MUNI
MED

# ANTIDIABETICS

Alena Máchalová



# Diabetes Mellitus

Chronic, metabolic, etiopathogenetically heterogeneous disease, the underlying feature is hyperglycemia:

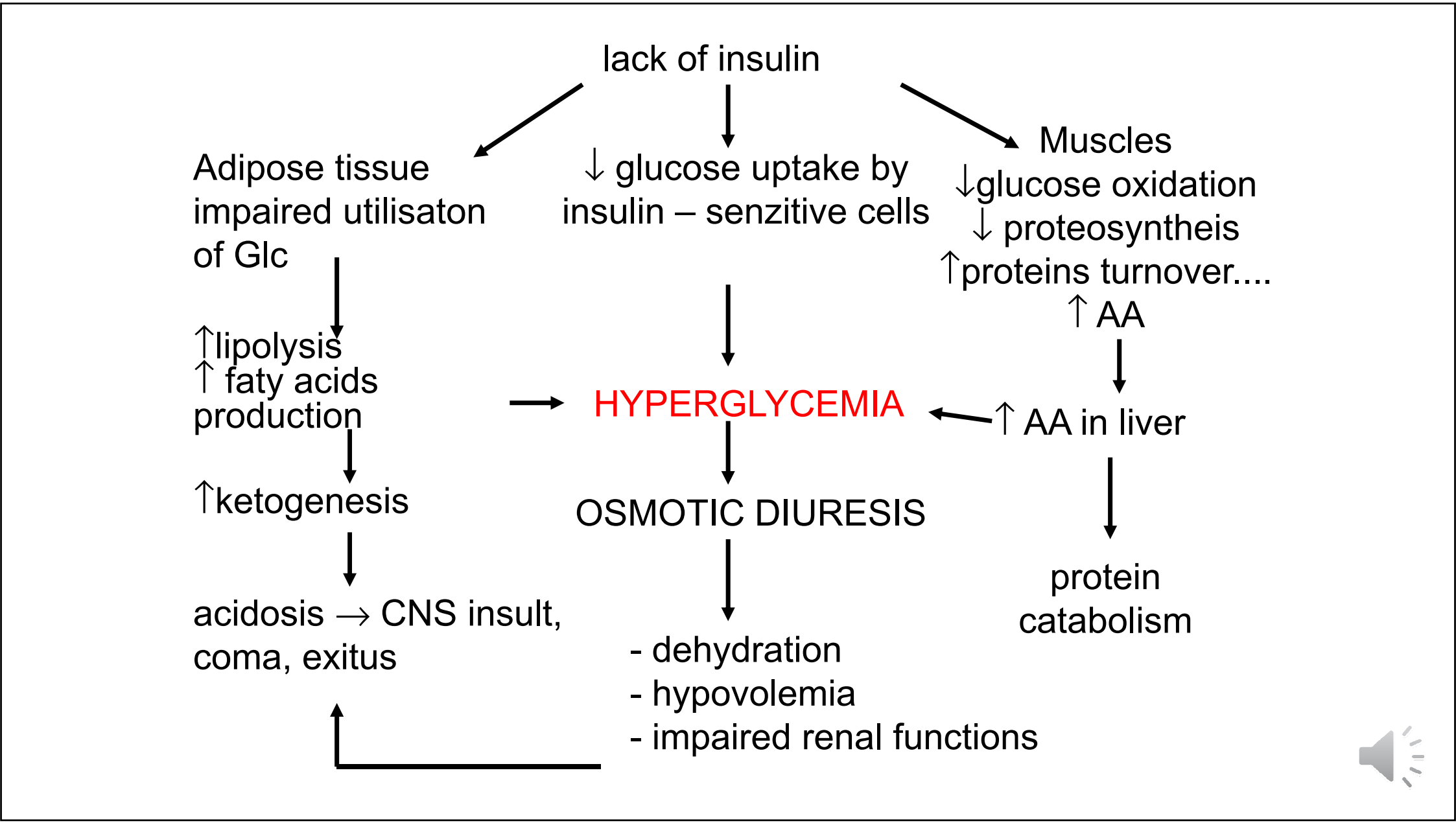
- **≤ 5.6 mmol/L**
- **IFG 5.6 (6,1) -6.9 mmol/L**
- **IGT** 2hPG ≥7.8 <11.1 mmol/L after oGTT

Due to the insufficient effect of insulin or its **absolute or relative deficiency**

The genetic predisposition of both forms of DM

# Statistics

- In 20 years there is a 10% increase in number of patients with diabetes
- 31.12.2006 there is about 750 000 of diabetics
- From this number 91,5 % is II. type, 6,7 % I.type, other forms are rare
- Absolute number of 2. type diabetics is constantly increasing
- Therapy of 2.type diabetes represents 5–10 % expenses in healthcare


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

# Acute diabetic syndrome

- hyperglycemia
- glycosuria, osmotic dehydration
- intracelular lack of Glu $\rightarrow$ catabolism, lipolysis
- metabolic acidosis
- deep breathing
- ketoacidotic coma

# Chronic diabetic syndrome

- protein glycation, autooxidation, peroxidation of lipids, lipoproteins
- micro / macro - angiopaties
- late complications of DM
  - Nefropathy
  - Diabetic foot
  - Infections
  - Retinopathy

# DM I.type

- absolute lack of insulin

  peak between 13 and 15 years, high mortality if not treated

A - autoimmune form

with antibodies

B - idiopatic form

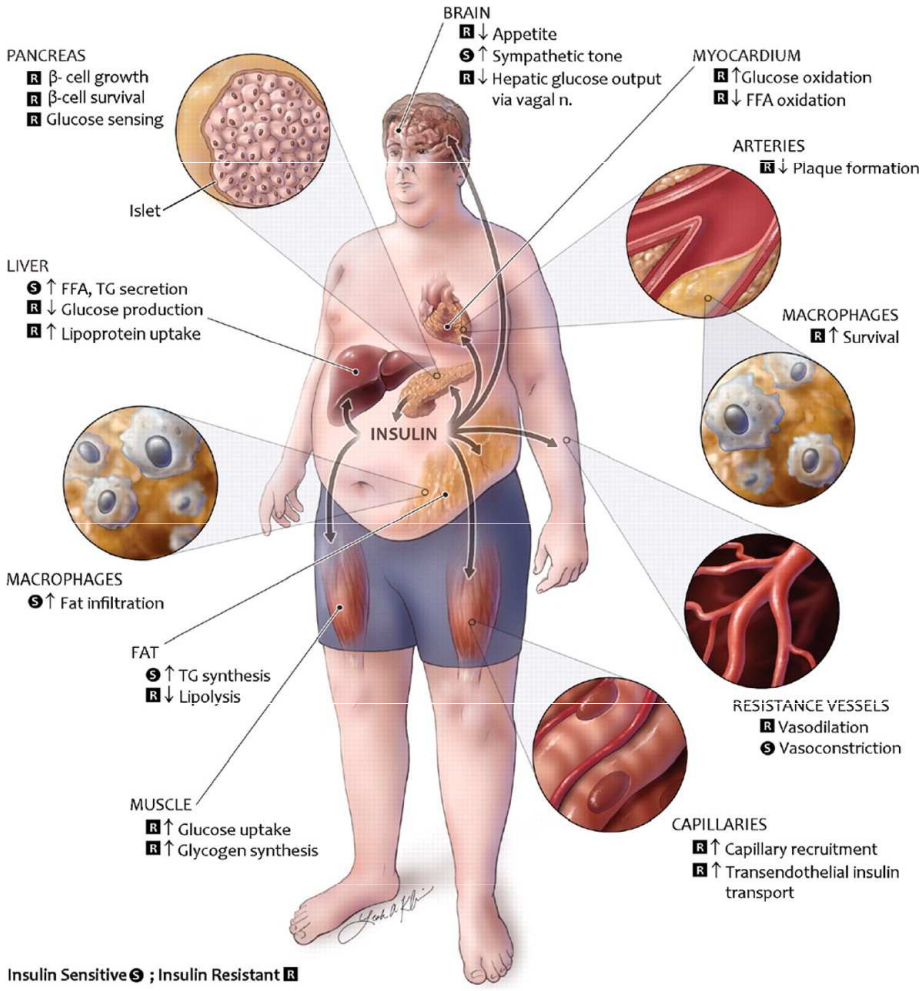
no antibodies

# DM II. type

- (cca 90 %)
- Relative lack of insulin due to
  - damaged production in beta cells
  - insulin resistance in peripheral tissues
- both conditions are mutually potentiating
- genetic and exogenous factors - obesity, stress, low physical activity
- peak between 45-65 years, 60-90 % with obesity

# Metabolic syndrome

- Insulin resistance
- Hypertension
- Hypertriglyceridaemia
- Disorders of glucose tolerance or diabetes
- Obesity type of apple (male type of obesity)



# Clinical symptoms

- **1.type** – more pronounced symptoms, fast onset (weeks)

- polyuria, polydypsia, nycturia, loss of bodyweight when eating normally, tiredness, weakness, loss of consciousness or coma (in children)

- **2.type** – less apparent symptoms, slow onset (months, years)

- others – organ complications – itching, impairs in vision, pain or formication*, neuralgias, problems with healing wounds, skin affections, bad teeth, loss of teeth, loss of erection, low libido…

* Formication is the sensation resembling that of small insect crawling on (or under) the skin when nothing is actually there

# Gestational DM

- **(3-5 % pregnant women)** → in 20 % non-obese and 60 % obese women develope DM type 2 in 15 - 20 years

- peak between 24.-28.week – anti-insulinary effects of placental hormones

- risks for foetus - diabetic foetopathy – large organs, high birth weight, hypoglycaemia after delivery, hyperbilirubinemia, hypocalcemia

big ≠ developed!

# OGTT

75 g of glucose in 200 ml of water
2 hours later sample 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

In pregnancy is cut-off value more strict: 8,5 mmol/l after 2 hours

# Secondary DM

- DM accompanying
  - pancreatic diseases
  - tumors of adrenal gland
  - hyperthyreosis
  - chronic renal insuficience
- Drug induced DM - glucocorticoids, thiazide diuretics, MAb (Pd-L, PD-1L, CTLA4)
- Toxins (streptozotocin)

# Rare subtypes of diabetes

**LADA** - latent autoimunne diabetes of adults

DM I. type manifesting in adults > 35 yrs, with normal weight and insulin sensitivity

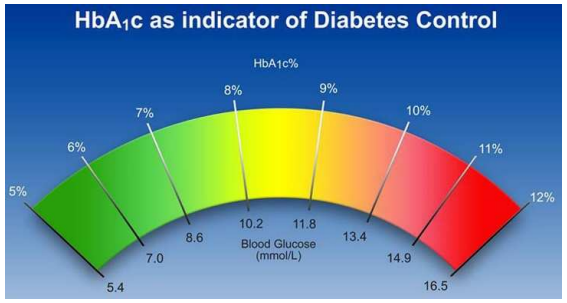
**MODY** - maturity onset diabetes of the young

DM II. type, < 25 yrs, more than 5 yrs treated by OAD/non-insulin

monogenous forms of diabetes (insulin transporter or insulin synthesis)

# Treatment of diabetes


| mmol/L | mg/dL | Interpretation |
|---|---|---|
| 2.0 | 35 | Extremely low |
| 3.0 | 55 | Low |
| 4.0 | 75 | Slightly low |
| 4.4 | 80 | Normal |
| 5.5 | 100 | Normal |
| 5 to 6 | 90-110 | Normal before meal in nondiabetics |
| 8.0 | 150 | Normal After meal in nondiabetics |
| 10.0 | 180 | Maximum After meal in nondiabetics |
| 15.0 | 270 | A little high to very high depending on patient |
| 20.0 | 360 | Very high |




- Lifestyle and regimen, diet, exercise
- Pharmacotherapy with insulin or GLDs
- Concomitant metabolic and CV disorders

HbA1c

# Insulin

# History

- 1869 – medicine student Paul Langerhans (Berlin) discovered unknown inslets of tissue
- 1889 – Minkowski – connection between panceras and diabetes in dog

Further work was interruped by the 1st world war (Paulescu – Budapest)

- 1921 – Banting + Best + Marjorie, Toronto

- Leonard Thompson – 14 ys, the 1st injection of insulin to a human patient 11.1.1922, died at 27
- Elizabeth Hughes Gosset – the first US pacient, 14 ys, 23,5 kg; died in 1981
- The first producer Eli Lilly and Company

C. H. Best and F. G. Banting ca. 1924

# 1921 – Banting + Best + Marjorie, Toronto

# Insulin - physiology

# Regulation of blood glucose

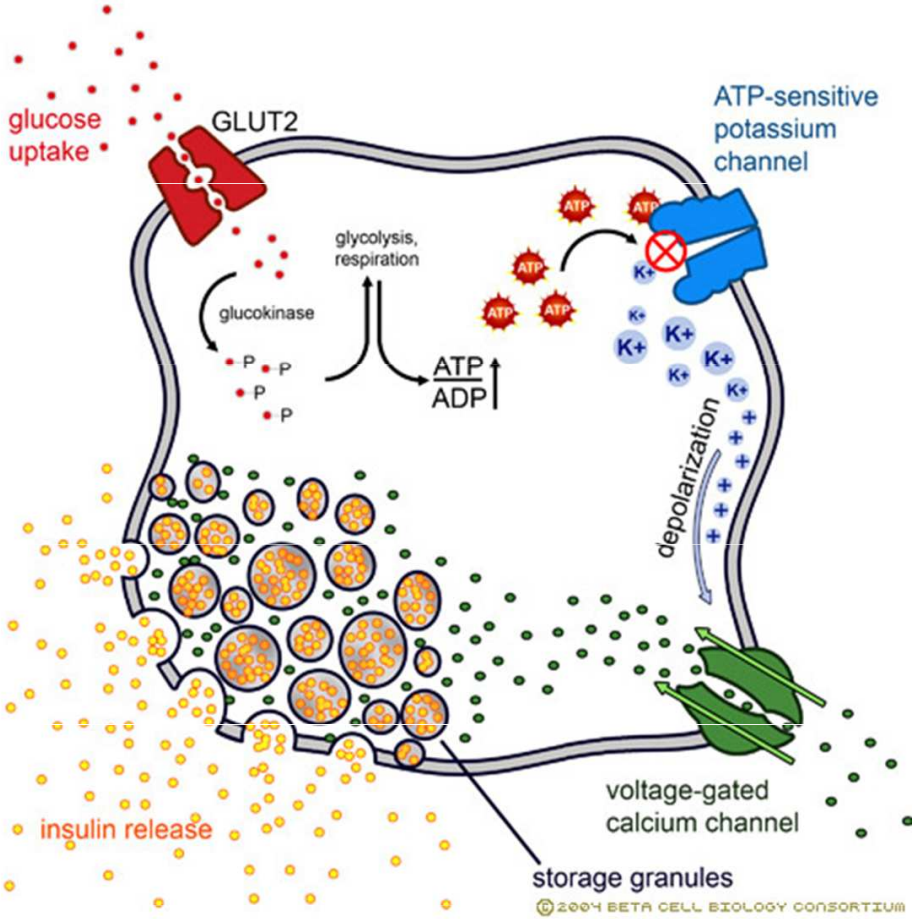
**1. hormonal** - antagonism with glucagon in the liver, cortisol muscle tissue, aldosterone and growth hormone

**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)


glucose
uptake
GLUT2
ATP-sensitive
potassium
channel
glycolysis,
respiration
glucokinase
ATP
ADP
depolarization
voltage-gated
calcium channel
insulin release
storage granules
©2004 BETA CELL BIOLOGY CONSORTIUM

## Insulin secretagogues

glucose
glucagon
fatty acids
GLDs

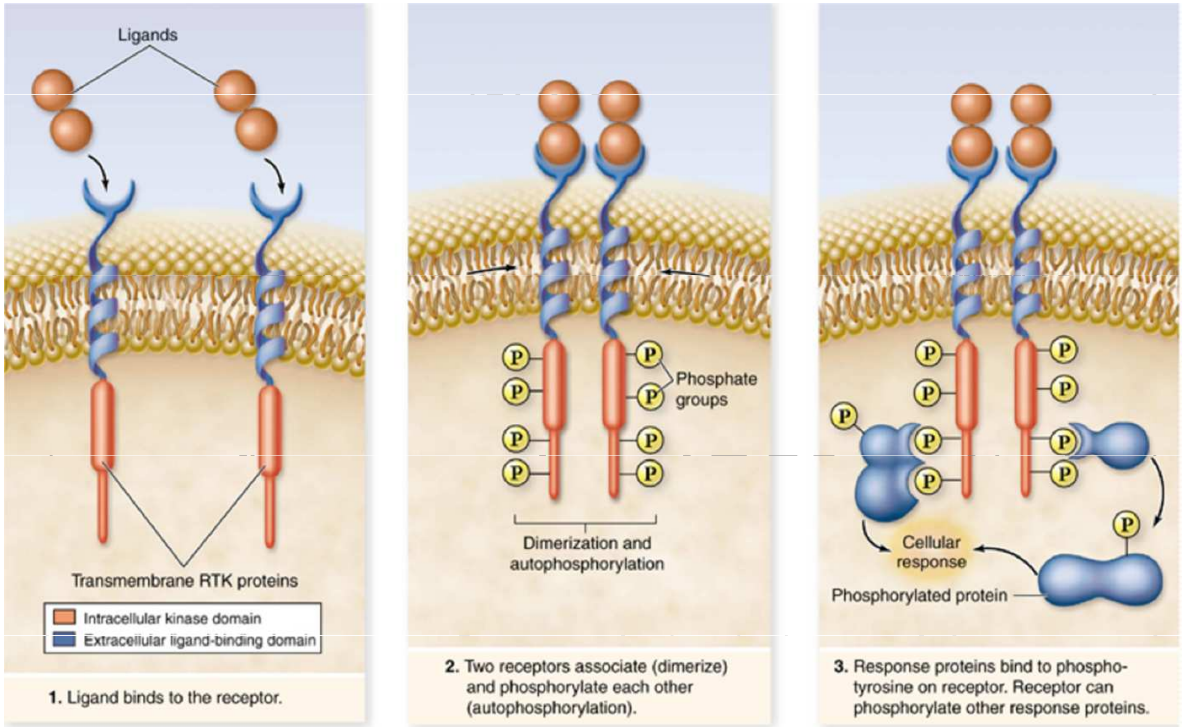
## Amplifiers of glucose-induced insulin secretion

gastrin, secretin, cholecystokinin
GLP1
beta-adrenergic stimulation ($\beta_2$, $\beta_1$)
AA (Lys, Arg, Leu)

## Factors decreasing insulin secretion

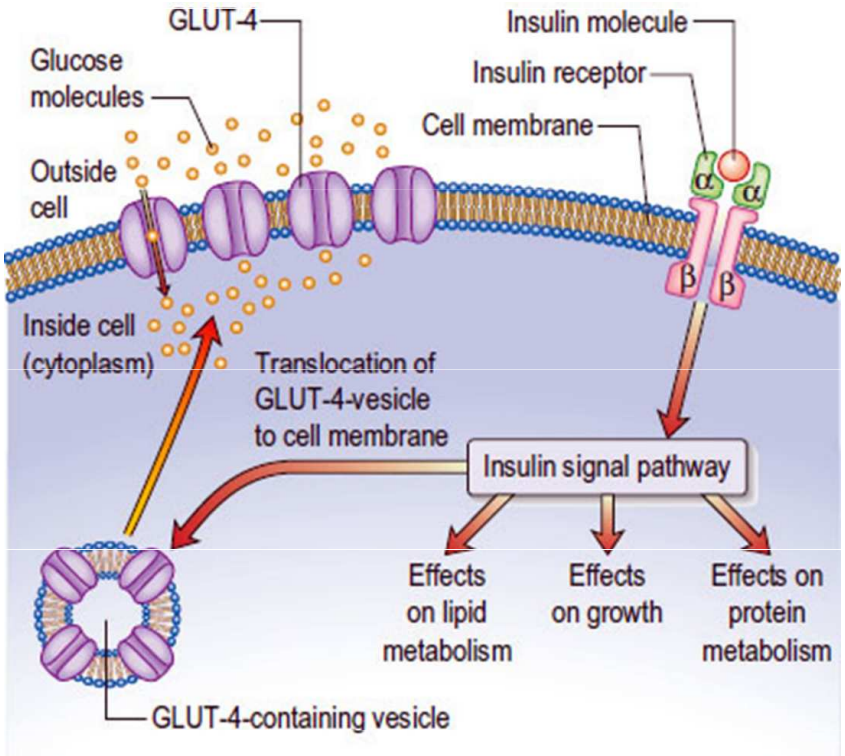
somatostatin
insulin (negative feedback)
$\alpha$-activation of sympathetic n. s. (adrenalin)
galanin (neuropeptide)

# Insulin receptor



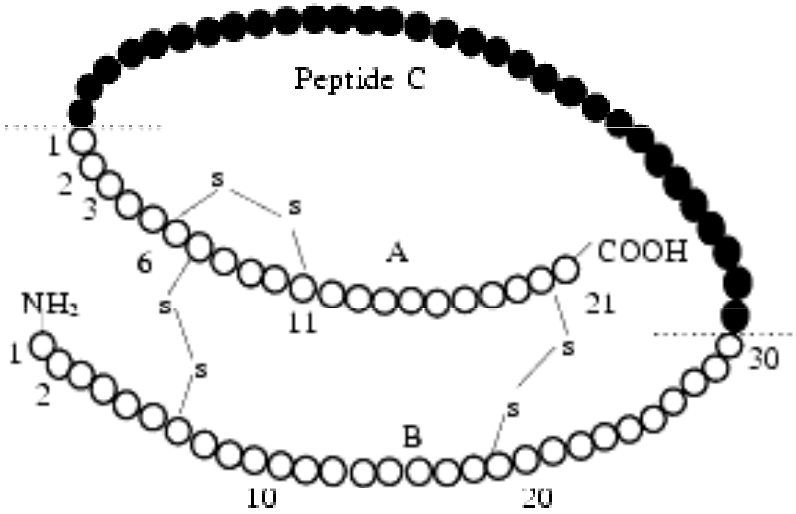

Lincová a kol. 2002

# Insulin receptor



# Insulin

lowmolecular protein, 2 chains
(A 21 AA, B 30 AA), 2 S-S bonds, 5808 Da




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

marker of endogenous secretion of insulin + signalling activity

# Pharmacokinetic parameters

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

  application site, vascularity, temperature, massage, sunbathing, vasodilatators

- D: no binding to plasmatic proteins, Vd = EC water

- M: fast metabolisation by proteases and transhydrogenases, in diabetics also degradation in kidneys

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

# Therapeutical use of insulin

- must be administered in
  - IDDM (DM I. Type)
  - ketosis, ketonuria nebo ketoacidosis

- patients with serious infection/gangrene
- patients younger than 30 years
- DM II where blood Glc. not normalized with  POAD, diet
- DM II patients, corticosteroids use, liver or kidney impairment

# Types and origin of insulin

**a) animal insulins**

- from porcine or bovine pancreas
- different primary structure
- purified but immunogenic
- monocomponent
- used till the 1980s, today only AUV

Insulins produced by recombinant techonology (since 1980s):

**b) human insulin**

- designation HM, identical structure

**c) insulin analogues**

- the primary structure of the protein is specifically altered to modify the pharmacokinetics

# Classification of insulins

## Short or rapid acting

- clear solutions without adjuvants or modifications slowing absorption
- possible i.v. application (the only type)

**Neutral aqueous solutions of HM insulins** (crystalline insulin, soluble insulin)
**disadvantage** – formation of hexameres in site of application

onset 30 min.
maximum 1 - 3 h
lenght 4 – 6 h


**Insulin analogues: insuliny lispro, aspart, glulisin**
more rapid action
**disadvantage** – in monotherapy is neccessary often administration

onset 10 - 20 min. aspart, 15-30 lispro
maximum 1 - 2 h
lenght 2 – 5 hod. (according to the dose)

# Classification of insulins

## Intermediate – acting insulins

- modifications of physical and chemical characteristics of preparation decrease its solubility and slow absorption
- only for s.c., i.m. admin


onset 1 - 2,5 h
maximum 4 - 8 h
lenght 12 - 24 h

**Isophan (NPH*)** – mixture insulin + protamin + zinc – cloudy solution due to crystals of protamin with insulin
**Semilente, Lente** (mixture of semilente + ultralente** in 30:70 ratio) – cloudy zinc suspensions of insulin

**Disadvantages**

- when used on night, maximum of the effect is at 4-6 am, risk of hypoglycaemia
- absorption may interindividually vary

*Neutral Protamine Hagedorn
**slow onset and prolonged duration, poorly soluble crystalised insulin

# Classification of insulins

**Long – acting insulins**

**Cloudy suspensions of large zinc-insulin crystals** with very slow absorption, s.c. administration

**ultralente -** poorly soluble crystalline insulin with slow onset and prolonged duration of action

onset 2 – 3 h
maximum 10-18 h
lenght 24 – 36 h

**Analogues** – clear appearance, less AE, lower weight gain

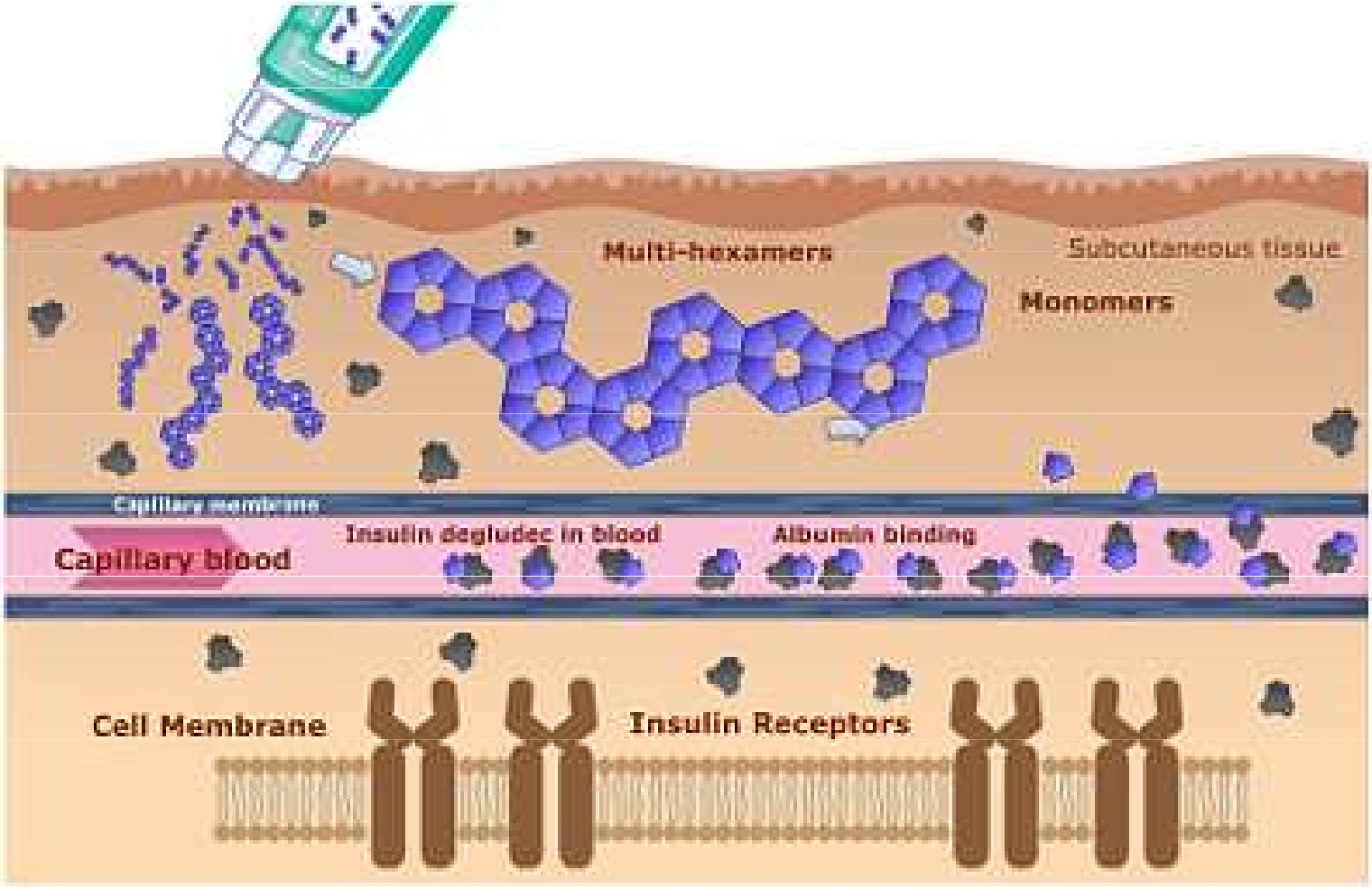
**detemir (Levemir)** = „predictable insulin“ – small interindividual variability

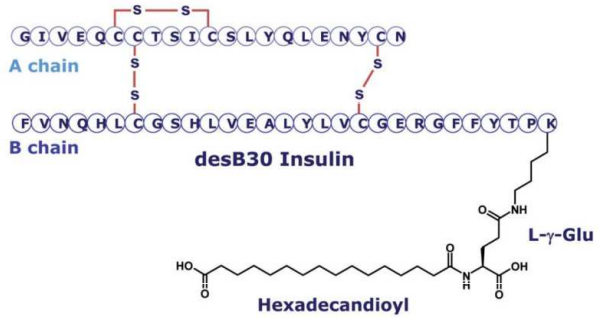
**glargin (Lantus, Abasaglar)** = „peakless insulin“ - even longer effect, flat curve action/time

**degludec (Tresiba)** = ultralong acting

onset 1-2 h
maximum 6 – 8 h detemir, no peak for glargin
lenght up to 24 h, 42 h for degludec

# Protraction mechanism for Degludec



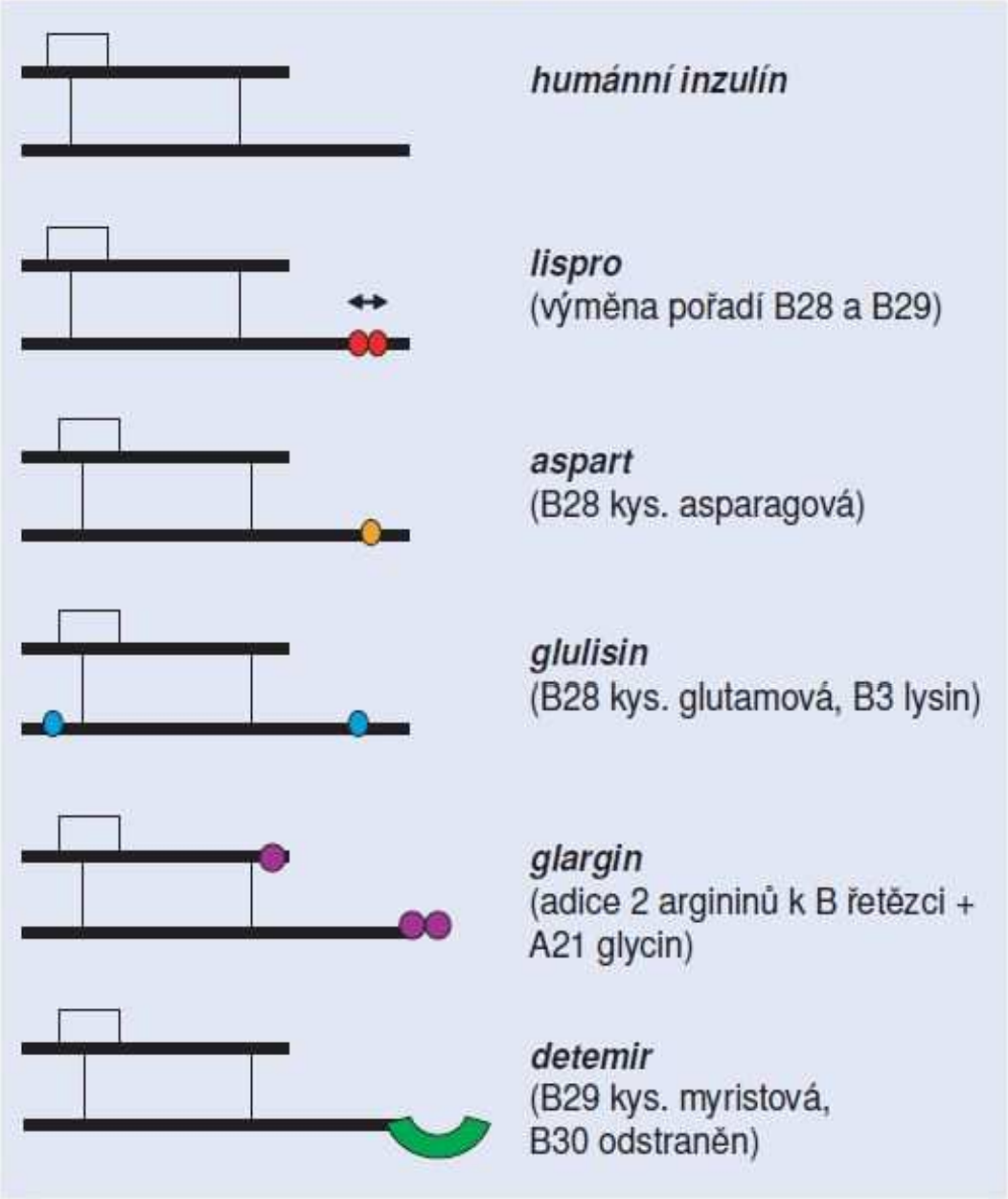
# Insulin preparations

Aqeous solutions – only short acting i.v.

Suspensions of insulin, suspensions of „zinc-insulin“, suspensions „protamin-zinc-insulin“ – never i.v.

Powder for inhalation

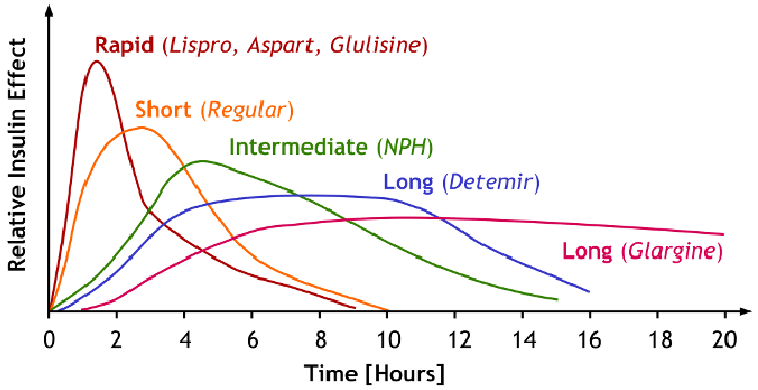
stabilised mixtures of insulin in different ratios

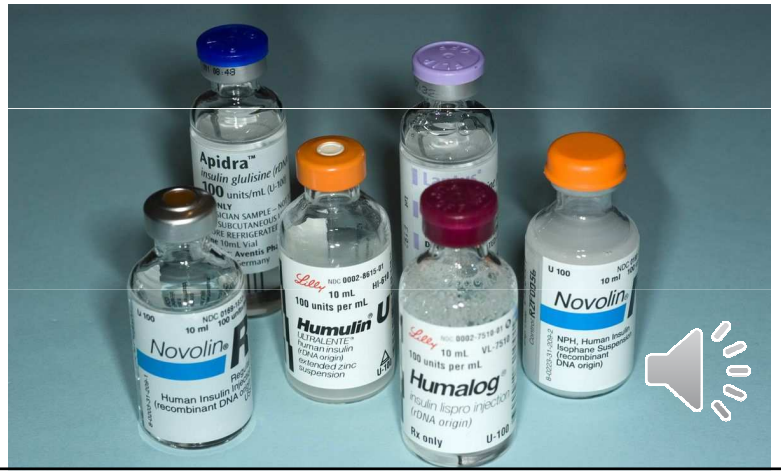



# Types of insulin analouges

INZULÍN A NOVINKY V LÉČBĚ INZULÍNEM, MUDr. Pavlína Piťhová, 4 / 2006 INTERNI MEDICINA PRO PRAXI

| Type of Insulin | Appearance | Action times after injection (in hours) |
|---|---|---|
| **Rapid-acting**<br>▪ Lispro (Humalog)<br>▪ Glulisine (Apidra)<br>▪ Aspart (NovoRapid) | Clear  | 2 4 6 8 10 12 14 16 18 20 22 24<br>**Onset:** 10 to 15 mins<br>**Peak:** 1 to 2 hours<br>**Duration:** 3 to 5 hours |
| **Intermediate-acting**<br>▪ NPH (Humulin-N, Novolin-NPH) | Cloudy  | 2 4 6 8 10 12 14 16 18 20 22 24<br>**Onset:** 1 to 3 hours<br>**Peak:** 5 to 8 hours<br>**Duration:** up to 18 hours |
| **Slow or long-acting**<br>▪ Glargine (Lantus)<br>▪ Detemir (Levemir) | Clear  | 2 4 6 8 10 12 14 16 18 20 22 24<br>**Onset:** 90 mins<br>**Peak:** None<br>**Duration:** up to 24 hours |



# Insulin RMP labeling

**„PUR“** - chromatophically purified
**„monocomponent“** - highly purified without contaminating impurities
(proinsulin, ins. fractions) - animal / human
**„HM“** - human

## Lenght of action:

1) short acting - **„rapid“**
2) intermediate - acting - **„Dep“ (D)** - semilente
3) intermediate - acting with prolonged duration of action - **„interdep“ (ID)** - lente
4) long - acting - **„superdep“ (SD)** - ultralente

# Delivery systems (self-administration)

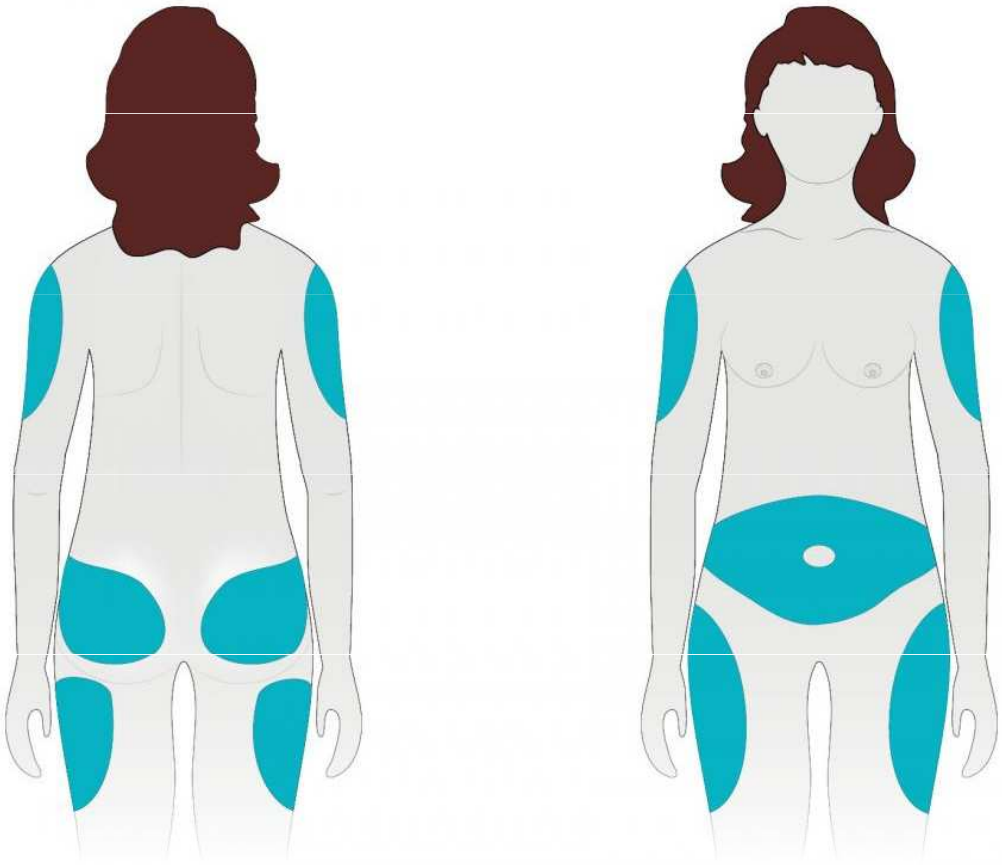

1) **Insulin injections** - calibrated by IU

2) **Insulin pens** - pen-sized injectors, + blood glucose detectors

3) **Insulin pumps** - automated administration of insulin (s.c. / i.v.)
according to glycemia

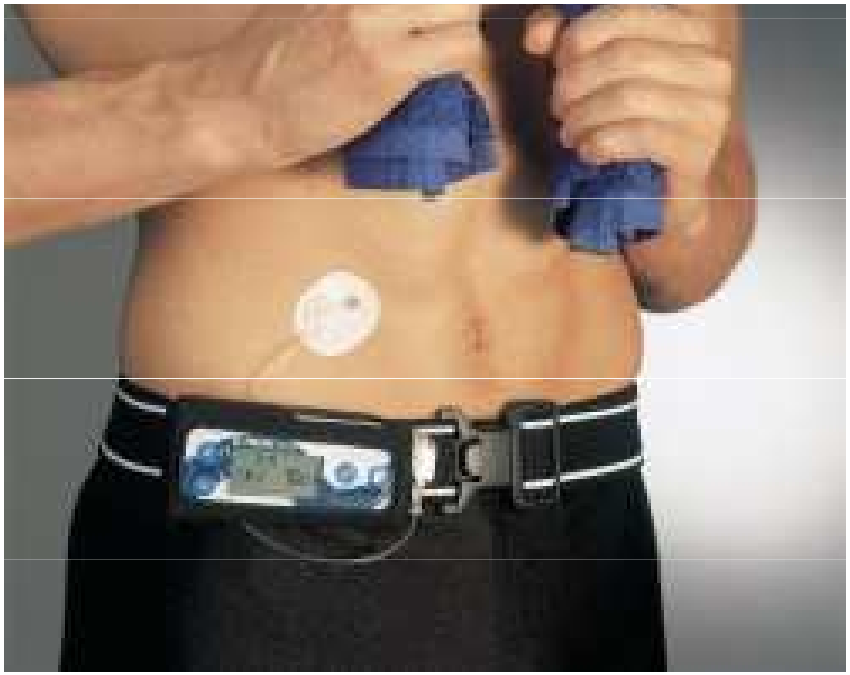
4) **Nasal** insulin delivery, insulin **inhalations**

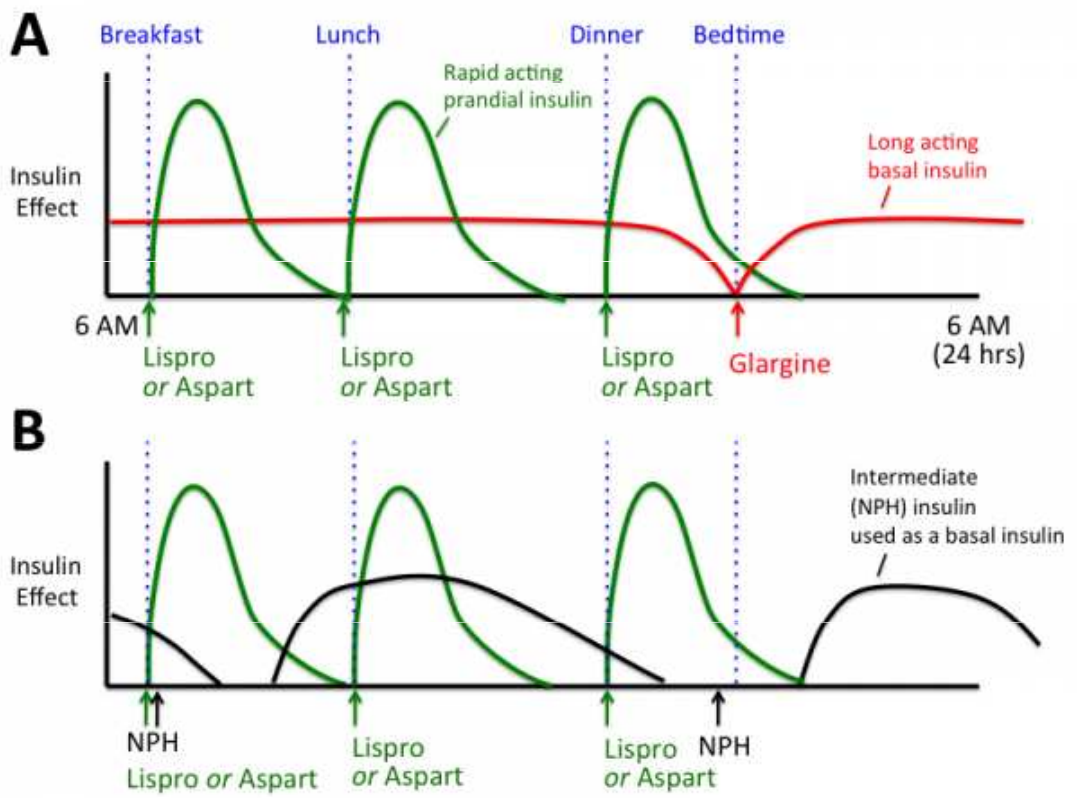
# Insulin injection sites

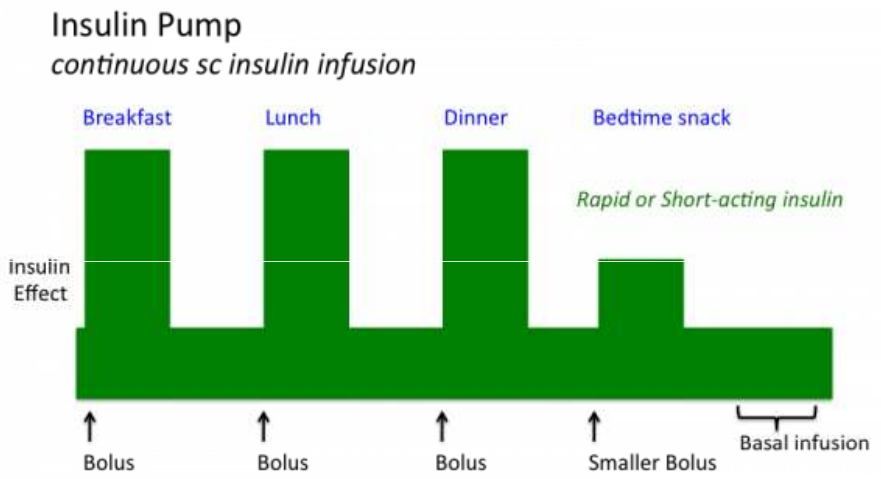


# Treatment strategies


- the lowest total daily dose
- monitoring of glycaemia
- intensified regimens = more doses → lower total dose and tighter compensation
- insulin pump





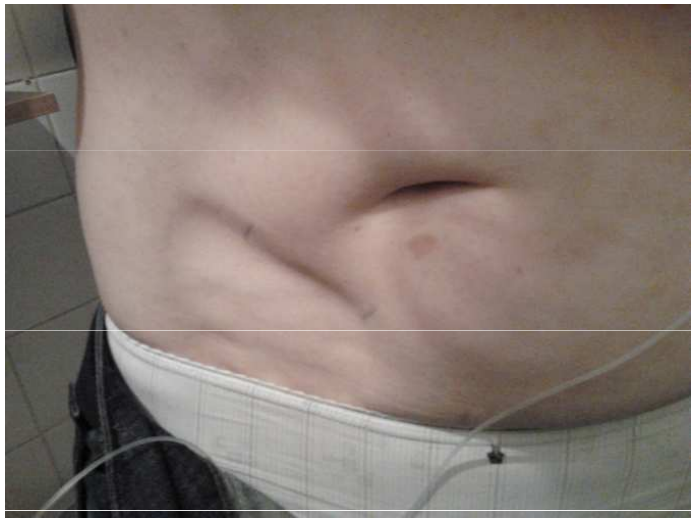

Examples of physiologic insulin delivery. **A)** Once-daily glargine serves as a basal insulin that is typically given at bedtime. Rapidly acting insulin are used as prandial insulins. This allows patients to change meal times at will. **B)** Intermediate-acting NPH, given twice daily, can be used as a basal insulin, and can be combined with a rapid-acting "prandial" insulin. This regimen (shown as a 50:50 dosage ratio) is more difficult to adjust because NPH has a 2 hour delay, limited duration of action, and a time course that gives it "prandial-like" properties. Figure adapted from DeWitt & Hirsch (2003)



https://tmedweb.tulane.edu/pharmwiki/doku.php/insulin_regimens

# Complications of insulin therapy

- hypoglycaemia
- allergy
- lipodystrophy
- insulin resistance - spec. antibodies
- weight gain



# Hypoglycaemia

Plasma glucose under 2,8 mmol/l

**Causes**

- Insulin overdose
- Vomiting, diarrhoea, delayed eating
- Physical strain
- Concomitant liver, heart or kidney insufficency

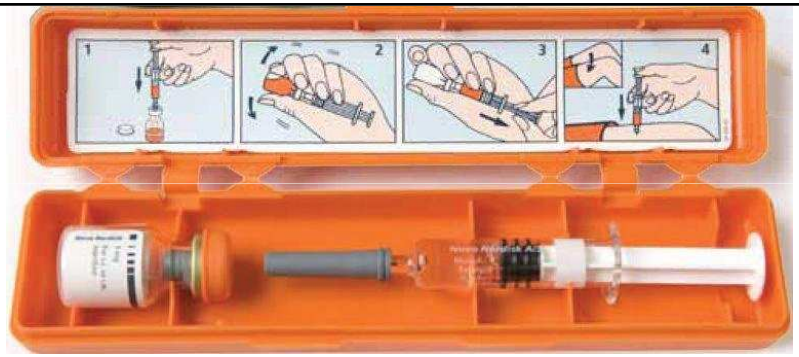
**Symptoms** – fast onset

- Agitation
- Tremor, sweating
- Hunger
- EEG changes, loss of conscousness, coma, death

**Therapy**:

- fast intake of sacharides/glucose i.v. (40% glukose 30-50 ml or more)
- glucagon + following glucose

# Glucagon



Increases glycaemia, heart contractility and heart rate

Decreases gastric and pancreatic secretion and smooth muscle tone

Therapeutical use

- Hypoglycaemia in DM (condition of glycogen reserves) – pen (s.c./i.m. or transanasal)
- Diagnostics in endrocrinology

AE – rare

- Nausea, vomiting
- Allergic reactions

# Antidiabetics = GLD
# (glucose lowering drugs)

MUNI
MED

# (Oral) antidiabetics (OAD, GLD)

The effect of most GLDs is bound to preserved insulin secretion

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

Indications:

- 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

# Classical approach in type 2 DM

1. Regimen changes : diet + exercise
2. GLD monotherapy
3. Combined GLD or GLD + insulin
4. Insulin

Drugs do not replace changes in lifestyle!!!

- age, weight, blood insulin level
- glycemia (fasting and postprandial)
- comorbidities, metabolic syndrome

## GLDs

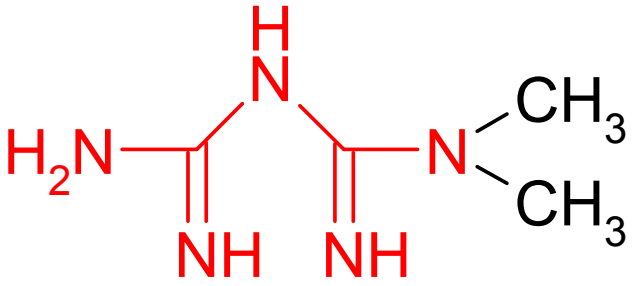
1. Biguanides (metformin)
2. Sulphonylurea derivatives
3. Thiazolidindiones
4. Inhibitors of intestinal glucosidases
5. Meglitinides
6. GLP1 (incretine) analoges
7. Inhibitors of DPP IV
8. SGLT2 (sodium-glucose cotransporter) inhibitors

# 1. Biguanides = metformin

„euglycemic agents“

**metformin**

- buformin, fenformin




**MoA:**

- increase sensitivity of peripheral tissues to insulin
- increase insulin binding to its receptor

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

**→ no hypoglycemia**

They need preserved insulin secretion for their effect

## Other effects:

- reduce hepatic gluconeogenesis
- decrease glucose absorption from GIT
- decrease LDL, VLDL, FFA, TAG
- increase fibrinolytic activity (inhibition PAI-1)

## AE

**lactic acidosis in renal insufficiency** (excreted by the kidneys as the active compound)

- nausea, GIT problems cca 20 % patients
- anemia (absorption of B12)
- **reduction of bodyweight**
- disulfiram effect

**KI:**

- Kidney diseases (GF under 60 ml/min/1,73 m2)
- alcoholism
- liver diseases

**Therapeutic use**

- **DM type 2 - 1st choice drug in obese patients**
- In all combinations (+ insulin, glitazones, SU, incretines…)

- Off-label – PCOS, anticancer effect (AMPK / mTOR)

**KI:**

- Kidney diseases (G
- alcoholism
- liver diseases

**Therapeutic use**

- **DM type 2 - 1st ch**
- In all combinations
- Off-label – PCOS, a

COVID-19 is an emerging, rapidly evolving situation.
Get the latest public health information from CDC: https://www.coronavirus.gov.
Get the latest research information from NIH: https://www.nih.gov/coronavirus.

angličtina čeština

Google Translate

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Find Studies | About Studies | Submit Studies | Resources | About Site | PRS Login

Home > Search Results > Study Record Detail

Save this study

# A Phase III Randomized Trial of Metformin vs Placebo in Early Stage Breast Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

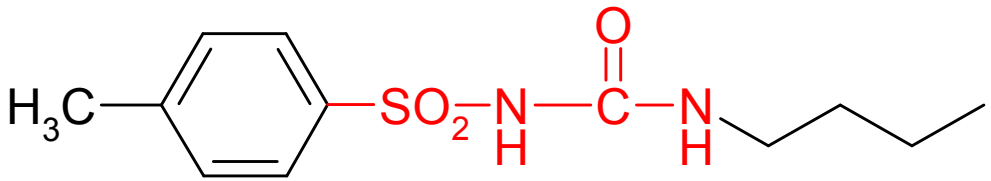
ClinicalTrials.gov Identifier: NCT01101438

Recruitment Status : Active, not recruiting
First Posted : April 12, 2010
Last Update Posted : April 2, 2020

**Sponsor:**
Canadian Cancer Trials Group

**Collaborators:**
National Cancer Institute (NCI)

# 2. Sulfonylurea derivatives (SU)

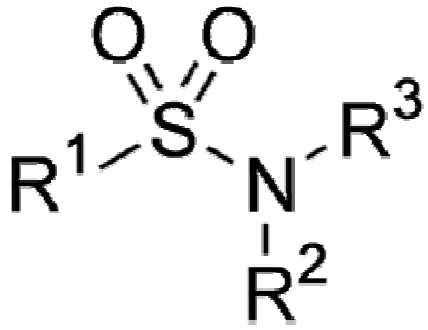



**MoA:**

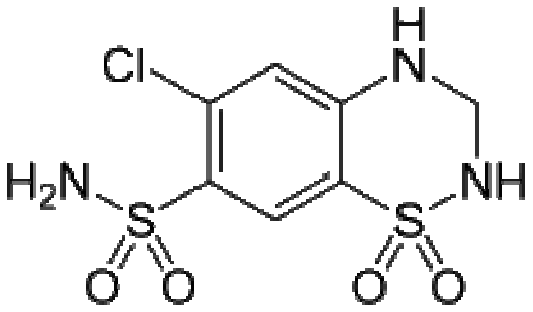
1) **pancreatic** – increase insulin release, but NOT synthesis

2) **extrapancreatic**

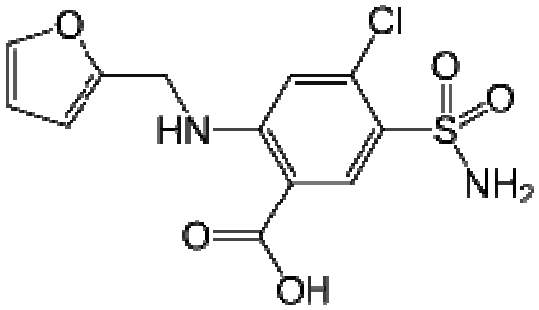
- potentiation of endogenous insulin effect on the target tissue
- reduction of hepatal glucose production
- reduction of hepatal insulin degradation
- reduction of serum glucagon levels
- increase the number of insulin receptor on ERYS, adipocytes, monocytes



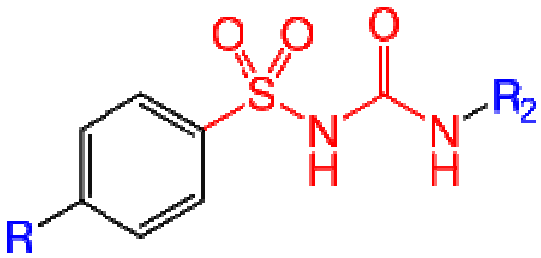

Sulfonamide
functional group



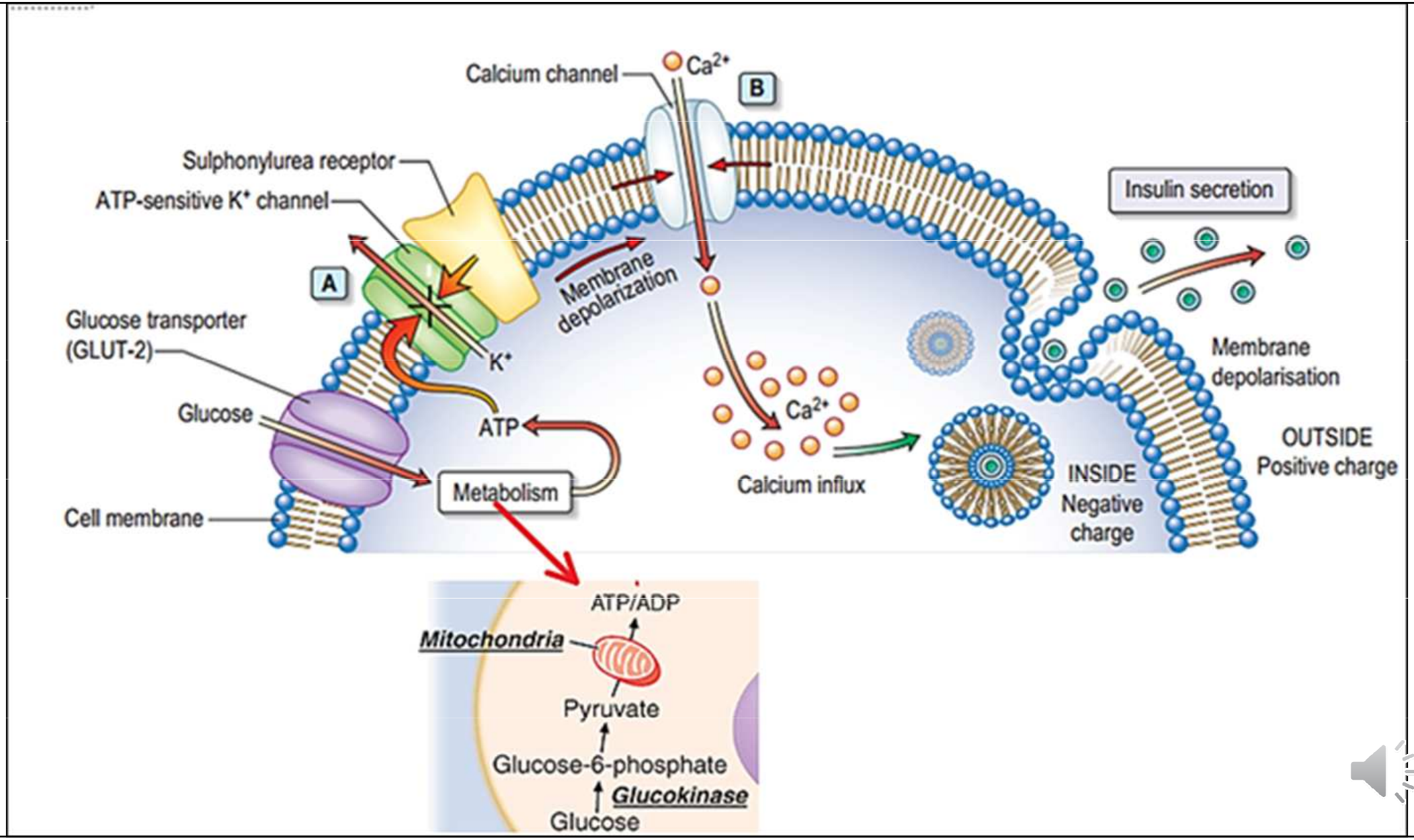

Hydrochlorthiazide




Furosemid




Sulfonylurea


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

# 2. Sulfonylurea derivatives (SU)

I. generation - **chlorpropamid**

**tolbutamid**

II. generation - **glibenklamid**

**glipizid**

**gliklazid**

**glikvidon**

III. generation - **glimepirid**

**2nd line of treatment, only exceptionally 1st choice in thin patients**

# 2. Sulfonylurea derivatives (SU)

**Adverse effects**

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

**Contraindications**

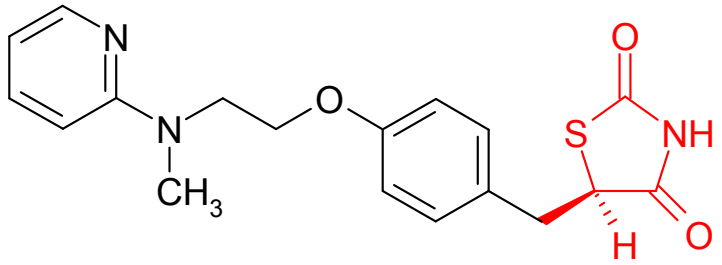
- hypoglycemia
- ketoacidosis
- renal/hepatal impairment
- pregnancy
- age
- hypersensitivity

# 3. Thiazolidindiones (glitazones)

**Drugs**: rosiglitazon

troglitazon

**pioglitazon**




**MoA**

- ligands of PPARγ (part of the steroid and thyroid superfamily of nuclear receptors)

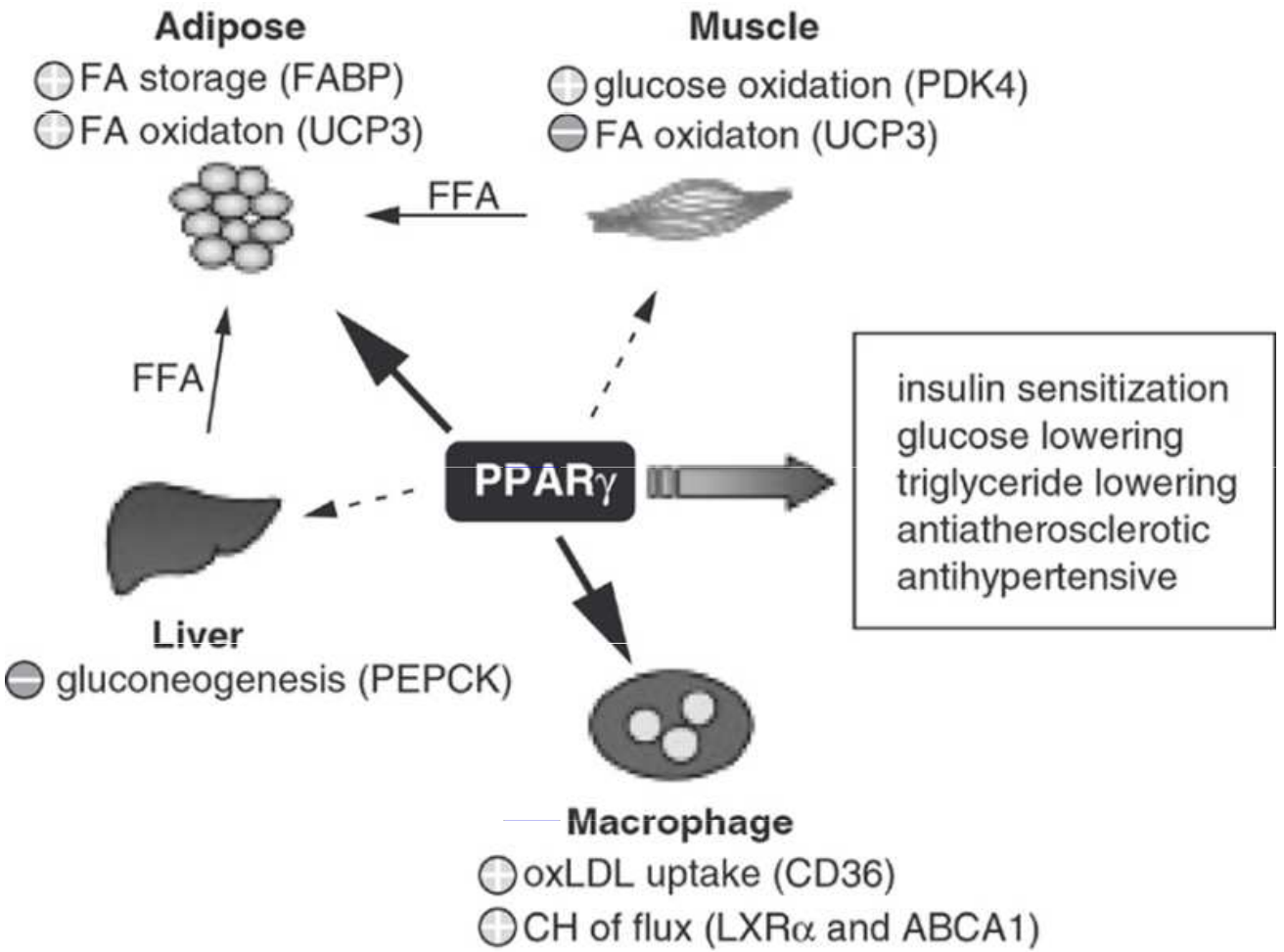
↓

modulate the expression of the genes involved in the metabolism of lipids and glucose

↓

increase the sensitivity of periphery to insulin

# 3. Thiazolidindiones (glitazones)



# 3. Thiazolidindiones (glitazones)

- decrease glycemia by positive effect on **insulin resistance**, important in pre-diabetic state
- better glucose utilisation in the muscle (↑ glycogen synthesis and glycolysis)
- some positive **metabolic effects**
  - ↓ production of FFA, TAG, peroxidation of LDL, ↑ HDL
  - ↓ TNFα, resistin (causes IR in peripheral tissues)
  - ↓ gluconeogenesis in liver
  - ↑ glucose oxidation and lipogenesis in adipose tissue

- CVS AE (rosiglitazone, 2010) !!!

# 3. Thiazolidindiones (glitazones)

**Therapeutic use**

- sensitizers of insulin receptors
- the onset of effect in 4 weeks
- not 1st line, used in combinations (metformin, SU)

„euglycemic drugs“ – do not act hypoglycemic on euglycemic individuals

**Side effects**

- Rosiglitazone **increased risk of heart attack and stroke**
- Troglitazone was withdrawn for **hepatotoxicity**
- Fluid retention
- Osteoporosis
- Weight gain

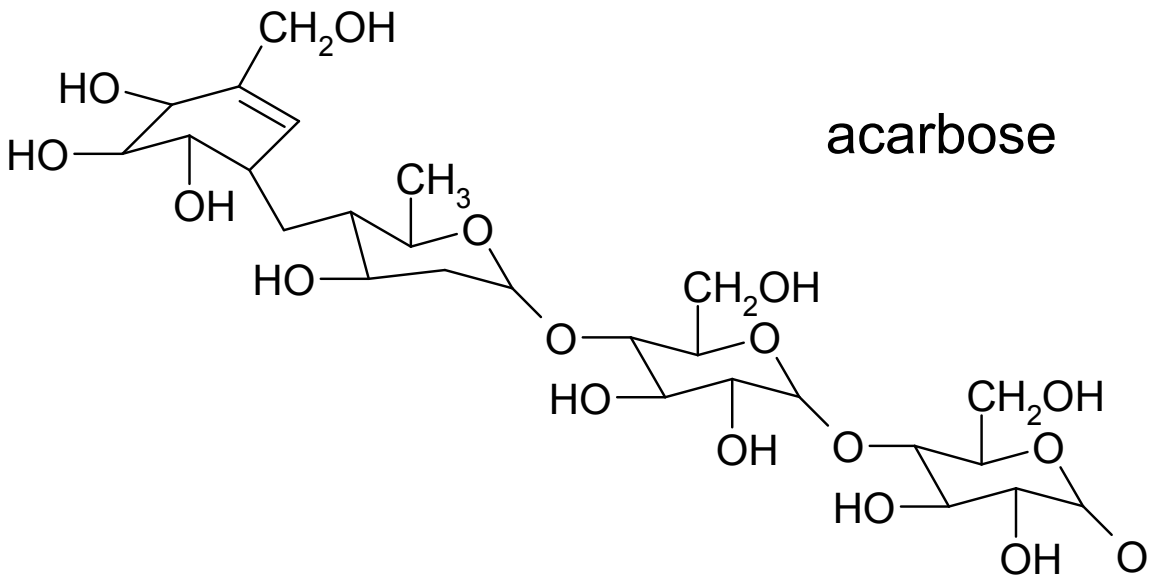
**Contraindications**

- Hypersensitivity
- Predisposition to heart failure
- Liver damage
- Pregnancy, lactation

# 4. Inhibitors of intestinal glucosidases

## Drugs

**acarbose**
miglitol
voglibose




## MoA

- reduce sacharides absorption from GIT
- competitive inhibition of the gut α – glucosidases (inhibits the cleavage of the polysacharides from the meal)
- Suitable for monotherapy and combinations

# 4. Inhibitors of intestinal glucosidases

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

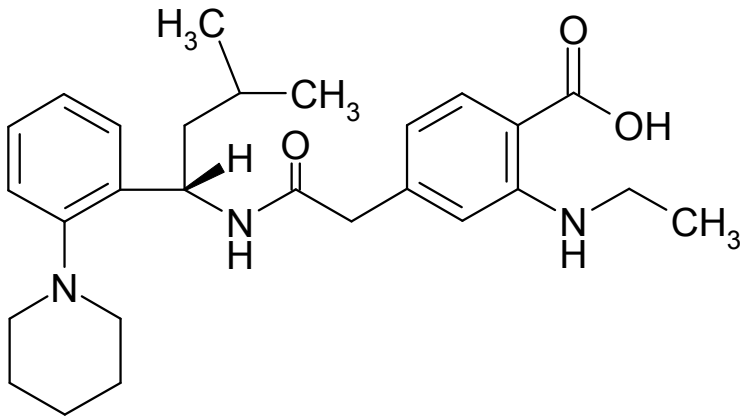
**In case of hypoglycemia sucrose can not be administered orally (necessary are monosacharides - Glu, Fru) / or Glucagon**

# 5. Meglitinides

**Drugs:** **repaglinid**

nateglinid (STARLIX, TRAZEC)

meglitinid




**MoA**

similar to SU-derivatives (bind to SUR, but different receptor site), fast onset

- through different receptor at $K^+$ channel
- 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

# 5. Meglitinides

**Pharmacokinetics:**

- good bioavailibility, fast effect!! – no meal, no tablet
- extensive protein binding (up to 98 %)
- metabolized - inactive compounds
- excreted mainly in faeces

# 5. Meglitinides

**Clinical use:**

- 2nd line, often combined with metformin - esp. if patient not sufficiently compensed
- alternative of the SU medication in patients with renal impairment (excreted into bile)
- administration before meals - rapid onset and fading effect for 4 hours
- skipping a meal = skipping a dose (risk of hypoglycaemia if taken)

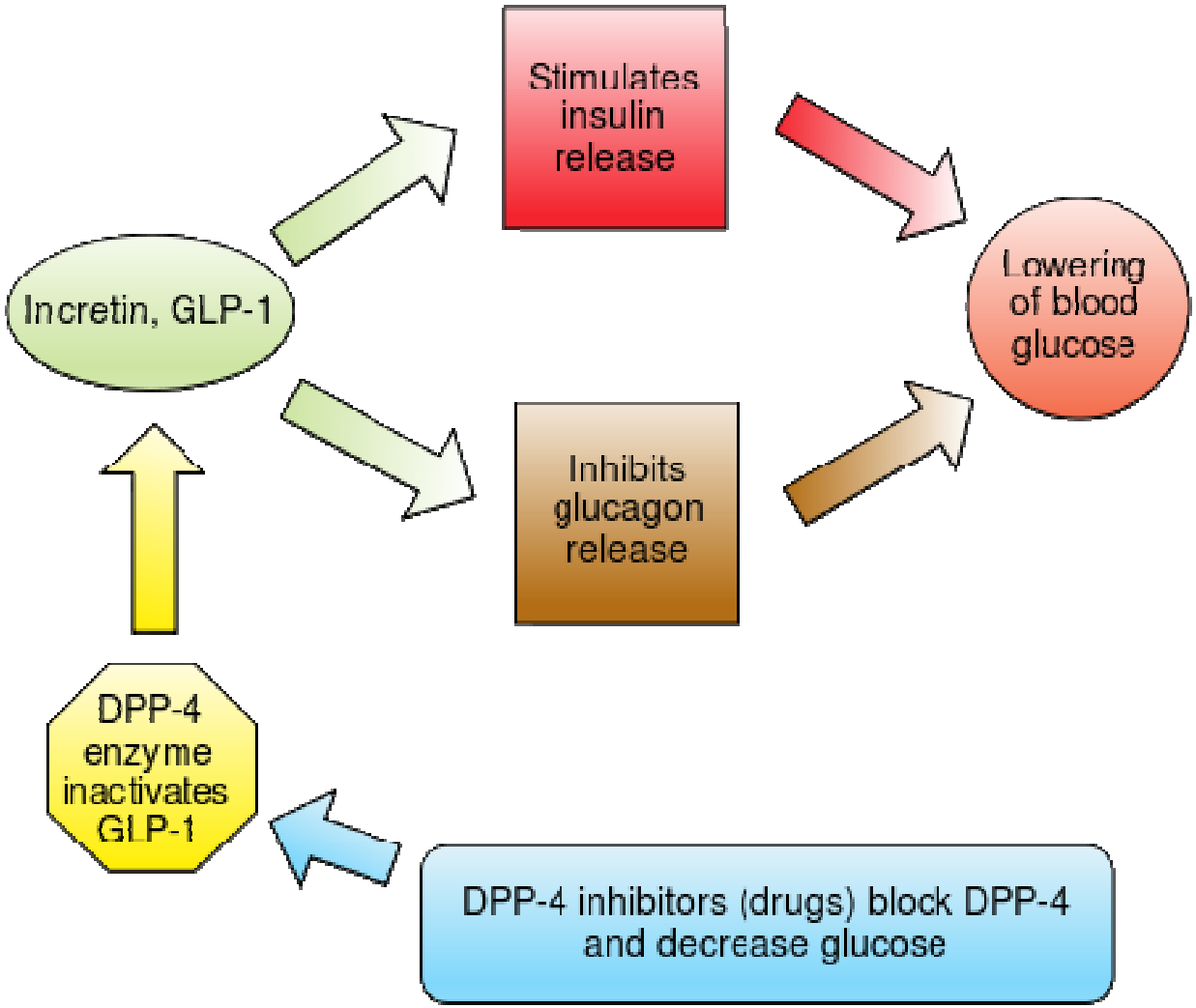
# 5. Meglitinides

**AE:**

- hypoglycemia
- nausea
- diarrhea
- joint pain

**Contraindications:**

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


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

# 6. GLP1 – Glucagon-like peptide 1 analogues

**exenatide, liraglutide**

**lixisenatid, semaglutide,** albiglutide

**s.c. administration !!!**

GLP1 is physiologically secreted postprandially, in DM2 not sufficient levels

*Heloderma suspectum,*
*Gila Monster*

**MoA:**

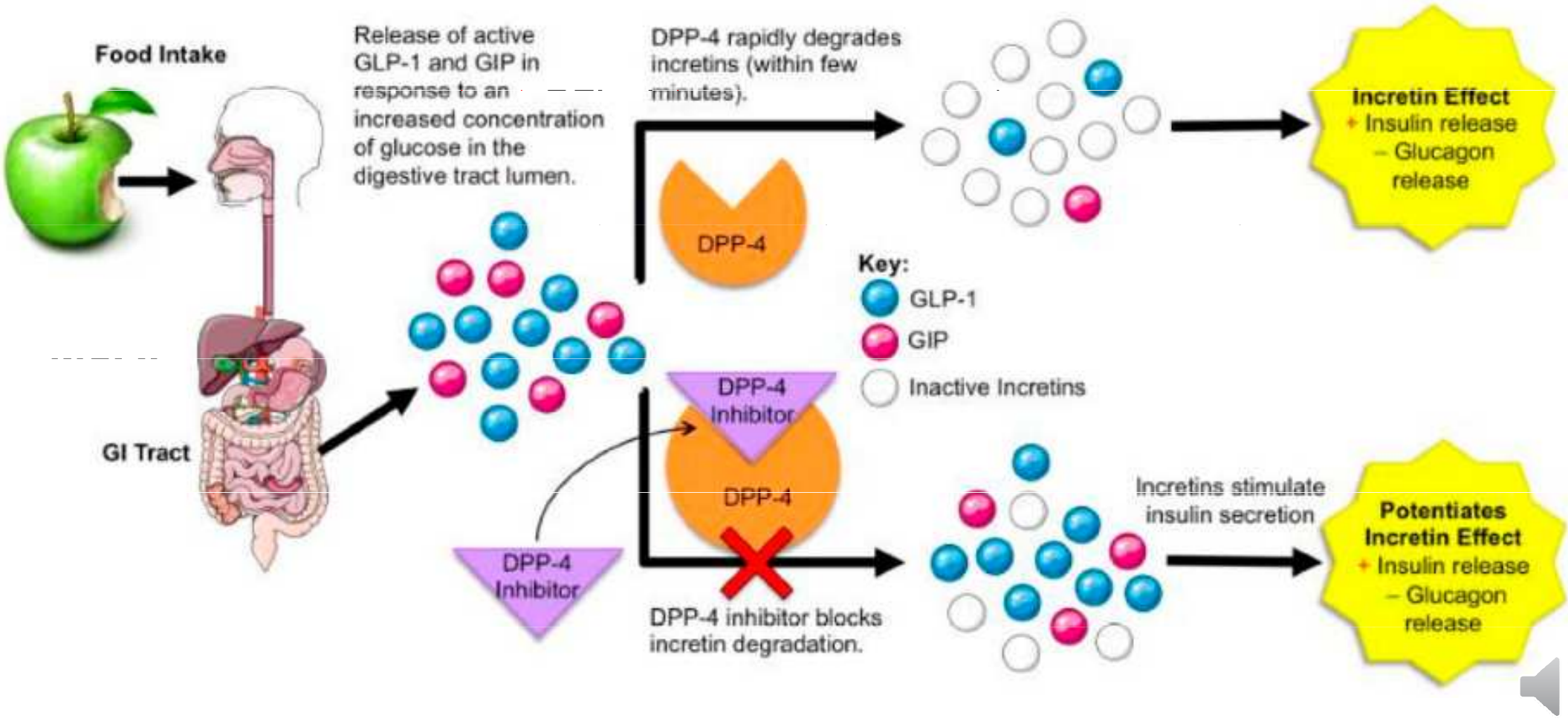
- ↑ insulin secretion (dependent on glycemia)
- ↓ glucagon secretion,
- prolong stomach content evacuation

Registered also as antiobesitics

(liraglutide, semaglutide)

# 7. DPP-IV inhibitors = Gliptins

dipeptidyl peptidase 4



# 7. DPP-IV inhibitors = Gliptins

**MoA:**

- inhibition of degradation of incretins (GLP1)
- effect lasts for 24 hod – 2-3x higher levels of GLP1

**Advantages:**

- no hypoglycemia
- stop progress of DM
- protection of B-cells
- better glycemic control than conventional drugs

# 7. DPP-IV inhibitors = Gliptins

dipeptidyl peptidase 4

**Therapeutic use:**

- DM 2 in combinatin with other GLDs
  - + metformin – 1st choice in insufficient compensation
  - + sulfonylurea derivate - in KI of metformin
  - + thizolidindione - in KI of metformin
  - + statin

**linagliptin**

**sitagliptin**

**vildagliptin**

**aloglitpin**

**AE:**

pancreatitis, hypoglycaemia (in combination with Insulin/SU)

# 8. SGLT2 inhibitors = glycosuric drugs

**sodium-glucose co-transporter**

- SGLT2 is
  - selectively exprimed in kidneys
  - responsible for reabsorption of Glc from the filtrate back to circulation (even in hyperglycaemia)
- glykosuric effect is apparent after a single dose and lasts for 24 hours
- size of glycosuric effect depends on Glc concentration and GFR, NOT levels of insulin
- glycosuria leads to
  - loss of energy → reduced bodyweight
  - mild increase of diuresis and natriuresis
  - Hb1Ac decrease by 0.8%

# 8. SGLT2 inhibitors = glycosuric drugs

**Therapeutic use:**

- Suitable for monotherapy as well as combinations CAVE hypoglyceamia in combination with insulin / SU
- Cardioprotective (AIM, stroke, renoprotective !! Convincing data from large studies

**CI, caveats:**

- over 75 years,
- kidney dysfunctions, concurrent loop diuretics,
- hypotension,
- electrolyte dysbalance

dapa**gliflozin**

cana**gliflozin**

empa**gliflozin**

ertu**gliflozin**

**AE:**

- thirst
- genital infections
- risk of lower limb amputations (mainly of the toe)
- hypoglycemia - in monotherapy the risk is minimal; in combination with insulin / der. SU risk high

## Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

## Monotherapy — Metformin — Lifestyle Management

| | |
|---|---|
| **EFFICACY*** | high |
| **HYPO RISK** | low risk |
| **WEIGHT** | neutral/loss |
| **SIDE EFFECTS** | GI/lactic acidosis |
| **COSTS*** | low |

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

## Dual Therapy — Metformin + — Lifestyle Management

| | Sulfonylurea | Thiazolidinedione | DPP-4 inhibitor | SGLT2 inhibitor | GLP-1 receptor agonist | Insulin (basal) |
|---|---|---|---|---|---|---|
| **EFFICACY*** | high | high | intermediate | intermediate | high | highest |
| **HYPO RISK** | moderate risk | low risk | low risk | low risk | low risk | high risk |
| **WEIGHT** | gain | gain | neutral | loss | loss | gain |
| **SIDE EFFECTS** | hypoglycemia | edema, HF, fxs | rare | GU, dehydration, fxs | GI | hypoglycemia |
| **COSTS*** | low | low | high | high | high | high |

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

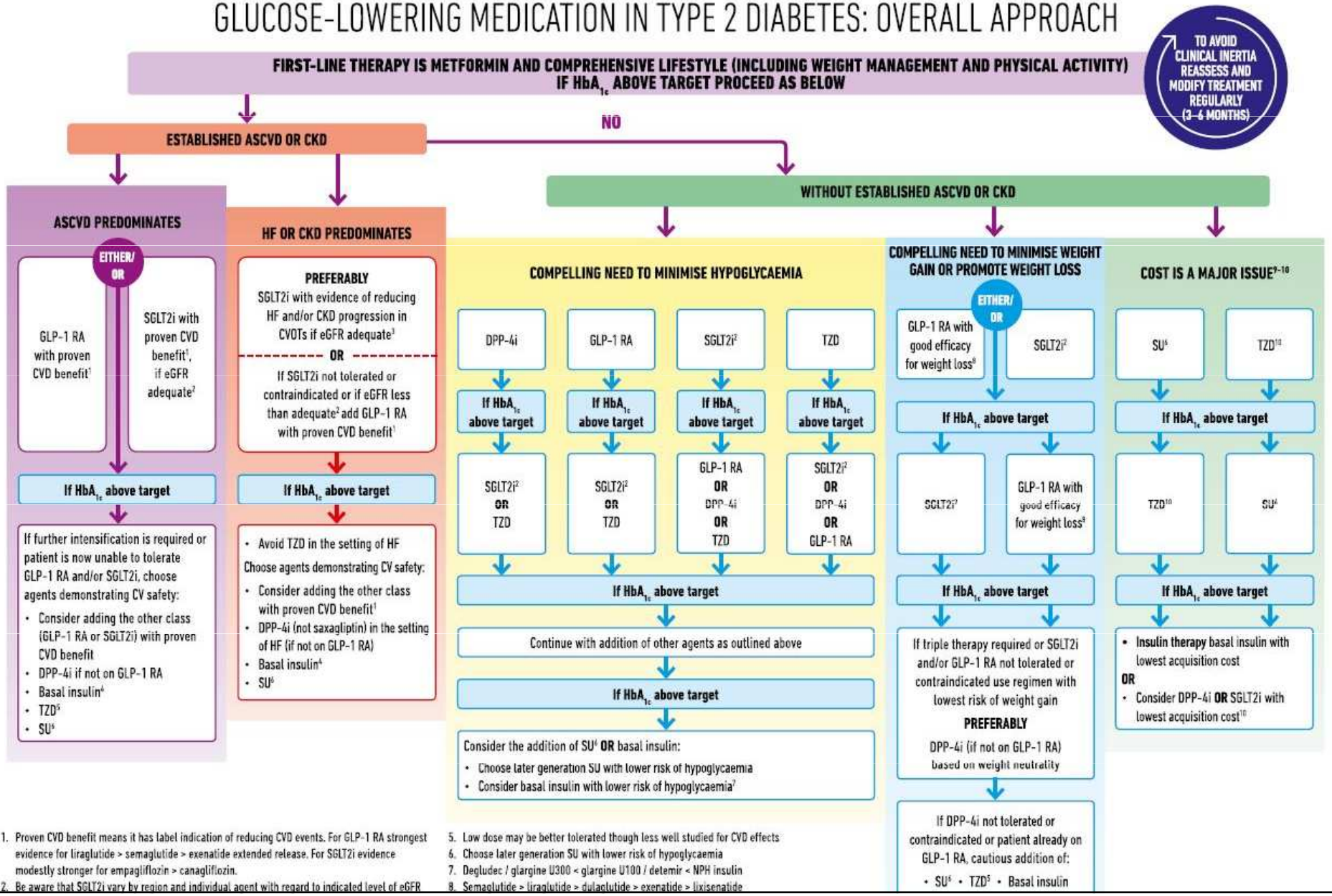
## Triple Therapy — Metformin + — Lifestyle Management

| Sulfonylurea + | Thiazolidinedione + | DPP-4 inhibitor + | SGLT2 inhibitor + | GLP-1 receptor agonist + | Insulin (basal) + |
|---|---|---|---|---|---|
| TZD | SU | SU | SU | SU | TZD |
| or DPP-4-i | or DPP-4-i | or TZD | or TZD | or TZD | or DPP-4-i |
| or SGLT2-i | or SGLT2-i | or SGLT2-i | or DPP-4-i | or SGLT2-i | or SGLT2-i |
| or GLP-1-RA | or GLP-1-RA | or Insulin[§] | or GLP-1-RA | or Insulin[§] | or GLP-1-RA |
| or Insulin[§] | or Insulin[§] | | or Insulin[§] | | |

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

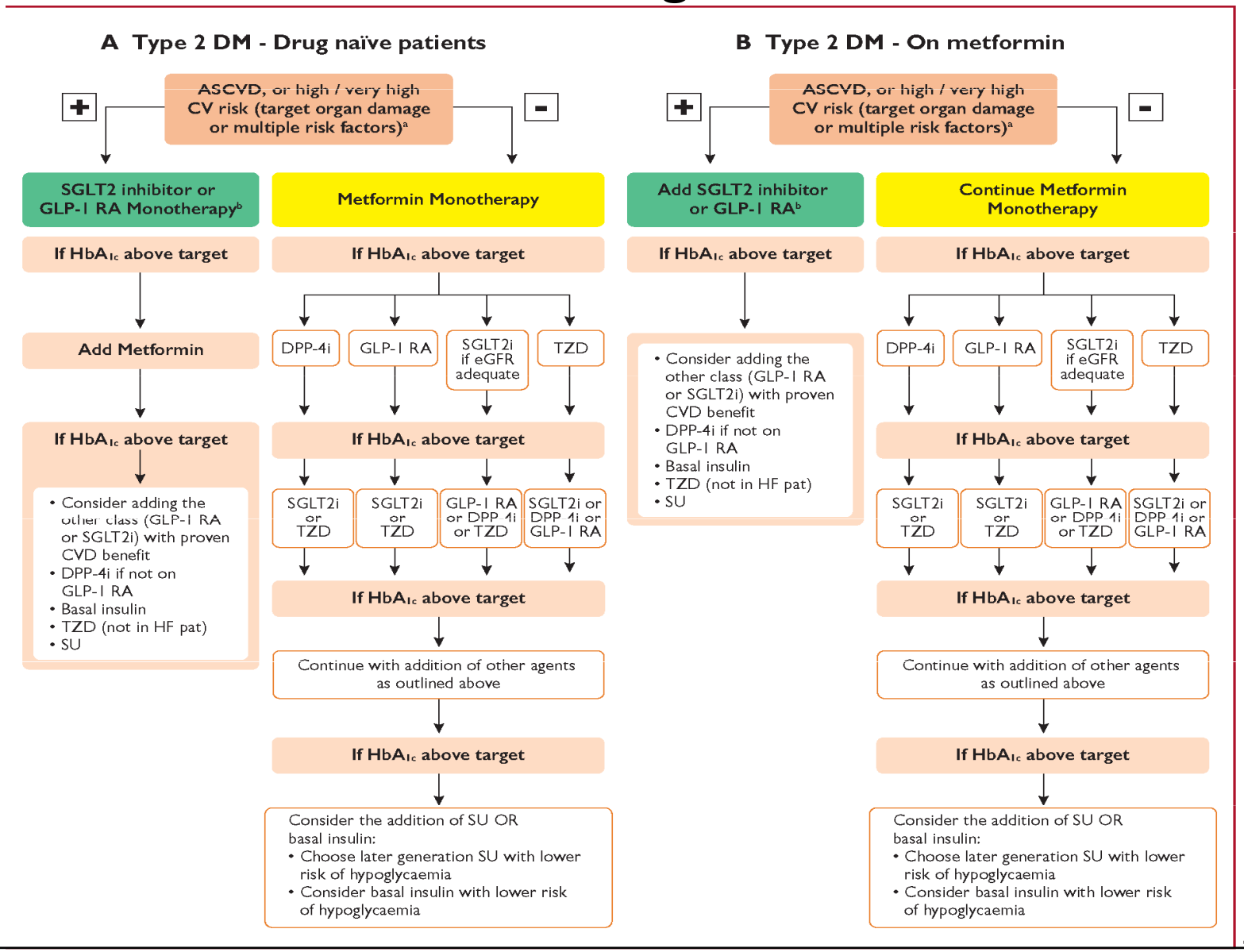
## Combination Injectable Therapy (See Figure 8.2)

# GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH




1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

# Patients with high CV risk



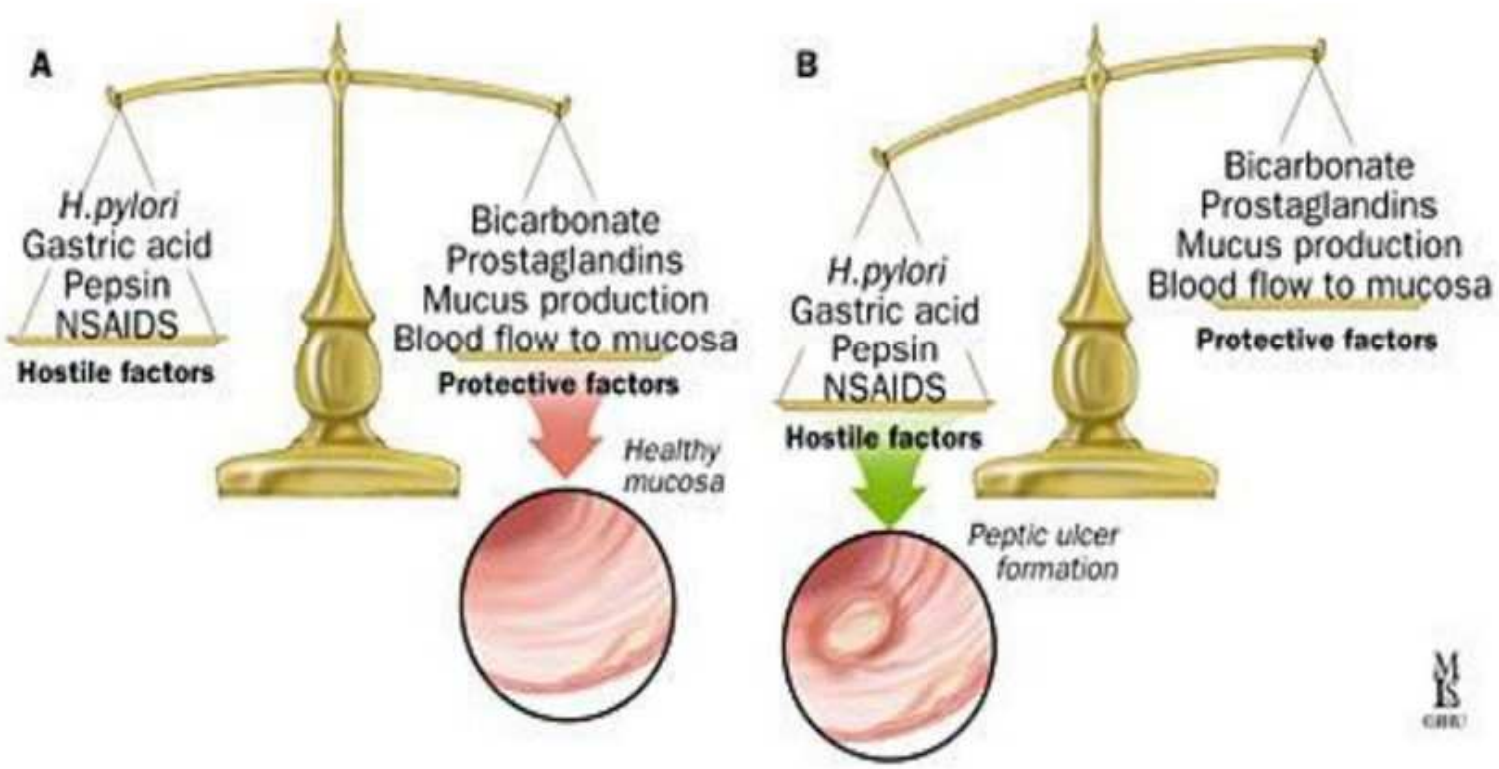
# Useful links

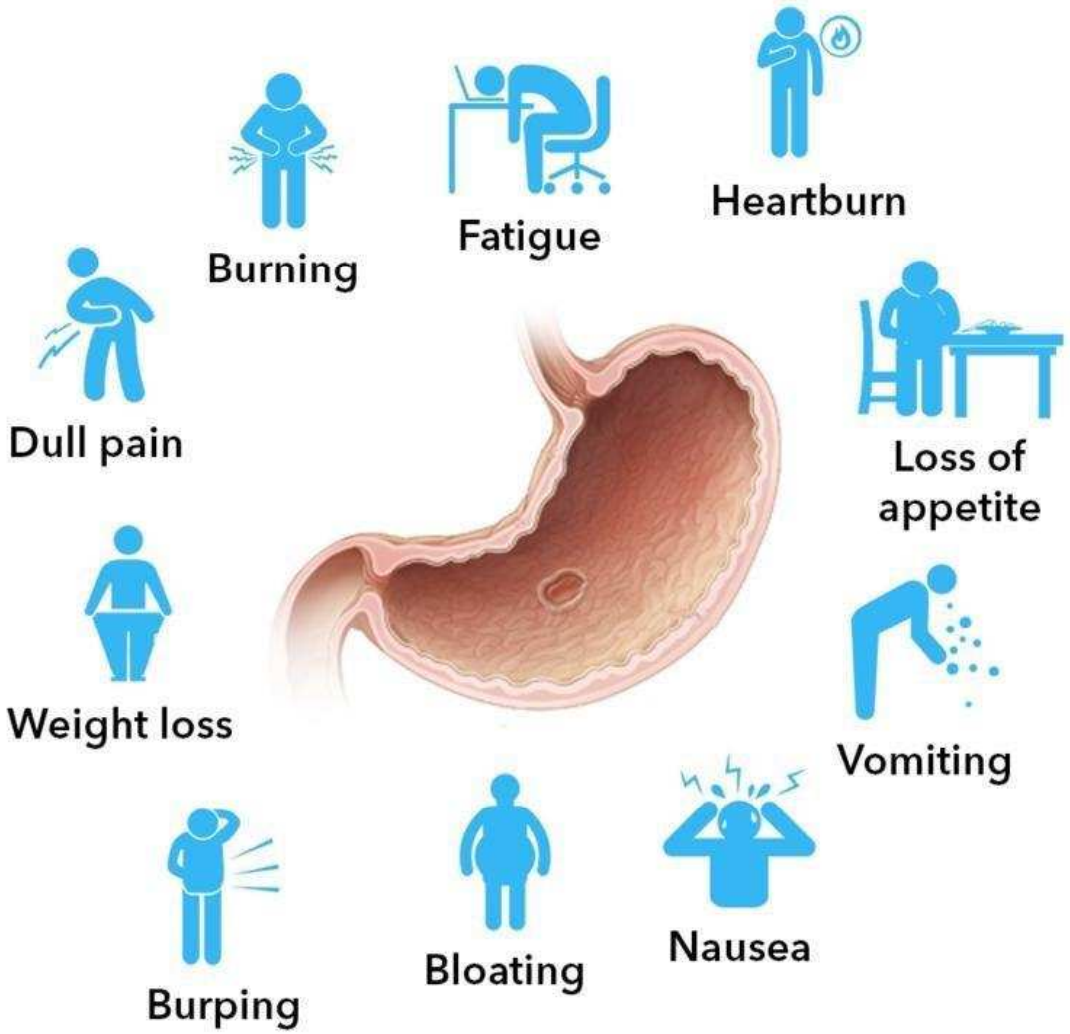
**American Diabetes Association**
http://www.diabetes.org/

# Drugs used in gastric ulcer disease

# Gastric ulcer disease

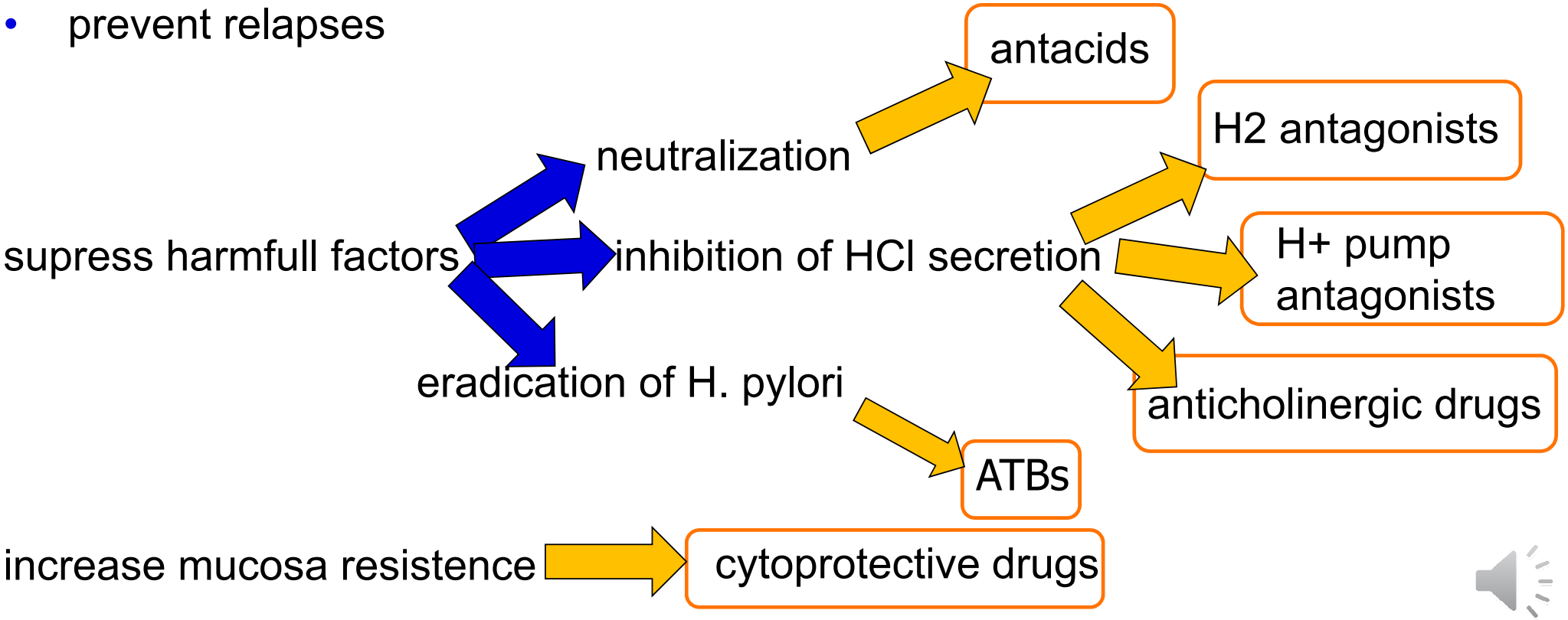
Peptic ulcers – result of dysbalance between protective and harmfull factors




Burning
Fatigue
Heartburn
Dull pain
Loss of appetite
Weight loss
Vomiting
Burping
Bloating
Nausea

# Main goals of the treatment

- supress pain
- improve healing (mucosa reparation)
- prevent relapses



# Antacids

- symptomatic therapy to reduce pain
- HCl neutralisation in stomach = increase in pH → decrease in pepsin activity (pH optimum 2)

- $NaHCO_3$ (strong, rapid relief from pain)
- $CaCO_3$ (strong, rapid relief from pain, not for chronic treatment absorption of $Ca^{2+}$)
- $MgO$ / $Mg(OH)_2$ (laxative)
- $Mg\,[AlO_2(OH)]$

} May be used in mixture $Mg(OH)_2 + Al_2O_3$

- $Al_2O_3$ (gel, long-lasting eff., constipation)
- $Bi(OH)_2NO_3$ (weak eff., supress H. pylori)



# Antacids

**Indications:**

- dyspepsia, hyperacidity, pyrosis
- reflux oesophagitis
- symptomatic treatment of GIT disorders
- begining of antiulcerous therapy
- rapid relief from pain

**AE:**

- absorption of **Ca, Mg** (cardiac complications)
- **Al** – constipation
- **Mg** – laxative effect
- decreased absorption of other drugs



# H2 antihistamines

**ranitidine**
**famotidine**

**Mechanism of action:**

- competitive H2 receptor antagonisms
- selective supression of HIS-induced secretion
- inhibition of intrinsic factor secretion (B12)

**Indications:**

- ulcer disease (primary and secondary, prevention of relapse)
- Zollinger-Ellison syndrome (↑gastrin)
- reflux oesophagitis
- prophylaxis of gastrotoxicity in NSAIDs treatment

**Adverse effects:**

- myalgia, diarrhoea, constipation
- CNS - confusion, glossolalia, headache
- endocrine - antiandrogenic efect (cimetidine) - impotence, gynekomastia
- blood – granulocytopenia, trombocytopenia, neutropenia..aplastic anemia (ranitidine)
- hepatotoxicity – ALT, AST

**Caution**: pass placental barrier



# Proton pump inhibitors

**omeprazole, esomeprazole**
**pantoprazole, lansoprazole**
**rabeprazole**

**MoA:**

**irreversible** inhibition of PP and supression of HCl secretion regardless the origin of the stimulus

(re-synthesis needed for regeneration of activity)

- administered as a pro-drugs
- acidic environment in the parietal cells → active metabolites
- enterosolvent coating, parenteral

**Indications:**

- H. pylori eradication in ulcer disease
- ulcer disease
- reflux oesophagitis
- Zollinger-Ellison syndrome (↑gastrin)
- prophylaxis of stress-induced ulcer
- prophylaxis of NSAIDs- induced gastropathy
- in risk groups of patients (e.g. LMWH, warfarin)

# Proton pump inhibitors

**AE:**

- dyspepsia,
- headache
- rarely cytopenia
- P450 inhibition

| Proton pump inhibitor (PPI) | Cytochrome P450 metabolism | Interaction potential* |
|---|---|---|
| Omeprazole | Major: CYP2C19<br>Minor: CYP3A4 | High |
| Esomeprazole | Major: CYP2C19<br>Minor: CYP3A4 | Moderate |
| Pantoprazole | Major: CYP2C19<br>Minor: CYP3A4 | Low |
| Lansoprazole | CYP2C19<br>CYP3A4 | Moderate |
| Rabeprazole | Major: Non-enzymatic<br>Minor: CYP2C19<br>Minor: CYP3A4 | Low |

| Proton Pump Inhibitor | Drug Interaction |
|---|---|
| Omeprazole<br>Esomeprazole | • Clopidogrel (Plavix/Clopilet/Ceruvin)<br>• Diazepam (Valium)<br>• Warfarin (Coumadin)<br>• Phenytoin (Dilantin)<br>• Citolopram (Celexa) |
| Ompreazole<br>Esomeprazole<br>Lansoprazole<br>Rabeprazole<br>Pantoprazole<br>Dexlansoprazole<br>Zegerid | • Viracept (Nelfinavir)<br>• Harvoni (Ledipasvir)<br>• Edurant (Rilpirvine)<br>• Digoxin (Lanoxin)<br>• Ketoconazole (Nizoral)<br>• Methotrexate (Trexall) |



# Selective parasympatolytics

pirenzepine

OBSOLETE

**Mechanism of action:**

- acetylcholine antagonism in M1/3 receptors
- convenient is **selective** inhibition
- supress CO2- 3 and mucus secretion
- similar action as H2 antagonists

**Indications:**

- peptic ulcer disease
- dyspepsia after NSAIDs treatment
- stress ulcer prevention

**CI:**

- glaucoma
- prostate hypertrophy
- urination disorders

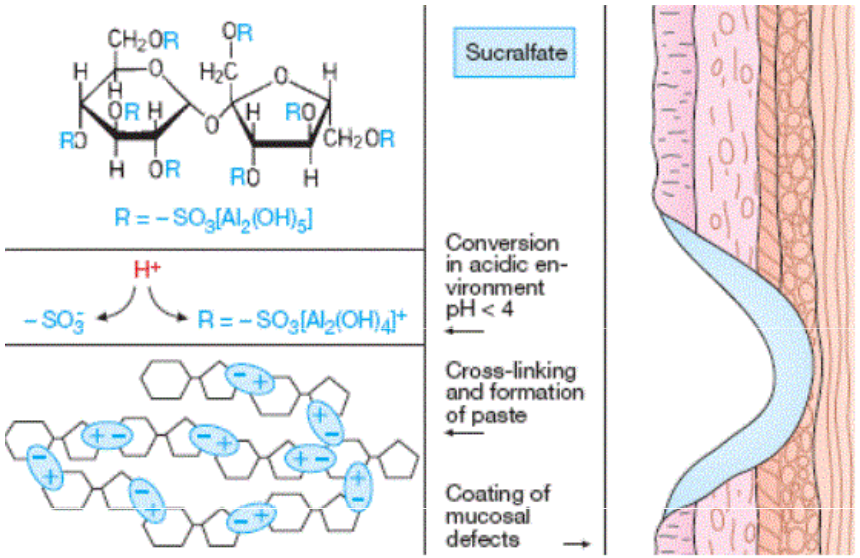
# Cytoprotectives

protective effect on the stomach mucosa

**sucralfate**
**bismuth salts**
**alginic acid**

**Sucralfate** = octasulfate of sucrose + aluminium hydroxide

- strong mucoprotective eff.
- needs acidic pH!!
- binds pepsin and bile acids
- incr. prostaglandins synthesis




**Sucralfate mechanism of action**

**AE:**

- not absorbed
- dyspepsia, Al- constipation
- decrease bioavailability of other drugs – tetracyclines, phenytoin, digoxine, cimetidine...

# Cytoprotectives

**Bismuth salts** = basic salts of bismuth and citric acid

- chelatation of proteins on ulcer surface → protective barrier
- PG secretion stimulation
- antibacterial action (eradication of H. pylori)

**Eicosanoids PGE1, PGI2** = main natural protective factors synthetised in gastric mucosa

- increase mucus and HCO3 production, perfusion
- unstable, only derrivatives administered as prevention of harmfull effects of NSAID
- Misoprostol - PGE1 - abortions!!!!

# Eradication of H. pylori

- G- bacteria, over 80 % are asymptomatic
- eradication decrease frequency of relapses to 0-10 %
- **complex therapy** - combination of 2 antibiotics – with H+ pump inhibitors for 1 – 2 weeks

**Tripple therapy:**

**PPI** + **amoxicilin** (2x 1000 mg) + **claritromycin/azithromycin** (2x 500 mg)

or **metronidazole** (2x 500 mg)

ev. sequential

In resistant pathogen + **tetracyclin or bismuth salts**

Thank you for your attention