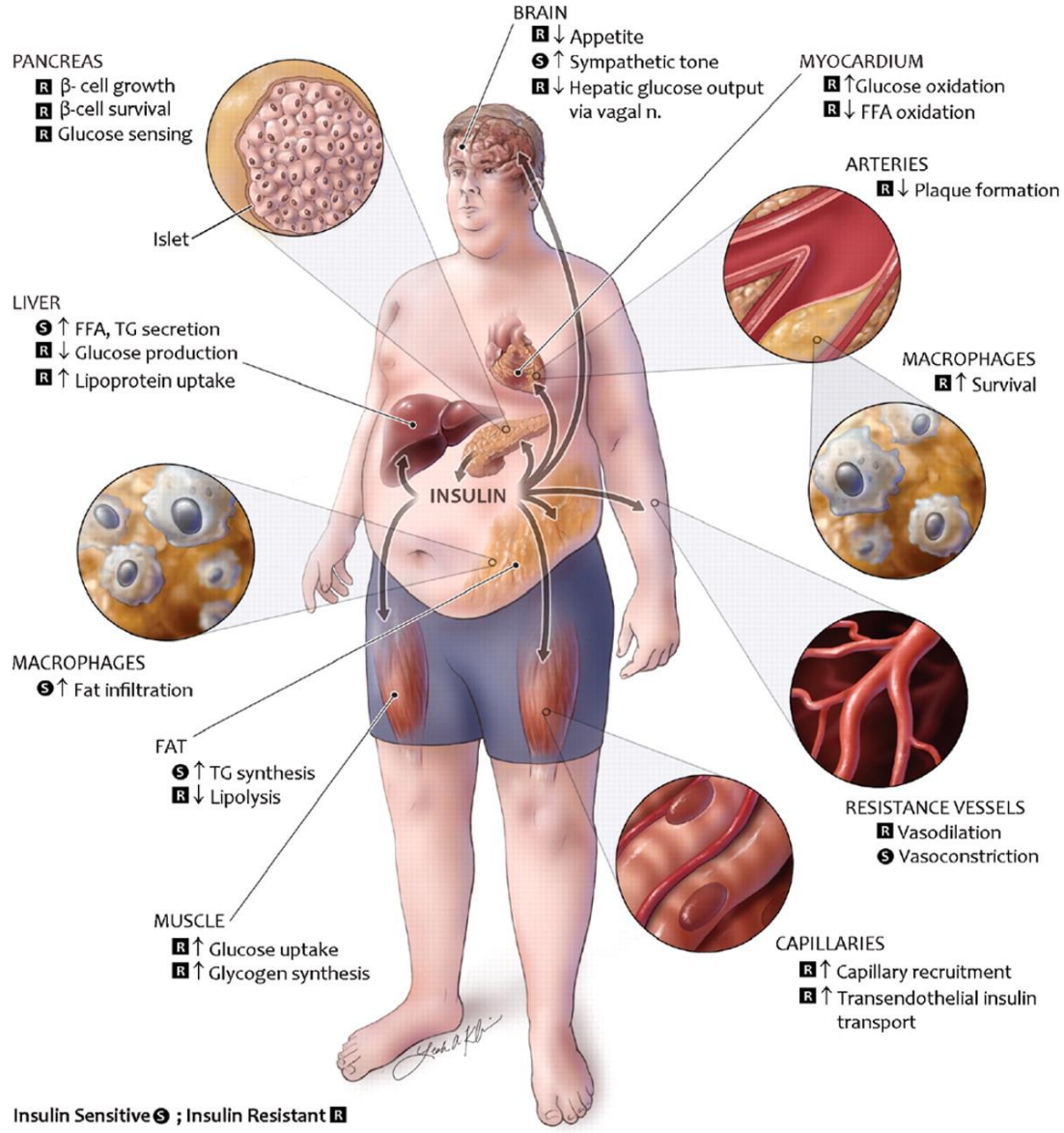
Insulin resistance

Hypertension

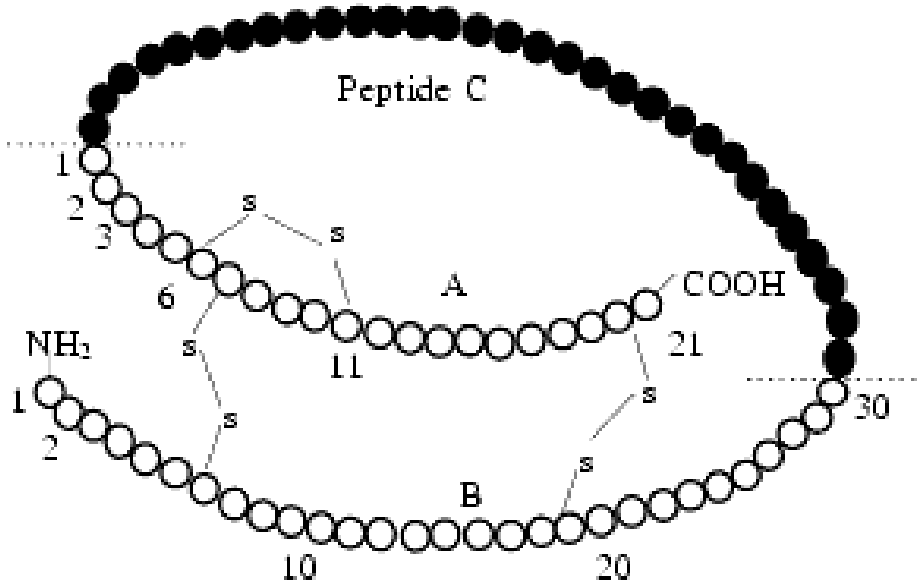
Hypertriglyceridaemia

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

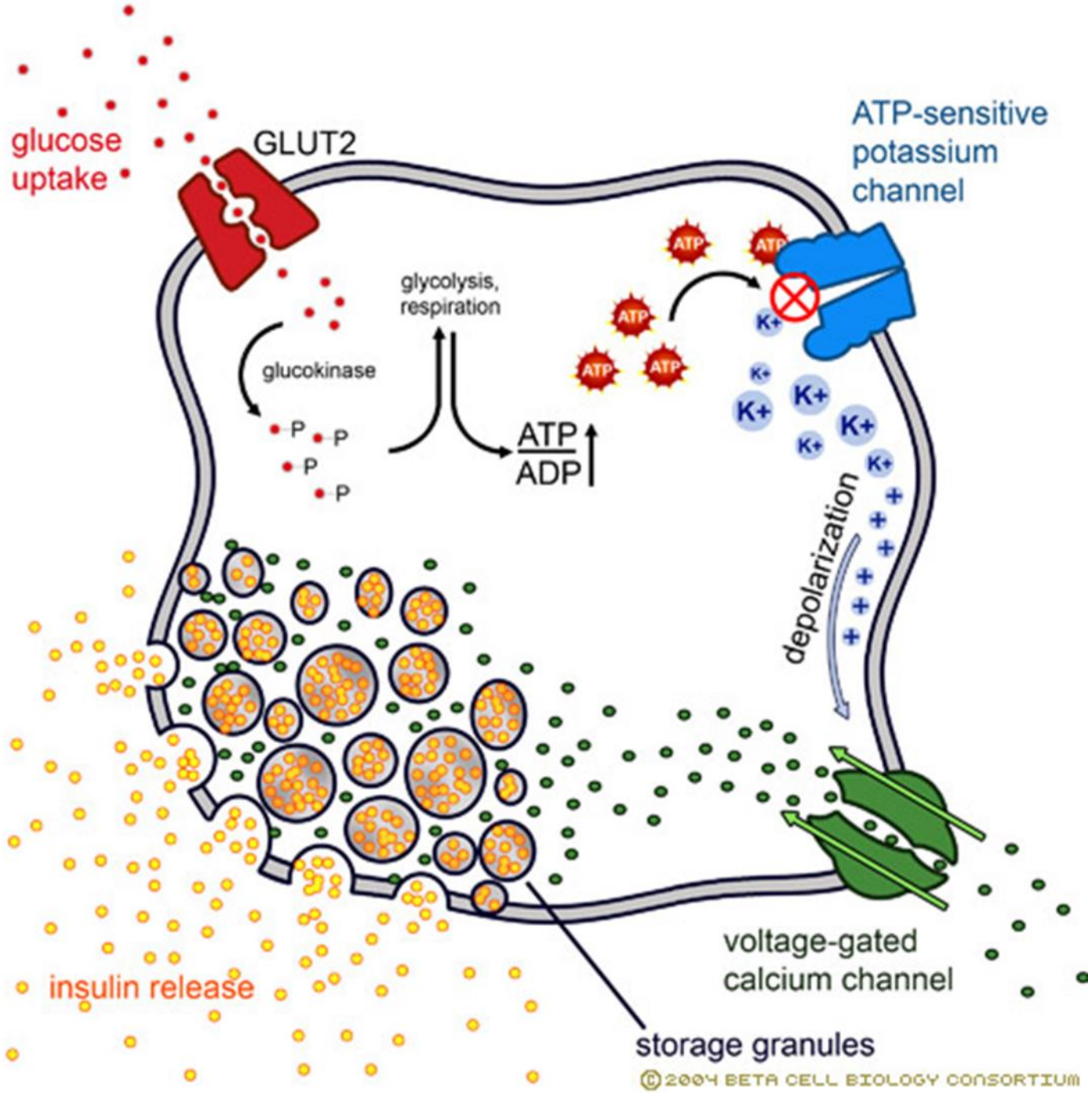
marker of endogenous secretion of insulin
(is not metabolized by the liver so quickly)

Pharmacokinetic parameters

- Inter- and intra-individual variability in absorption (25-50 % after *s.c., i.m*.)

  - appl. site, vascularity, temperature, massage, sunbathing, vasodilatators

- $T_{1/2}$ 7-10 min.


glucose uptake
GLUT2
ATP-sensitive potassium channel
glycolysis, respiration
glucokinase
ATP
ADP
depolarization
voltage-gated calcium channel
insulin release
storage granules
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insulin secretagogues

glucose

glucagon

fatty acids

OAD

amplifiers of glucose-induced I. secretion

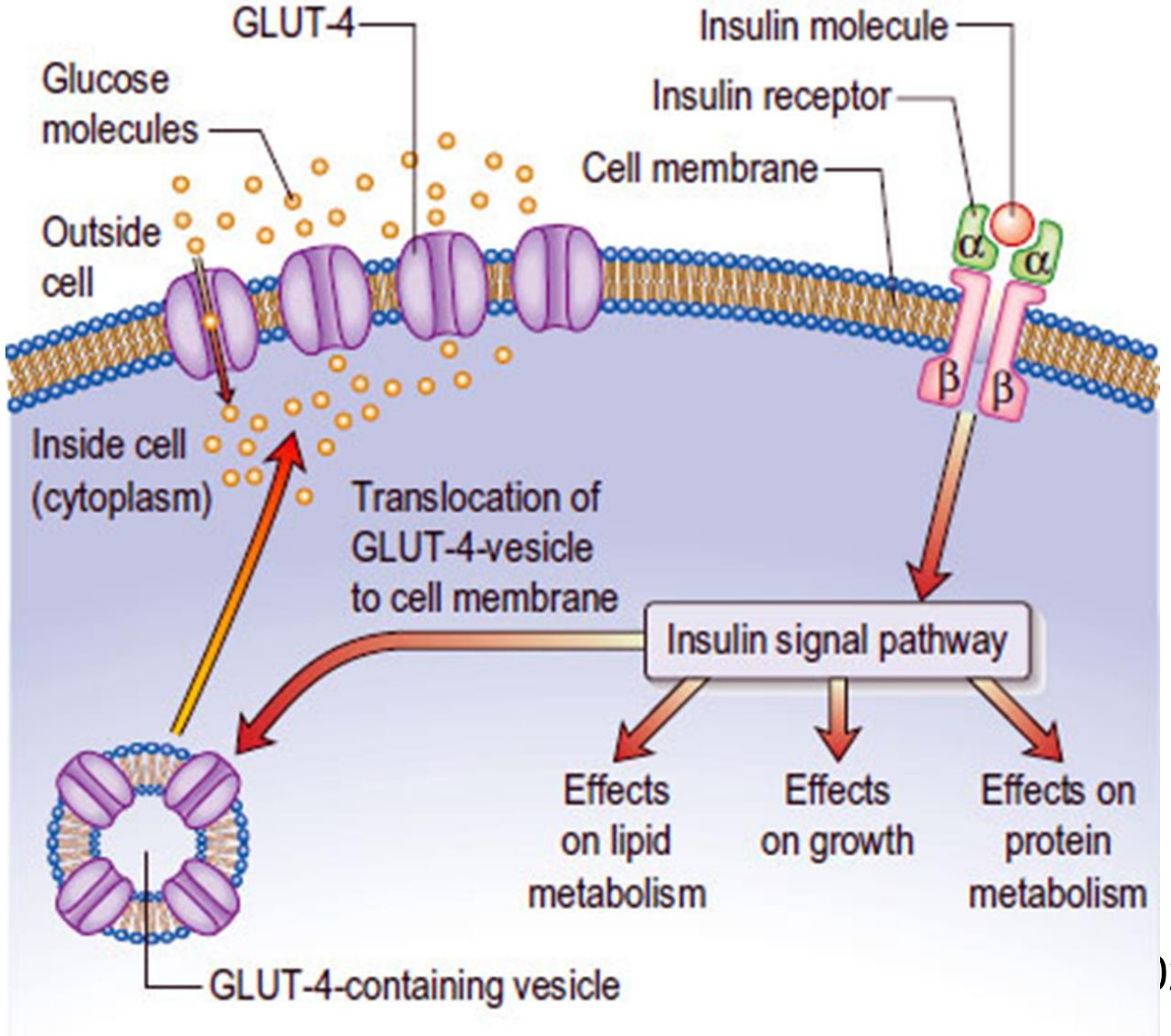
gastrin, secretin, cholecystokinin

GLP1

Beta-adrenergic stimulation

AA (Lys, Arg, Leu)

Insulin receptor



Types 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 infetion/gangrene

- DM II when 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

suspesions of „zinc-insulin“

suspensions „protamin-zinc-insulin“

Σ 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 effect - 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.

Insulin preparations

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 action 1 - 2.5 hours

Maximum 4 - 8 hours.

Action 12 - 24 hours.

Insulin preparations

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

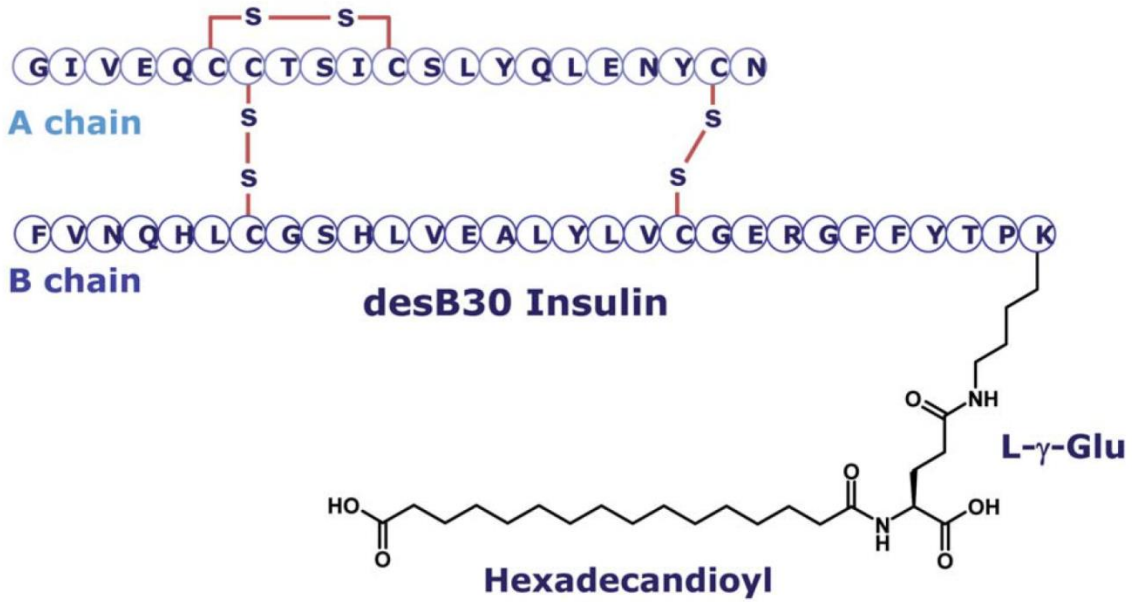
Biosimilars of glargine – **Abasaglar**

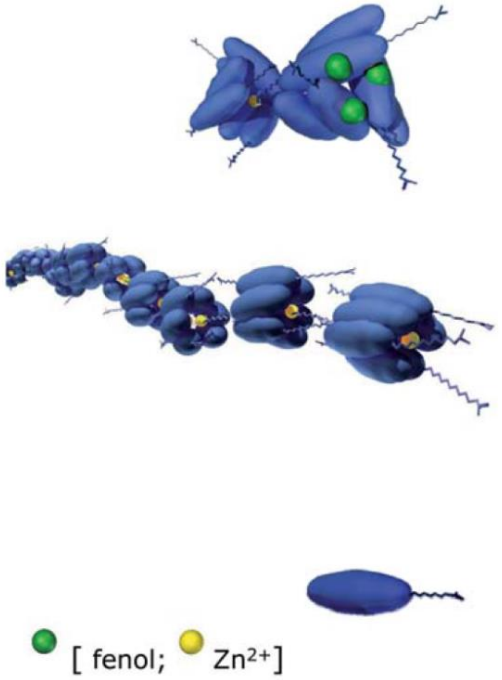
Glargin U300 – slow release from s.c. depo,longer halflife lower variability less hypoglycemia during night

PEG lispro- long acting insulin (!)

- polyethylenglycol, ↑ hydrodynamic size, slow absorption, degradation

Degludec





Solution of degludec

subQ depo

absorption

Insulin preparations

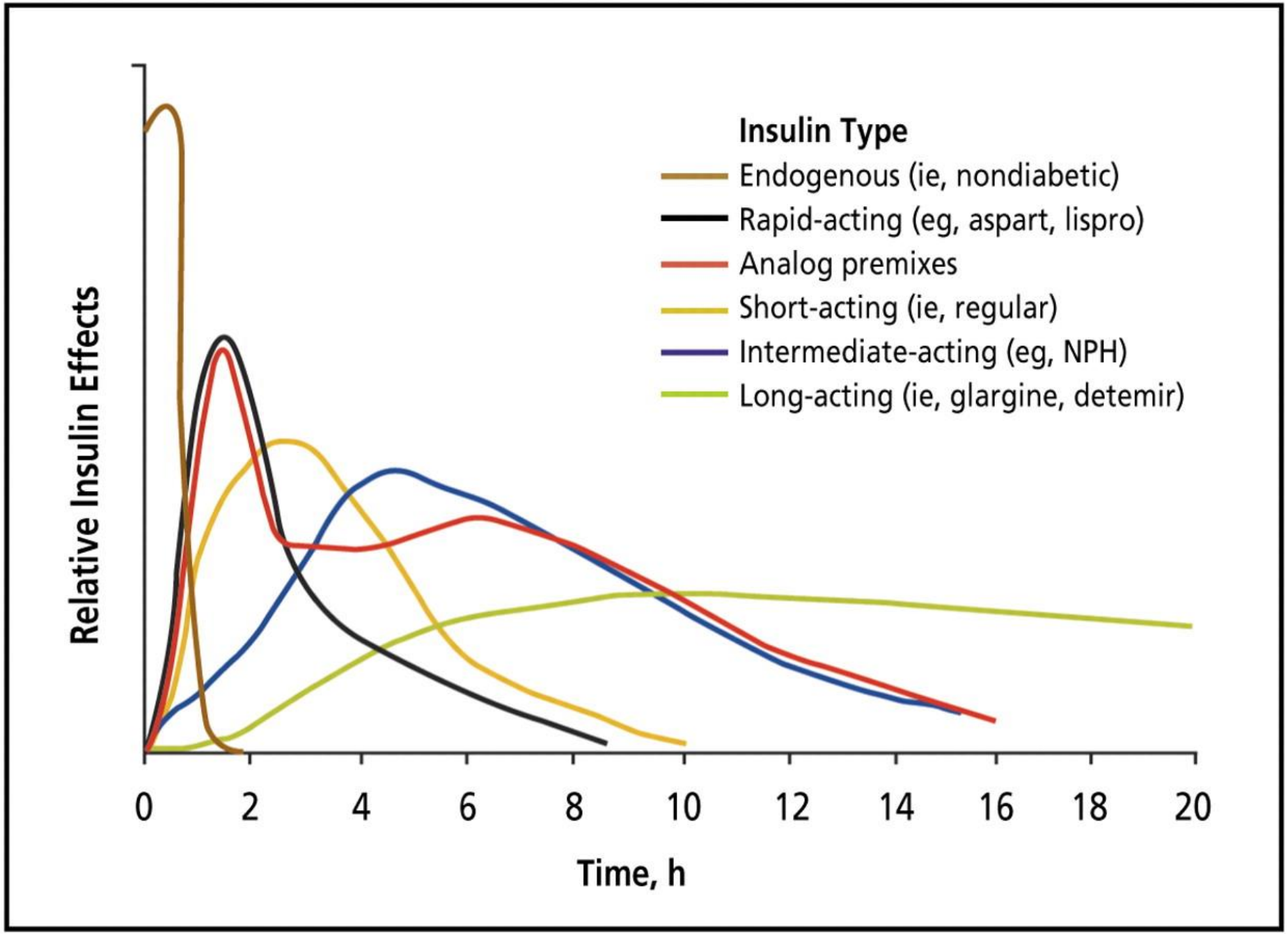
solutions/suspensions of insulin

suspesions of „zinc-insulin“

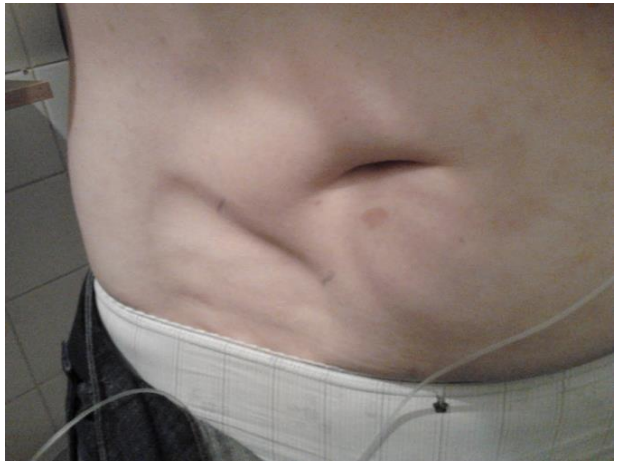
suspensions „protamin-zinc-insulin“

Σ insulin as a mixture of mono-/di-/tetra-/hexamers

+ pH, stability, isotonicity adjusted


Insulin Type
Endogenous (ie, nondiabetic)
Rapid-acting (eg, aspart, lispro)
Analog premixes
Short-acting (ie, regular)
Intermediate-acting (eg, NPH)
Long-acting (ie, glargine, detemir)
Relative Insulin Effects
0
2
4
6
8
10
12
14
16
18
20
Time, h

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 ?

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, cardial 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 panceratic secretion
- smooth muscle relaxation (cAMP)

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

Antidiabetics

(GLD = glucose lowering drugs)

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 (AOD)

The effect of most OAD is boubd to the ability of insulin secretion

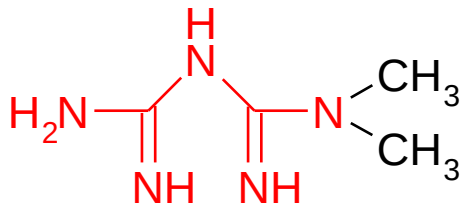
Most OAD are contraindicated in pregnancy (metformin may be used)

- 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

Metformin

Contraindications:

Kidney disease (creatinine above standard, 130 µmol / l)

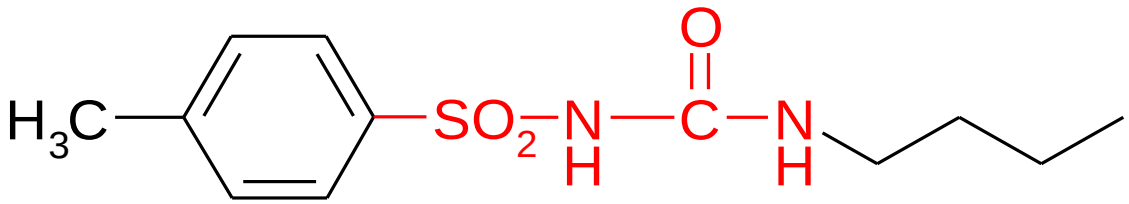
Alcoholism, liver disease - because of a higher risk of lactic acidosis

Therapeutic Use Type 2 DM, drug of choice (especially in obese patients) Non-obese in combinations (with insulin, glitazones, analogues, SU, incretins, gliflozines)

OFF label indication: PCOS (polycystic ovary syndrome)

anticancer effect (AMPK / mTOR)

sulfonylurea derivatives (SU)

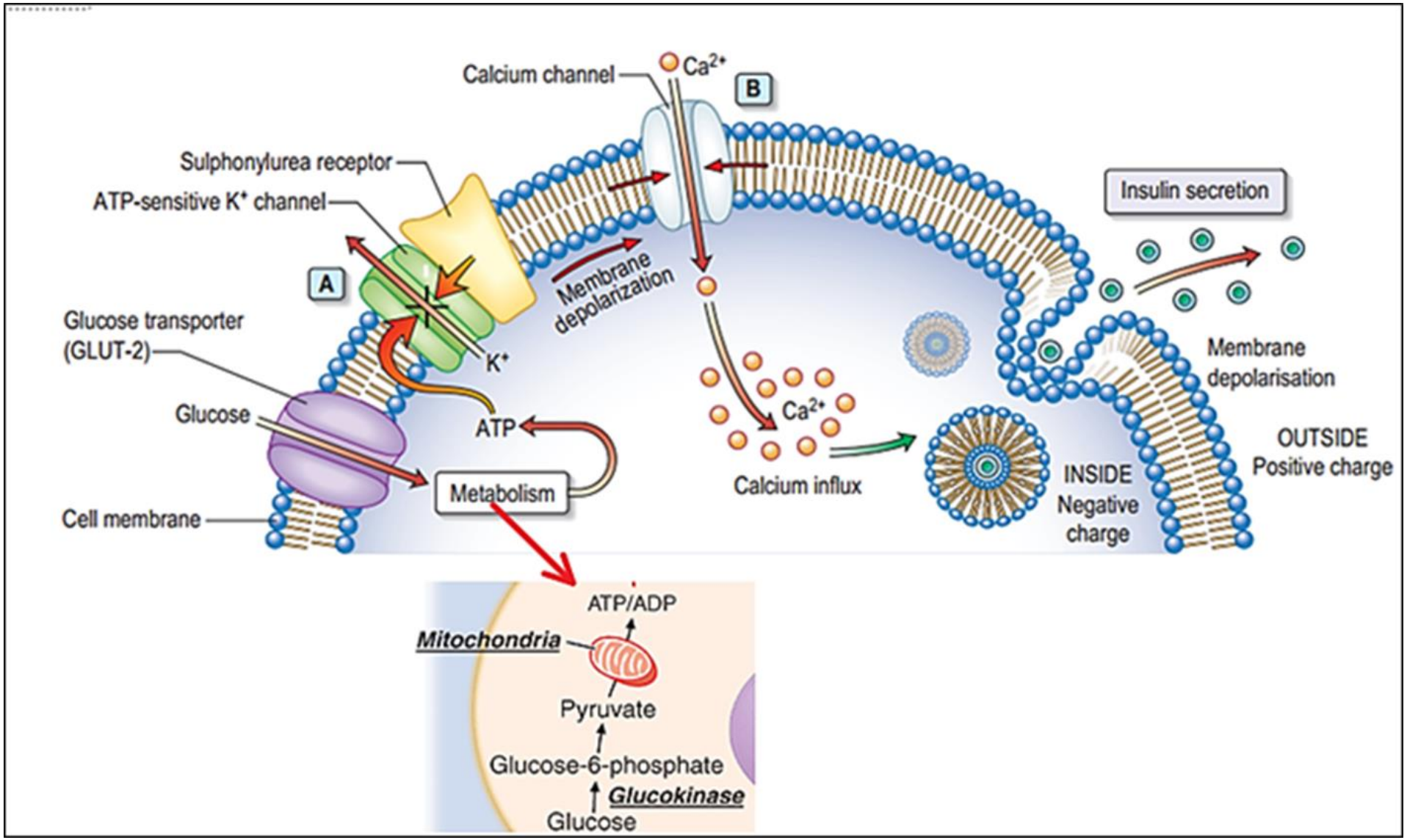


Tolbutamide

mechanism of action

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

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


Calcium channel
Ca^{2+}
B
Sulphonylurea receptor
ATP-sensitive K^+ channel
A
Membrane depolarization
Insulin secretion
Glucose transporter (GLUT-2)
K^+
Glucose
ATP
Metabolism
Cell membrane
Ca^{2+}
Calcium influx
Membrane depolarisation
OUTSIDE
Positive charge
INSIDE
Negative charge
ATP/ADP
Mitochondria
Pyruvate
Glucose-6-phosphate
Glucokinase
Glucose

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

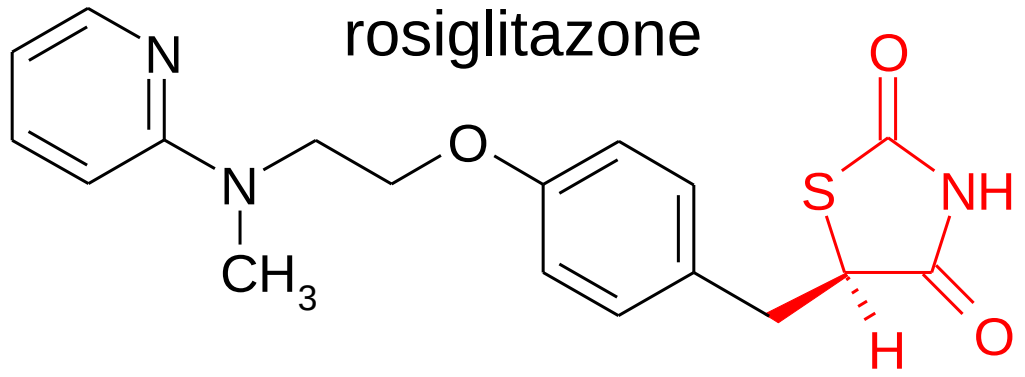
pregnancy, hypersensitivity

Thiazolidinediones

rosiglitazon

pioglitazon

troglitazon



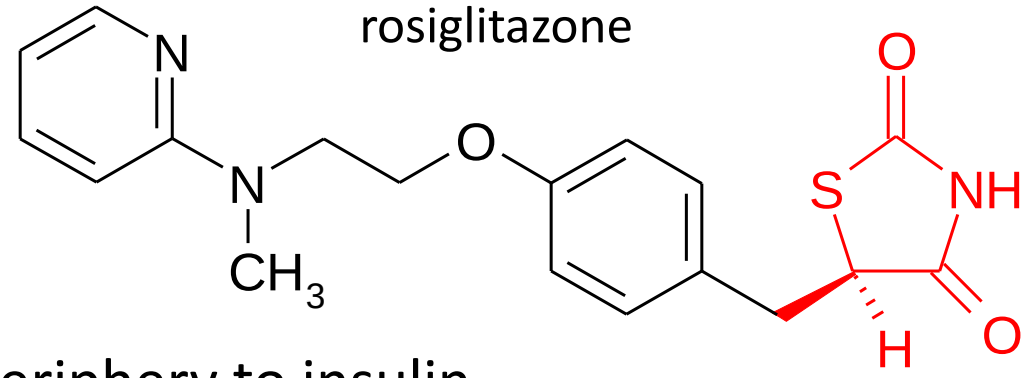
Mechanism of action

- increase the sensitivity of periphery to insulin

- ligands of PPARγ (part of the steroid and thyroid superfamily of nuclar receptors) modulate the expression of the genes involved in the metabolism of lipids and glucose

Thiazolidinediones

Mechanism of action



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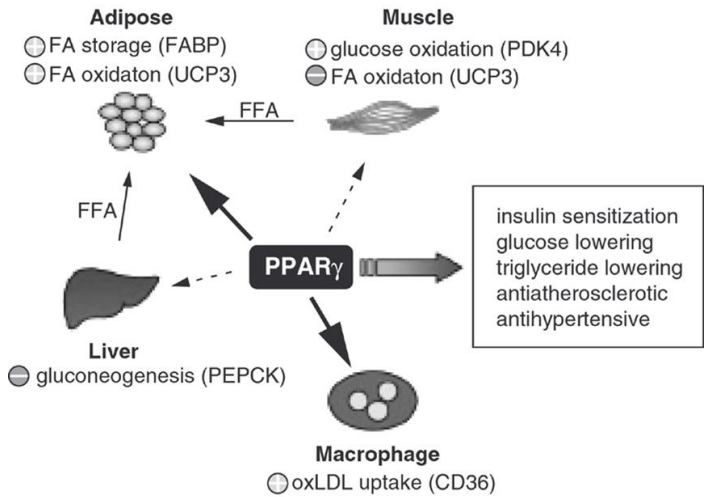


Thiazolidindiones

- 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

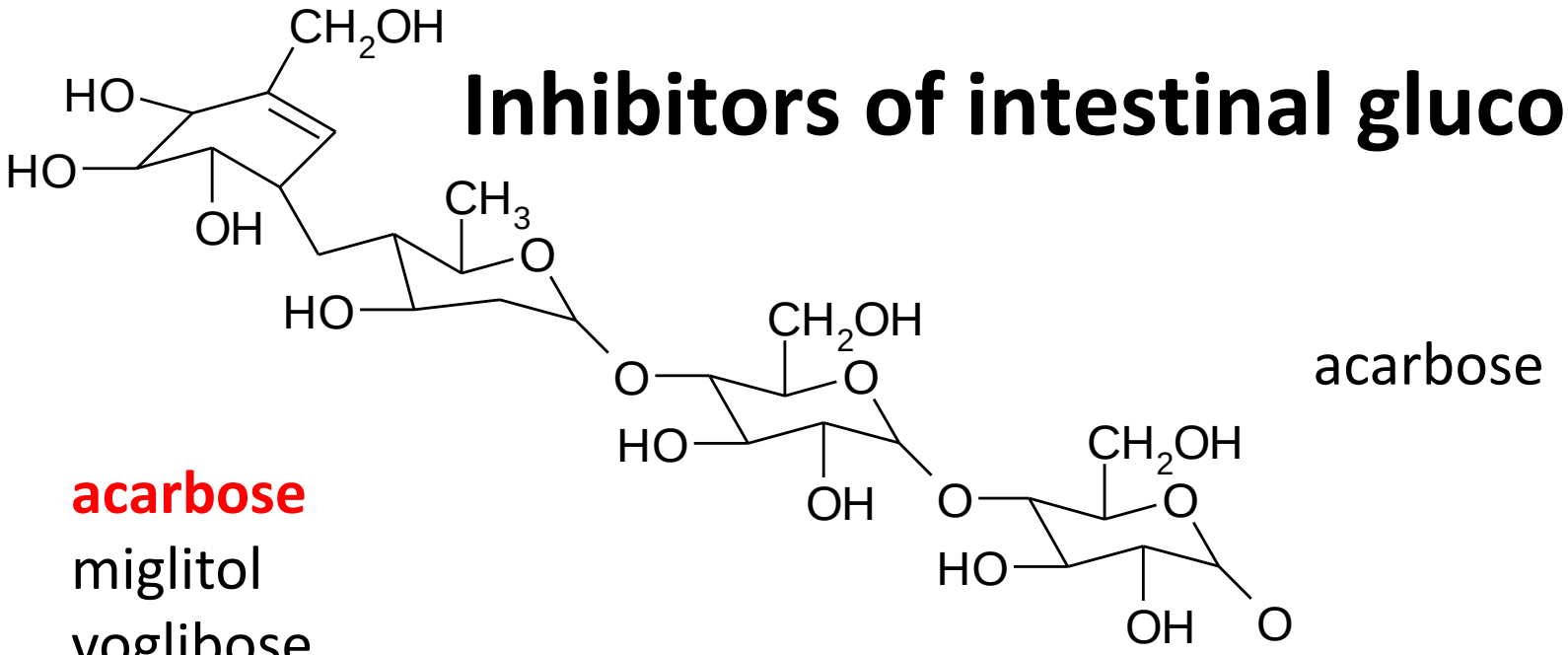
Hypersensitivity

Predisposition to heart failure

Liver damage

Pregnancy, lactation

Inhibitors of intestinal glucosidase



acarbose

acarbose
miglitol
voglibose

Mechanism of the action

- reduce sacharides absorption from GIT
- competitive inhibition of the gut α - 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 rech the systemic blood, miglitol does
- „educative drugs“- consequences in bad compliance

In hypoglycemia and the simultaneous treatment with other

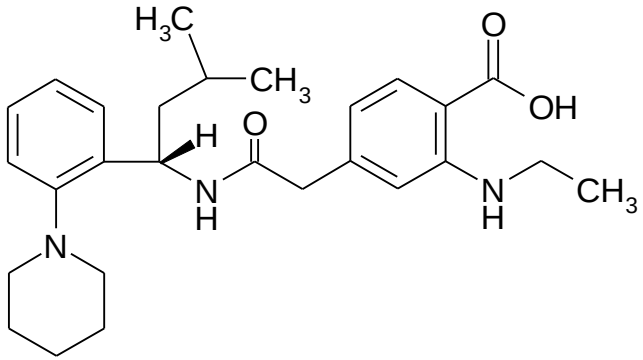
POADs can not be administered sucrose
(monosacharide necessary - Glu, Fru) or Glucagon

Meglitinides

repaglinid

nateglinid

meglitinid



repaglinide

Mechanism of the action

similar to SU-derivatives:

block ATP- sensitive K^+ channel in membrane of beta-cells, depolarisation of membrane, activation of voltage-gated Ca^{2+} channel, influx Ca^{2+} , insulin release

through different receptor at K^+ channel

Meglitinides

repaglinid

nateglinid

meglitinide

Pharmacokinetics:

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

Clinical use

- combined with metformin - esp. if patient not suffciently compensed
- alternative of the SU medication in patients with renal impariment (excreted into 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

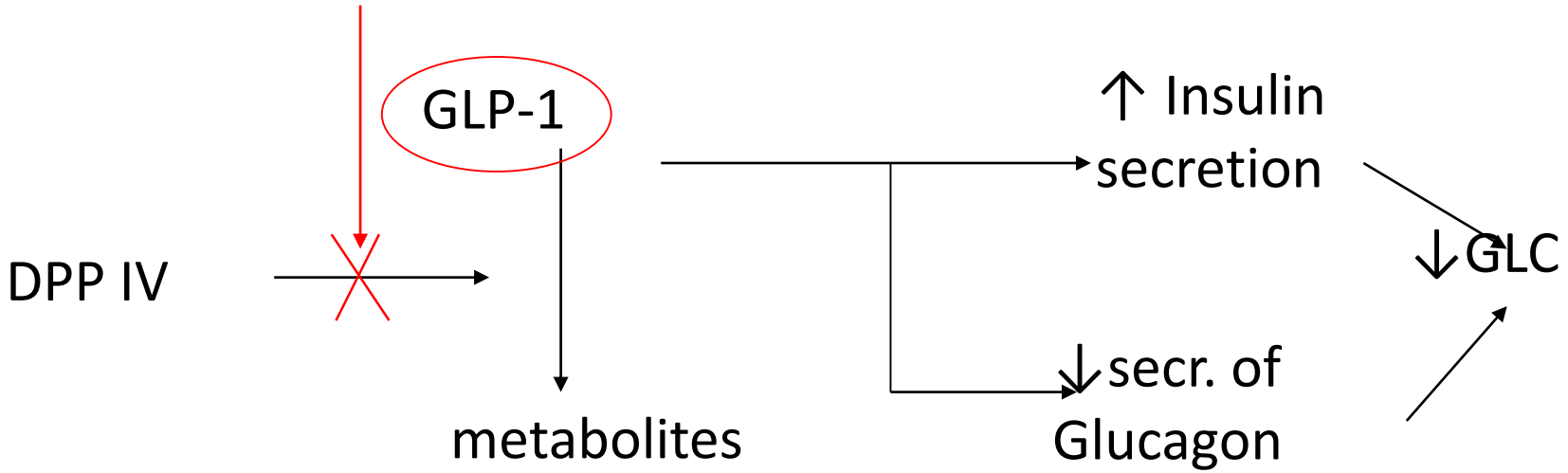
lixisenatid, albiglutide

s.c. administration

- GLP1-physiologically secreted postprandially, in DM II insufficiently

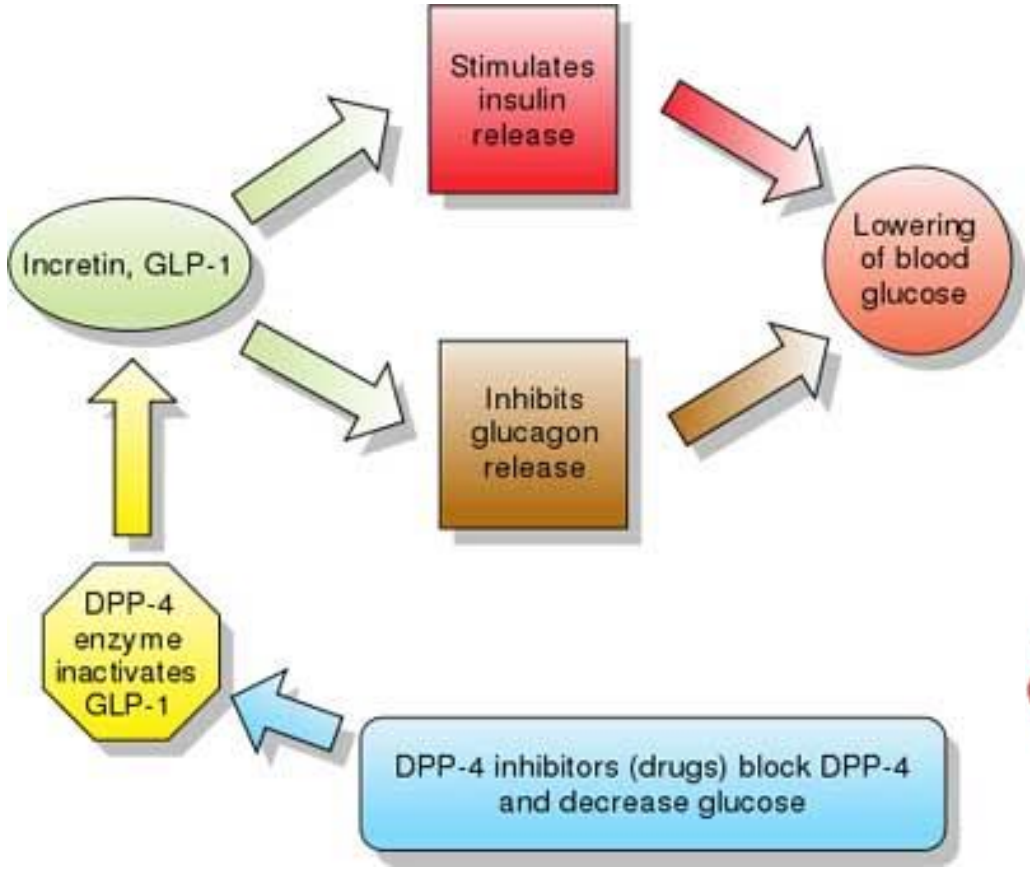
- stimulate insulin secretion (dependent on glycemia) inhibit glucagon secretion, prolong stomach content evacuation

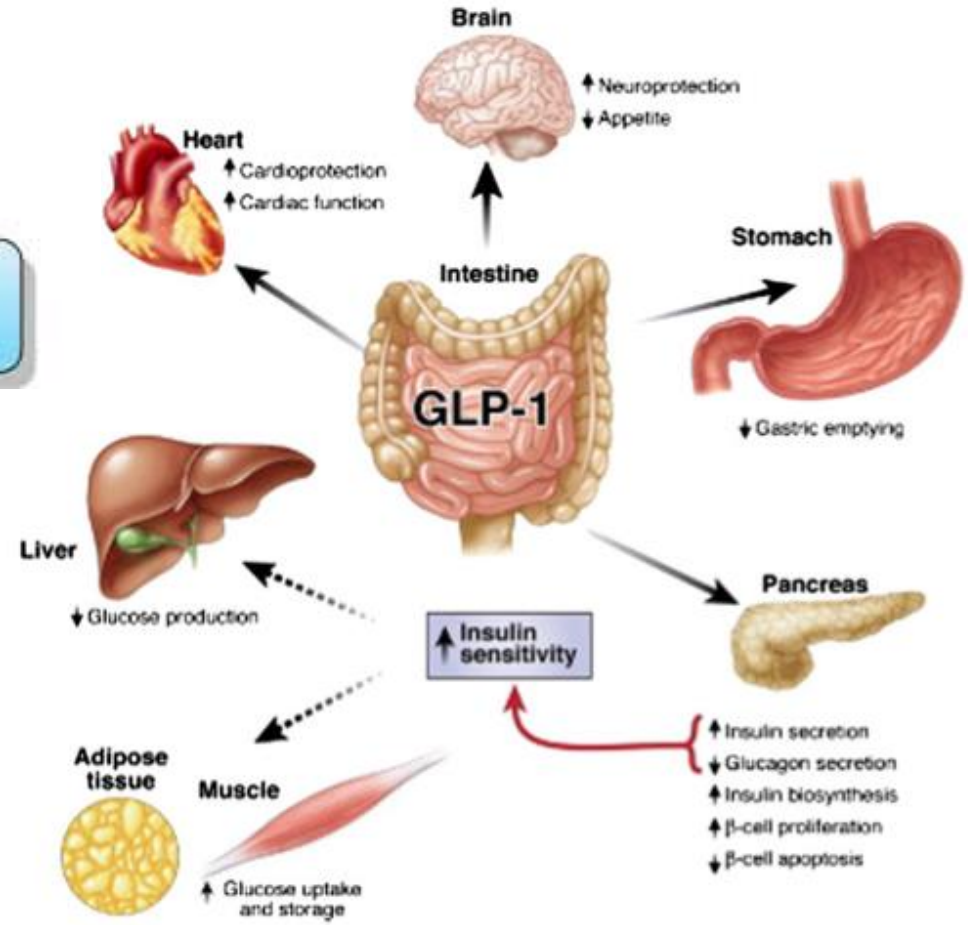
i DPP IV : inhibitors of dipeptidyl peptidase 4; *syn. „Gliptins“*



- **Advantages**: no hypoglycemia, stops progressin of ilness
- Nowadays: in combinatin with others (POADs)

  better glycemic control than conventional drugs


Stimulates insulin release
Incretin, GLP-1
Lowering of blood glucose
Inhibits glucagon release
DPP-4 enzyme inactivates GLP-1
DPP-4 inhibitors (drugs) block DPP-4 and decrease glucose


Brain
Neuroprotection
Appetite
Heart
Cardioprotection
Cardiac function
Intestine
Stomach
GLP-1
Gastric emptying
Liver
Glucose production
Pancreas
Insulin sensitivity
Insulin secretion
Glucagon secretion
Insulin biosynthesis
β-cell proliferation
β-cell apoptosis
Adipose tissue
Muscle
Glucose uptake and storage

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

- 24-hour effect - 2-3-fold increase in GLP-1 concentrations
- Protects B cells
- fixed combinations (eg with metformin)
- **linagliptin, sitagliptin, vildagliptin, aloglitpin**
- For the treatment of T2DM fixed combination with metformin/SU glitazone/statin

SGLT2 (sodium-glucose cotransporter) Inhibitors

- Increased reabsorbtion in kidney in DM2
- Inhibition SGLT2 = controlled glucosuria
- Cardioprotective, renoprotective !! Convincing data from large studies

- dapagliflozin, canagliflozin, **empagliflozin**
- Hb1Ac decrease by 0.8%
- BMI decrease (negative energy Bilance)

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%

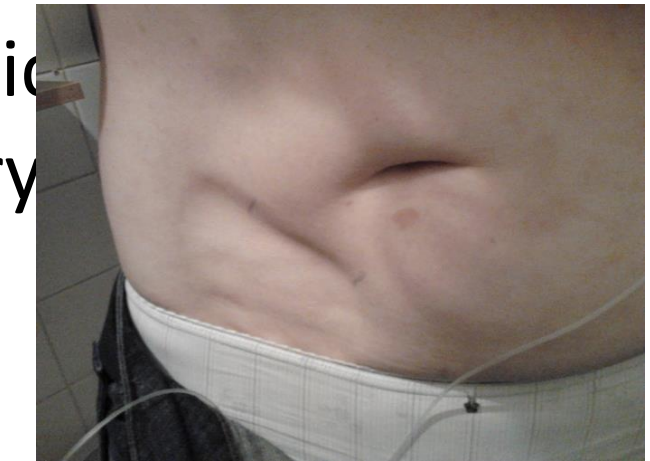
- u DM I. type *i.v*. glucagon

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 applic (scheme), esthetic surgery



DM - Complications

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

Diabetic neuropathy – gabapentin, pregabaline, carbamazepine, TCA, duloxetine

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

DM - Complications

Diabetic retinopathy - protein glycation, small vessels collagenisation; microangiopathy

Diabetic foot - micro- and macrovascular impairments,

a) neuropatic - warm, non-sensitive, dry, complicated with neuropathic ulcer, oedema
b) ischemic - cold, without pulsations
c) neuroischemic - ulcerations, gangrene