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ANTIDIABETICS

Alena Máchalová

Diabetes Mellitus

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

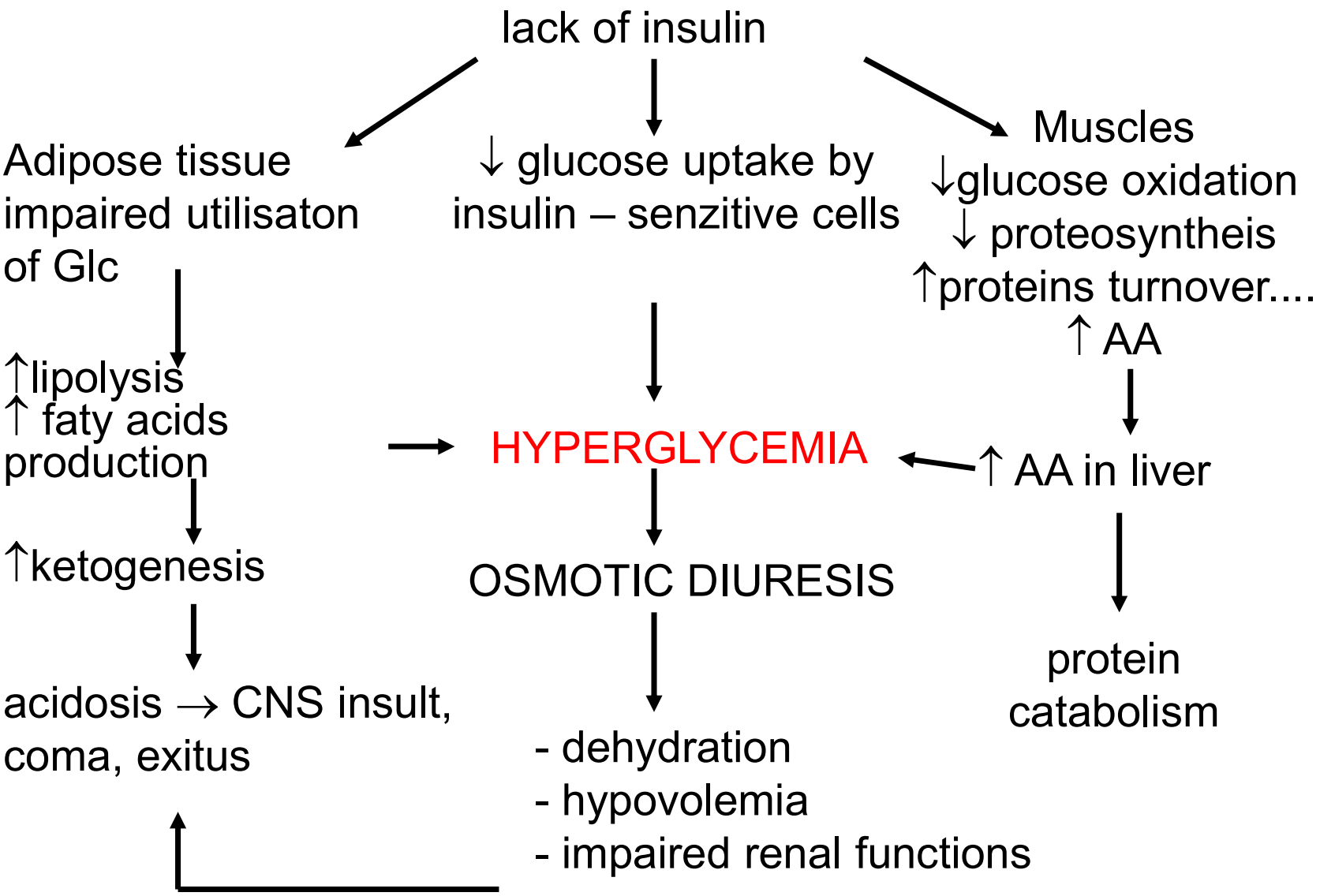
- **≤ 5.6 mmol/L**
- **IFG 5.6 (6,1) -6.9 mmol/L**
- **IGT** 2hPG ≥7.8 <11.1 mmol/L after oGTT

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

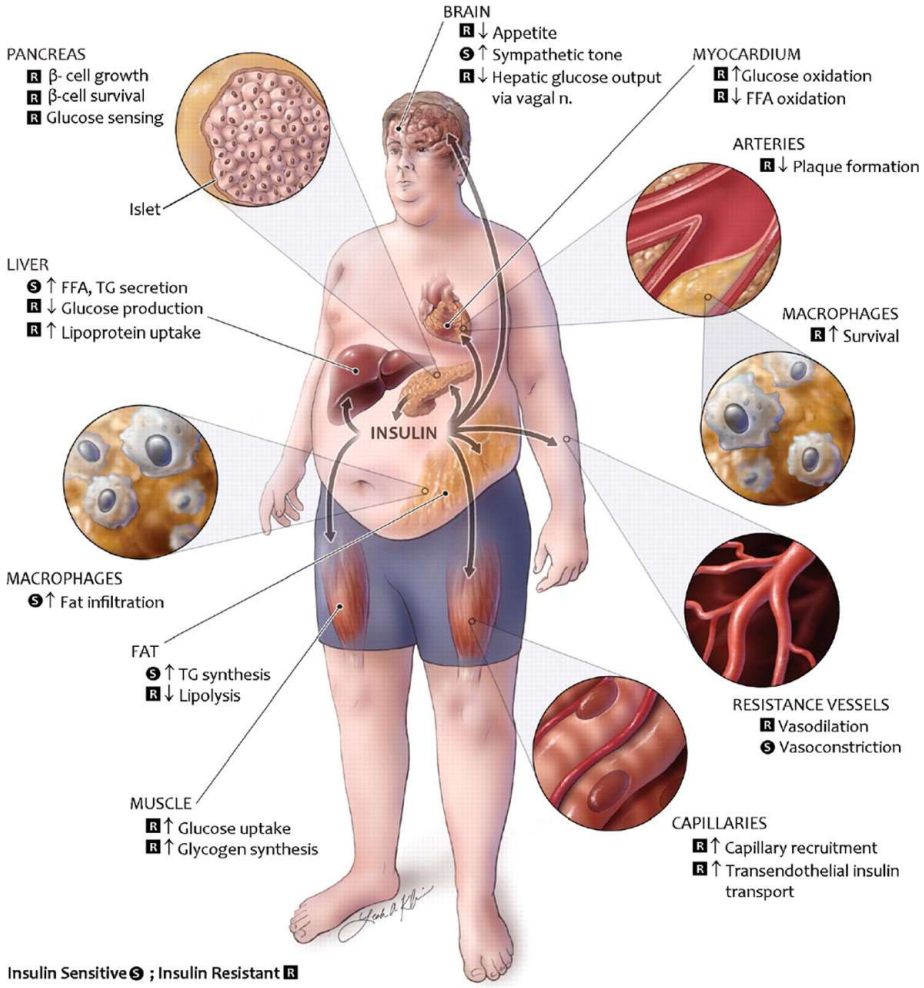
  no antibodies

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 insects 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

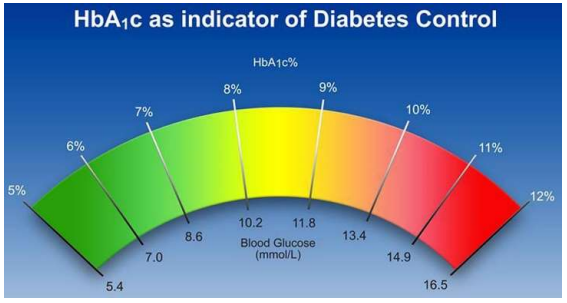
MODY - maturity onset diabetes of the young

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

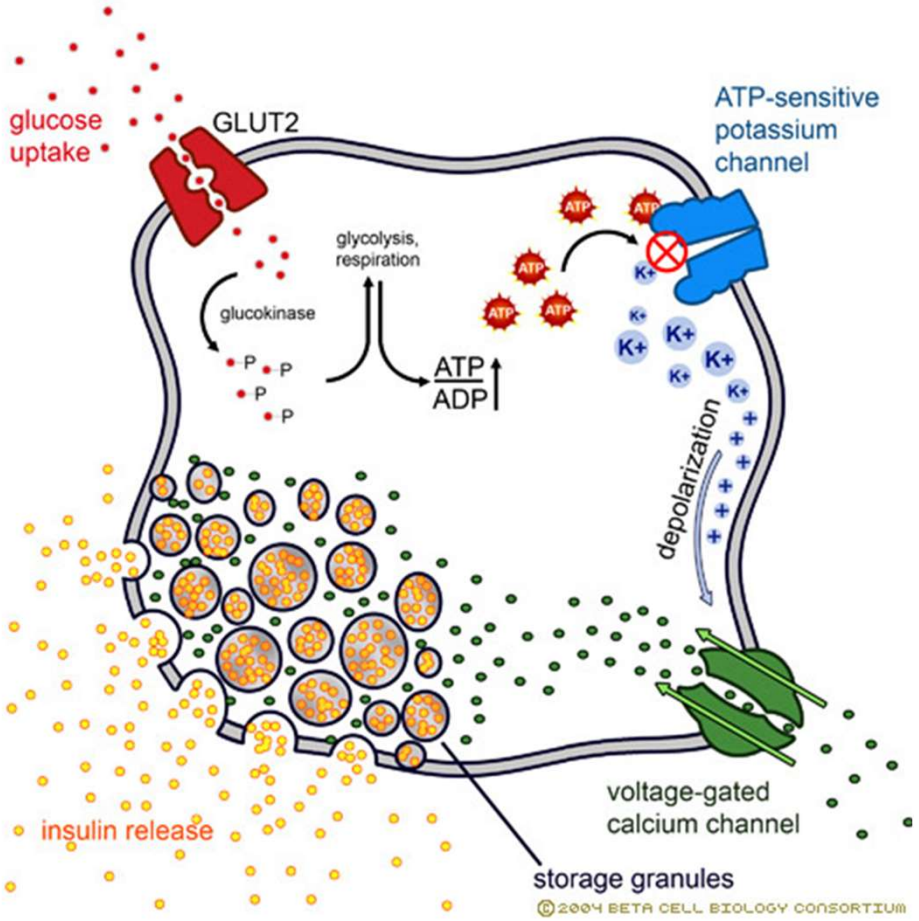
1. hormonal - antagonism with glucagon in the liver, cortisol muscle tissue, aldosterone and growth hormone

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
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Insulin secretagogues

glucose
glucagon
fatty acids
GLDs

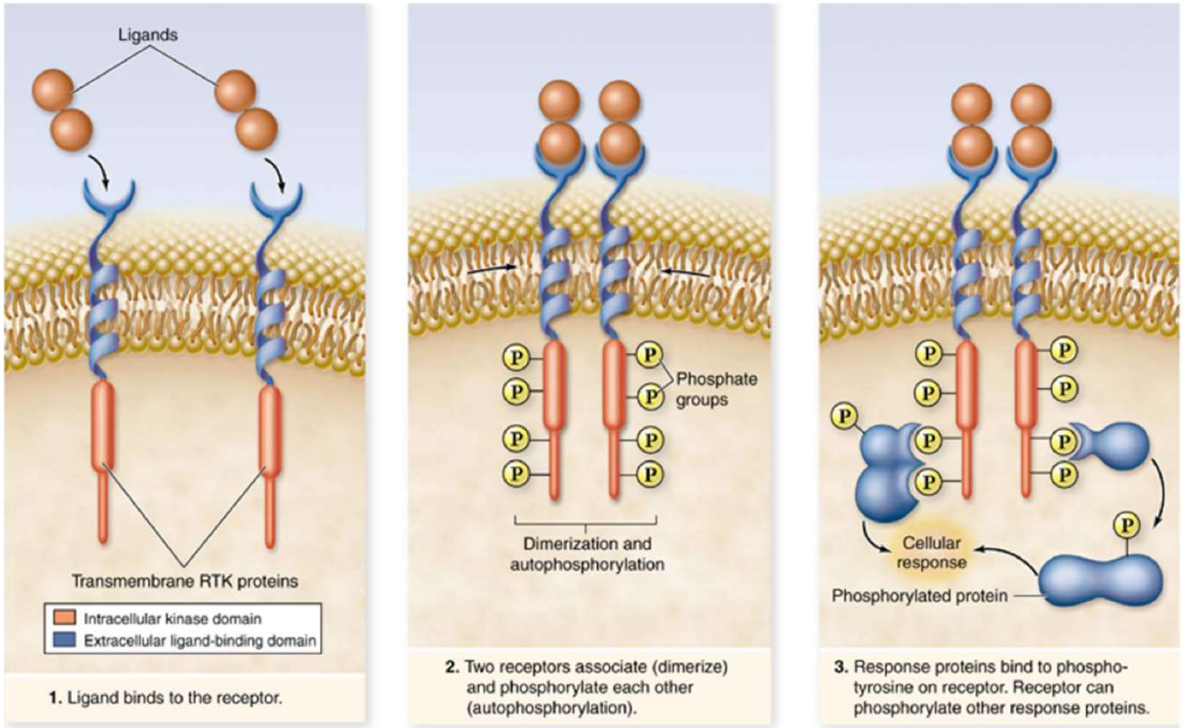
Amplifiers of glucose-induced insulin secretion

gastrin, secretin, cholecystokinin
GLP1
beta-adrenergic stimulation (β_2, β_1)
AA (Lys, Arg, Leu)

Factors decreasing insulin secretion

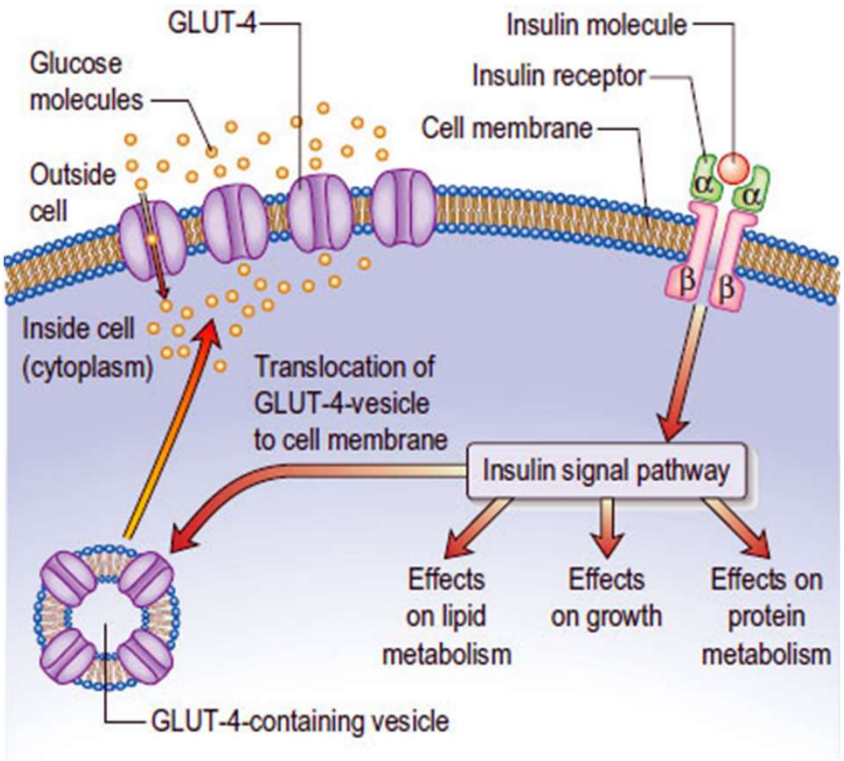
somatostatin
insulin (negative feedback)
α-activation of sympathetic n. s. (adrenalin)
galanin (neuropeptide)

Insulin receptor



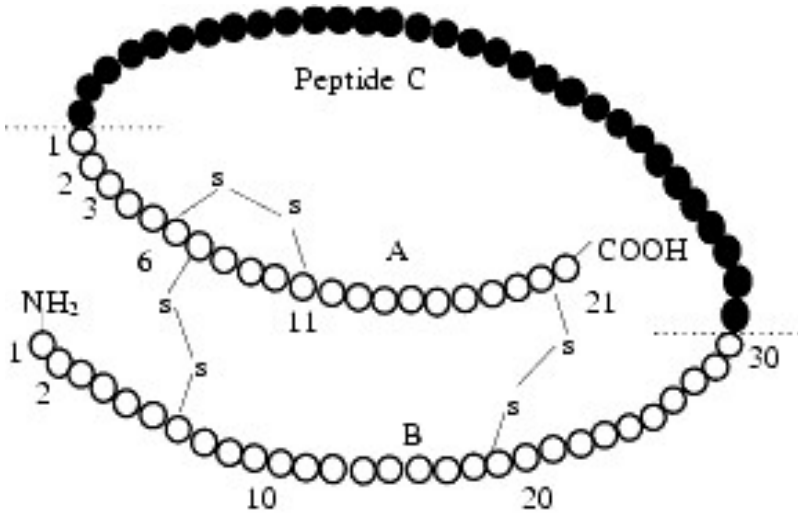
Lincová a kol. 2002

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

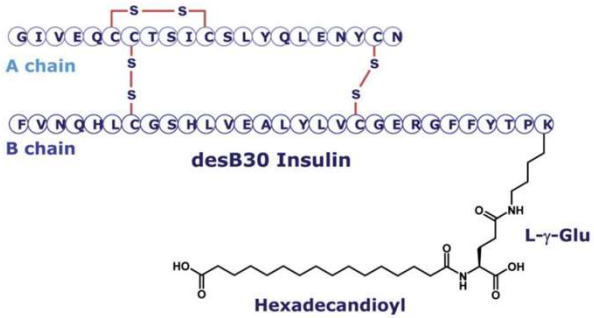
detemir (Levemir) = „predictable insulin“ – small interindividual variability

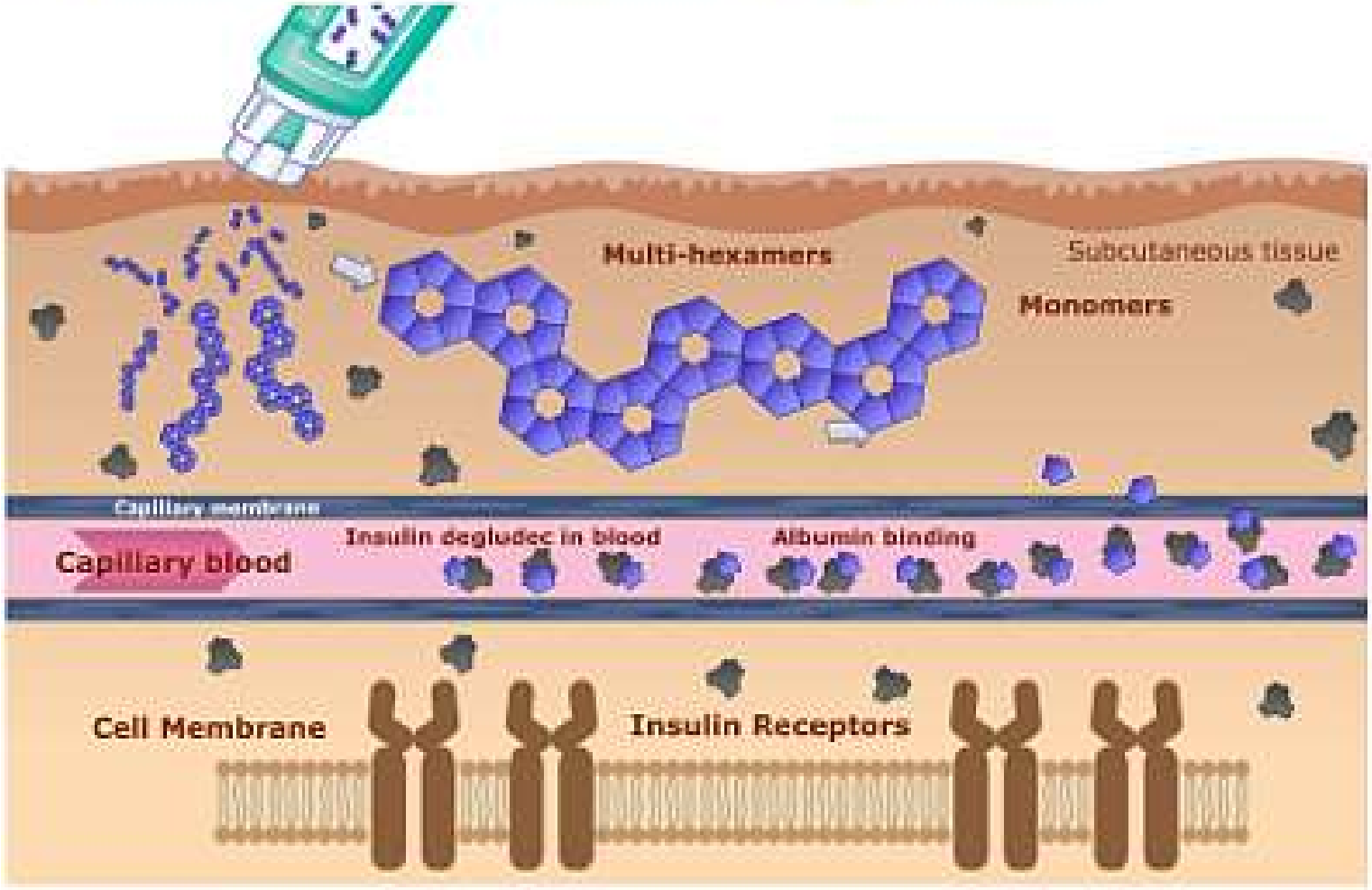
glargin (Lantus, Abasaglar) = „peakless insulin“ - even longer effect, flat curve action/time

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





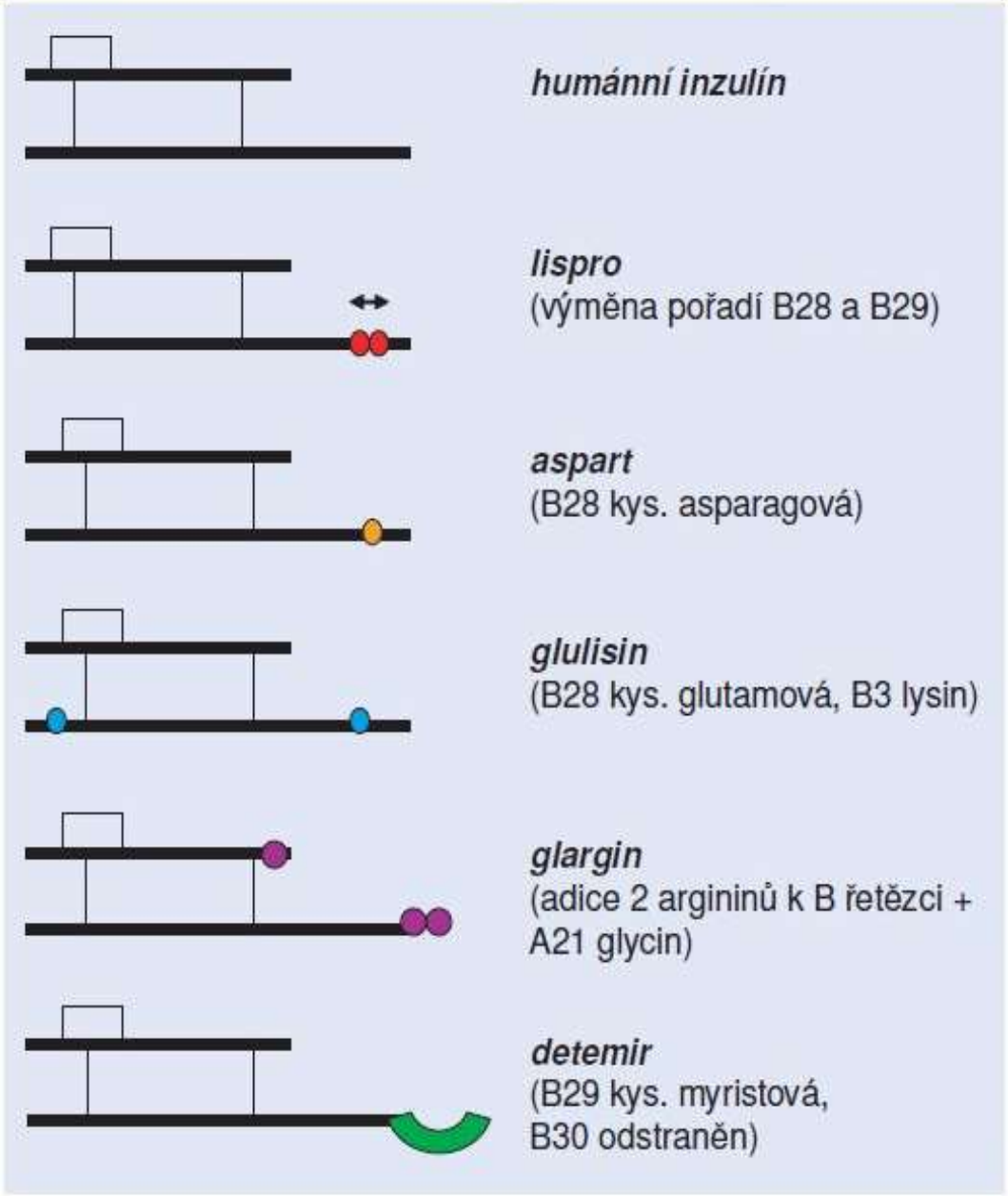
Insulin preparations

Aqeous solutions – only short acting i.v.

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

Powder for inhalation

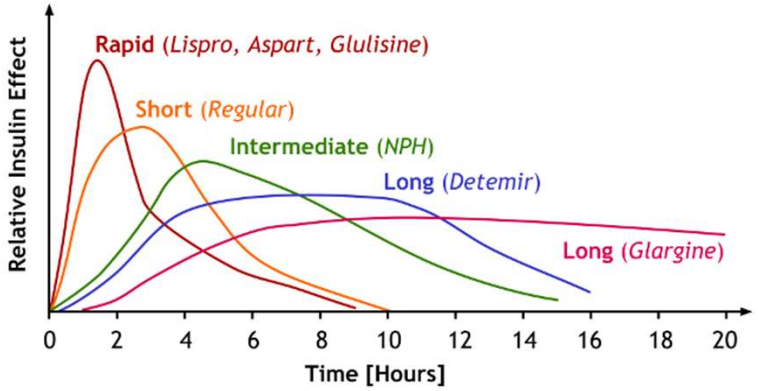
stabilised mixtures of insulin in different ratios

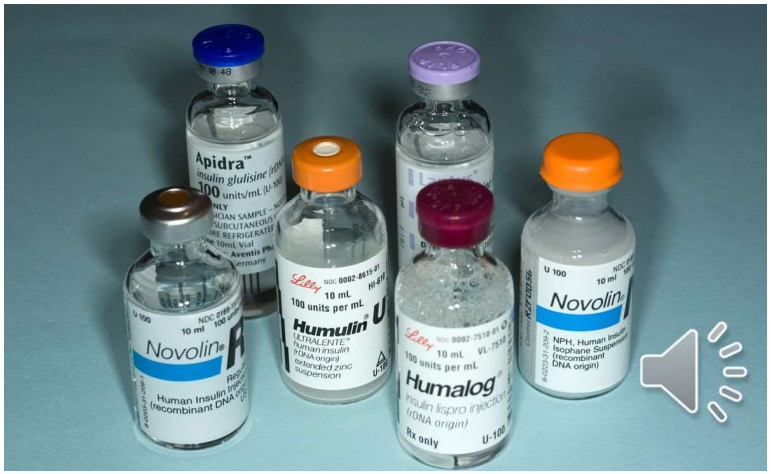


Types of insulin analouges

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 ▪ Lispro (Humalog) ▪ Glulisine (Apidra) ▪ Aspart (NovoRapid)	Clear 	2 4 6 8 10 12 14 16 18 20 22 24 **Onset:** 10 to 15 mins **Peak:** 1 to 2 hours **Duration:** 3 to 5 hours
Intermediate-acting ▪ NPH (Humulin-N, Novolin-NPH)	Cloudy 	2 4 6 8 10 12 14 16 18 20 22 24 **Onset:** 1 to 3 hours **Peak:** 5 to 8 hours **Duration:** up to 18 hours
Slow or long-acting ▪ Glargine (Lantus) ▪ Detemir (Levemir)	Clear 	2 4 6 8 10 12 14 16 18 20 22 24 **Onset:** 90 mins **Peak:** None **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)

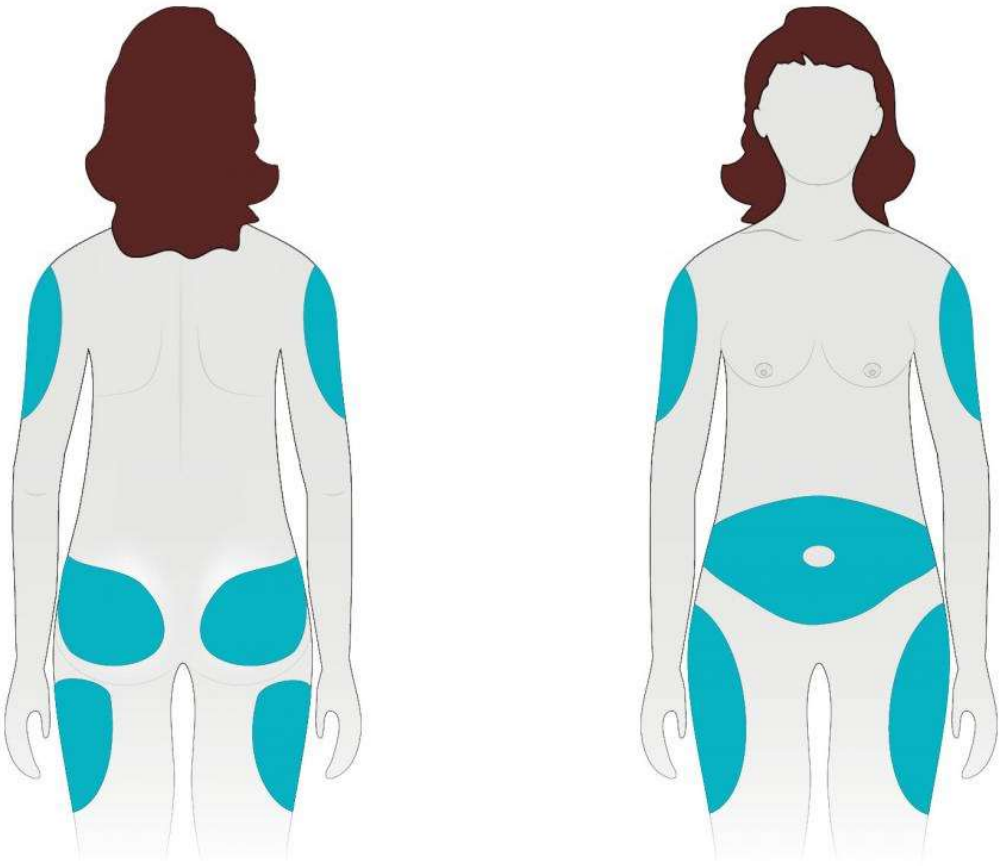
1) **Insulin injections** - calibrated by IU

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

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

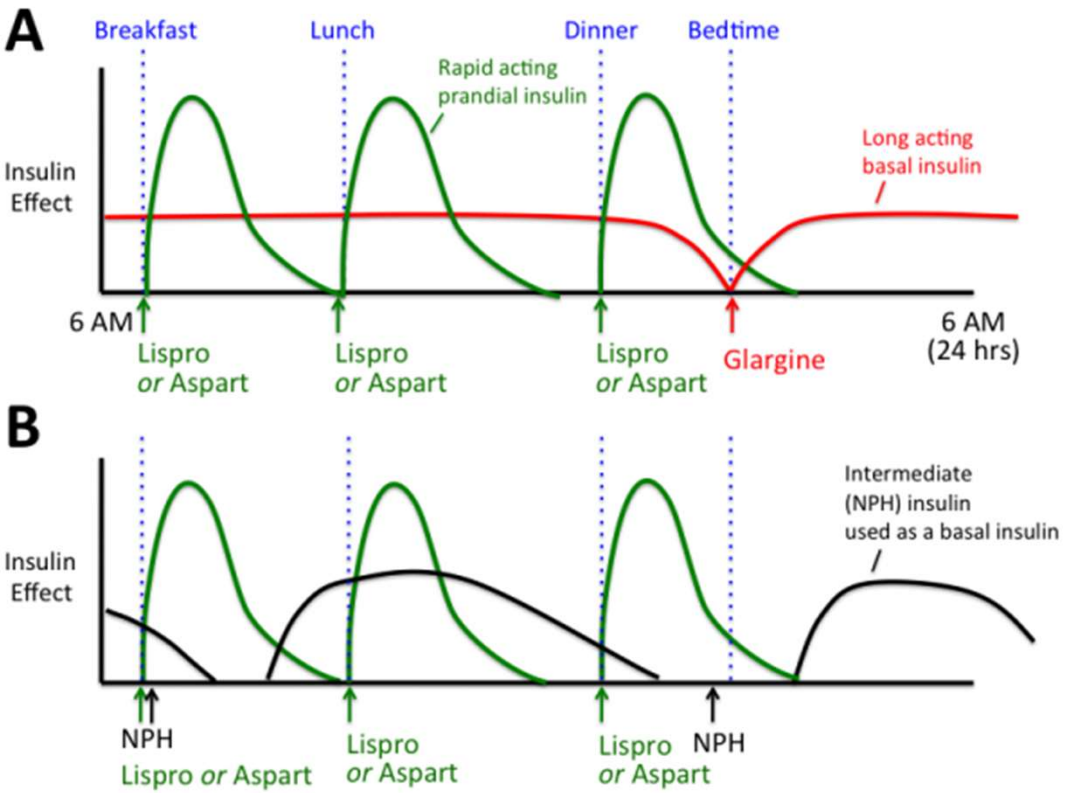
4) **Nasal** insulin delivery, insulin **inhalations**

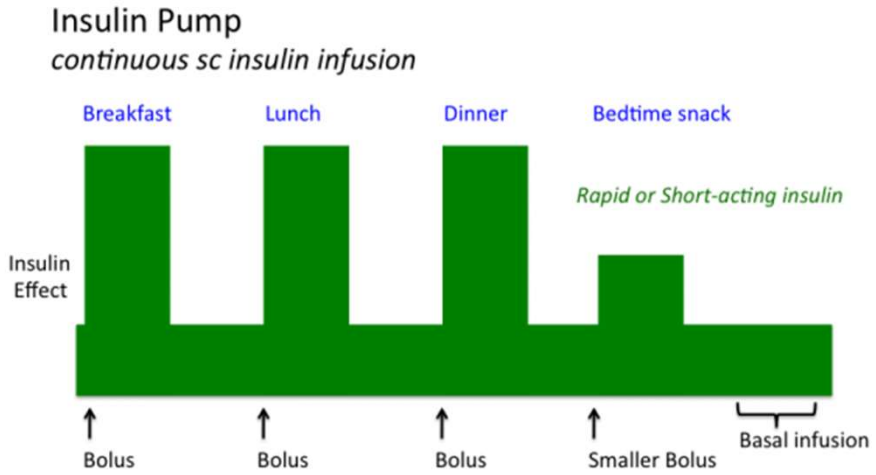
Insulin injection sites



Treatment strategies

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



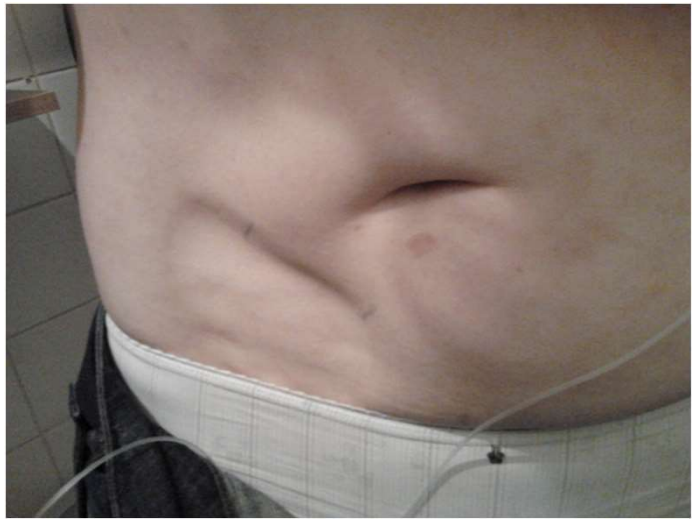


Examples of physiologic insulin delivery. **A)** Once-daily glargine serves as a basal insulin that is typically given at bedtime. Rapidly acting insulin are used as prandial insulins. This allows patients to change meal times at will. **B)** Intermediate-acting NPH, given twice daily, can be used as 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

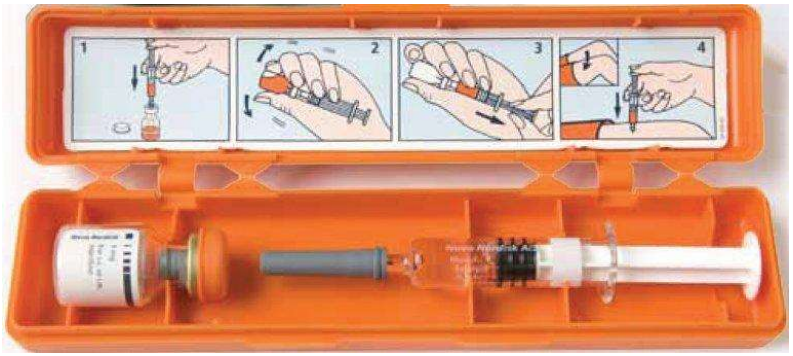
Plasma glucose under 2,8 mmol/l

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)

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(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

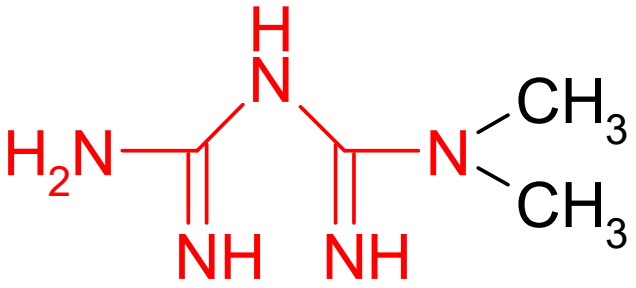
1. Biguanides (metformin)
2. Sulphonylurea derivatives
3. Thiazolidindiones
4. Inhibitors of intestinal glucosidases
5. Meglitinides
6. GLP1 (incretine) analoges
7. Inhibitors of DPP IV
8. SGLT2 (sodium-glucose cotransporter) inhibitors

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

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

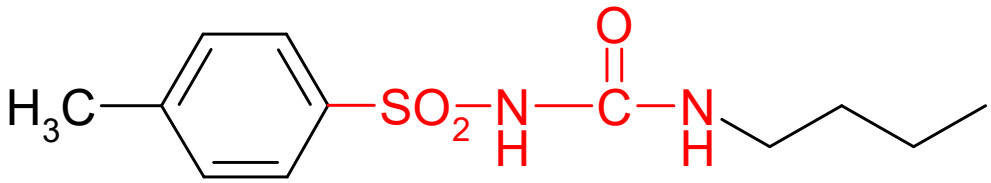
ClinicalTrials.gov Identifier: NCT01101438

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

Sponsor:
Canadian Cancer Trials Group

Collaborators:
National Cancer Institute (NCI)

2. Sulfonylurea derivatives (SU)

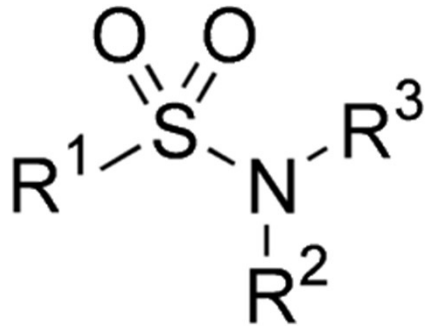


MoA:

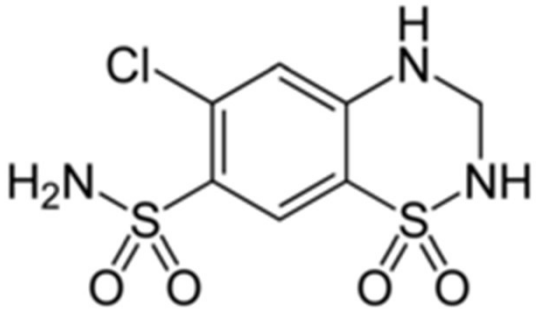
1) **pancreatic** – increase insulin release, but NOT synthesis

2) **extrapancreatic**

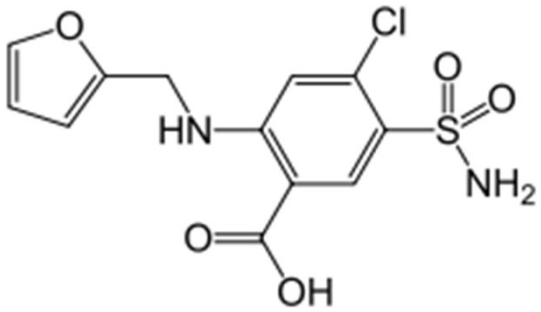
- potentiation of endogenous insulin effect on the target tissue
- reduction of hepatal glucose production
- reduction of hepatal insulin degradation
- reduction of serum glucagon levels
- increase the number of insulin receptor on ERYS, adipocytes, monocytes



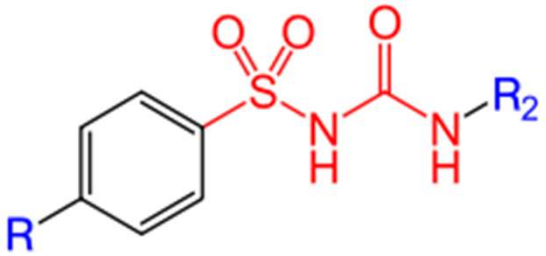
Sulfonamide
functional group



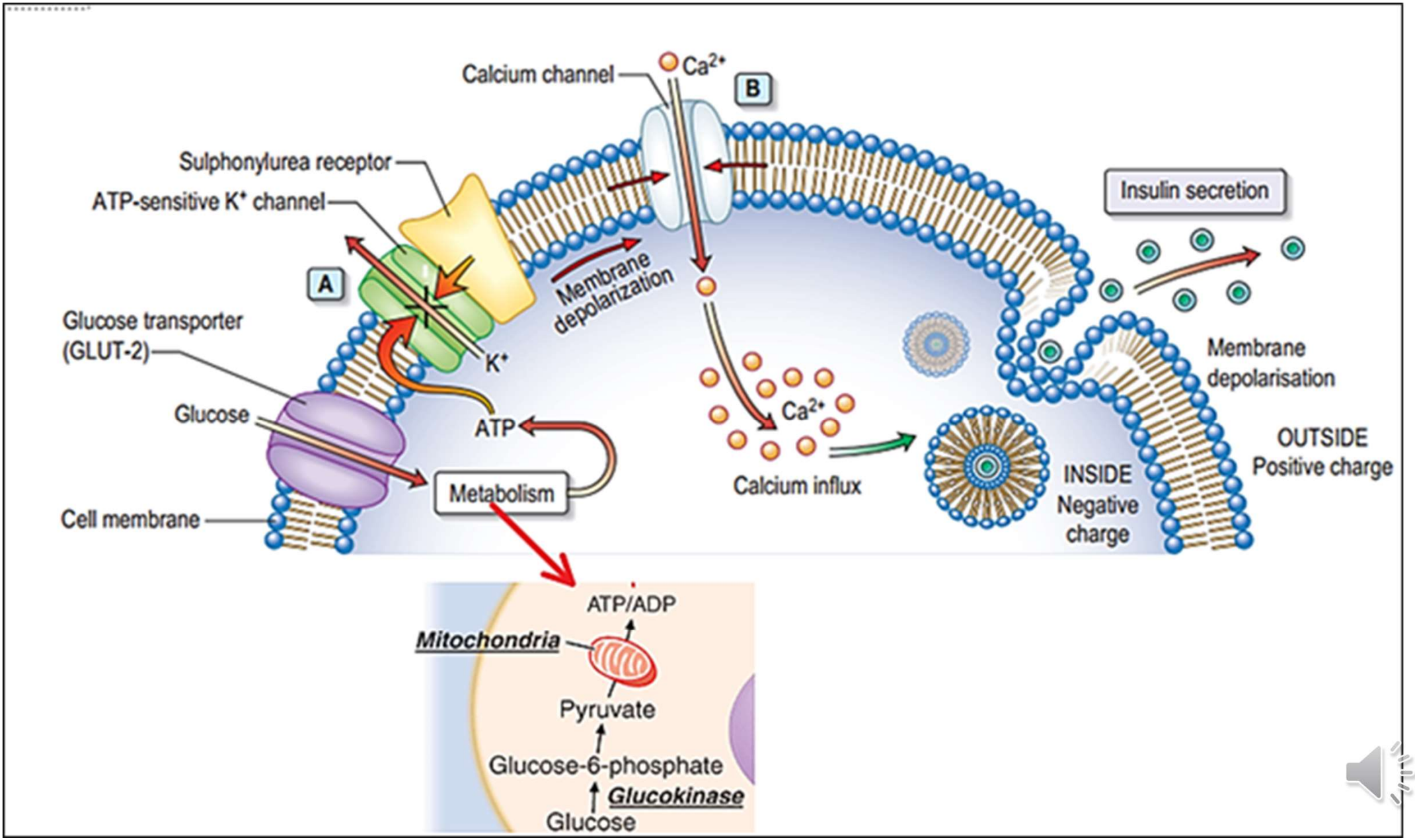
Hydrochlorthiazide



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

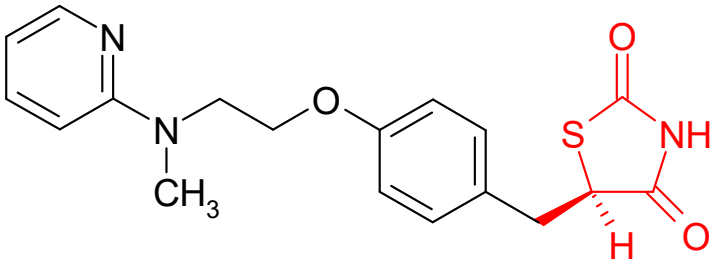
- hypoglycemia
- ketoacidosis
- renal/hepatal impairment
- pregnancy
- age
- hypersensitivity

3. Thiazolidindiones (glitazones)

Drugs: rosiglitazon

troglitazon

pioglitazon



MoA

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

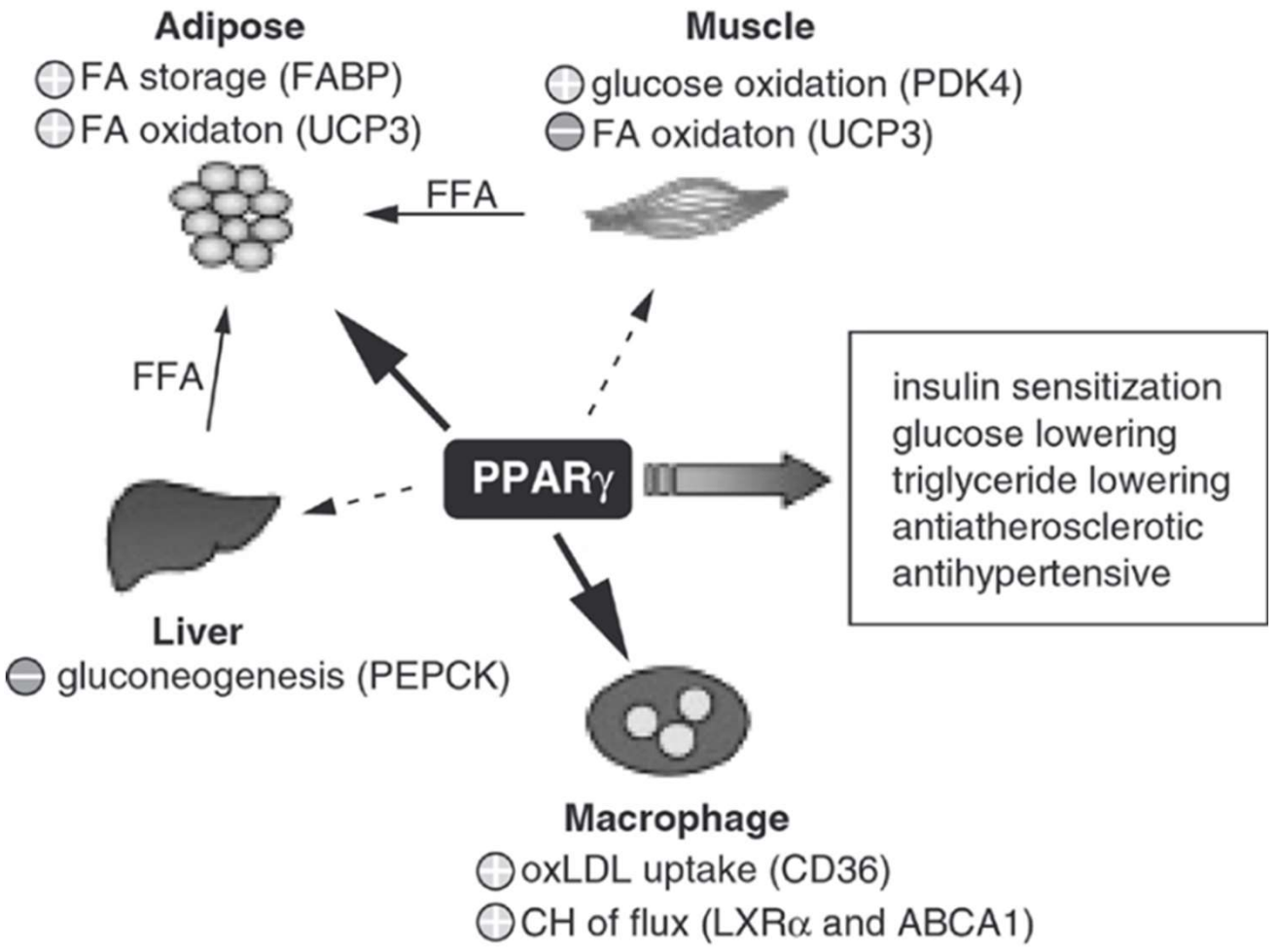
↓

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

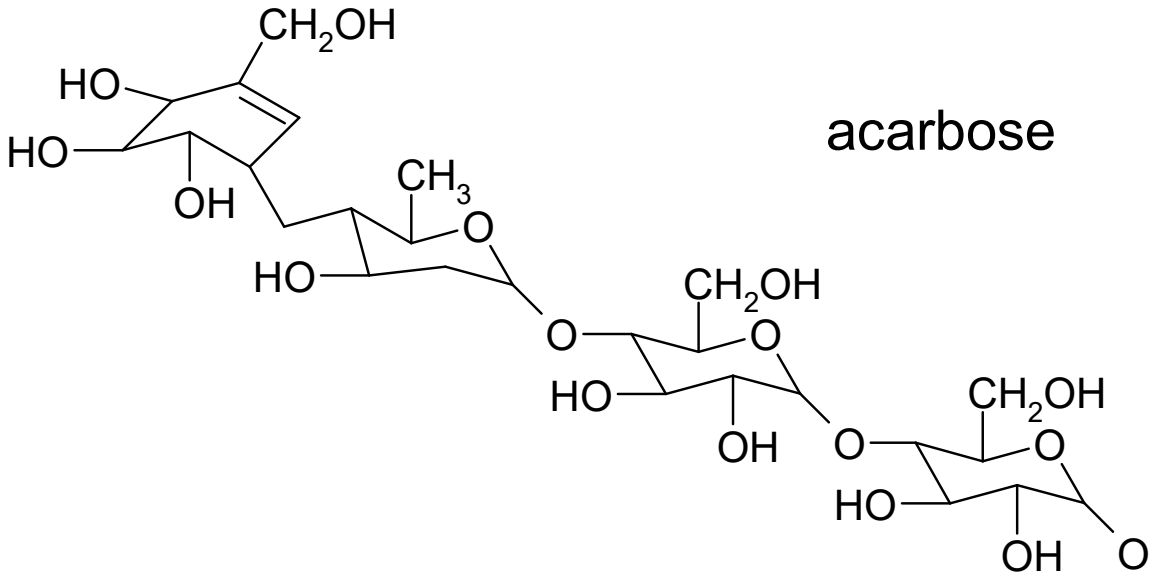
Contraindications

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

4. Inhibitors of intestinal glucosidases

Drugs

acarbose
miglitol
voglibose



acarbose

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

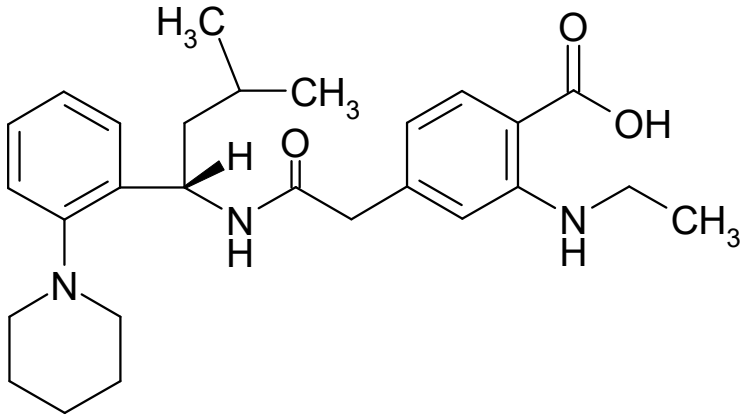
In case of hypoglycemia sucrose can not be administered orally (necessary are monosacharides - Glu, Fru) / or Glucagon

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)

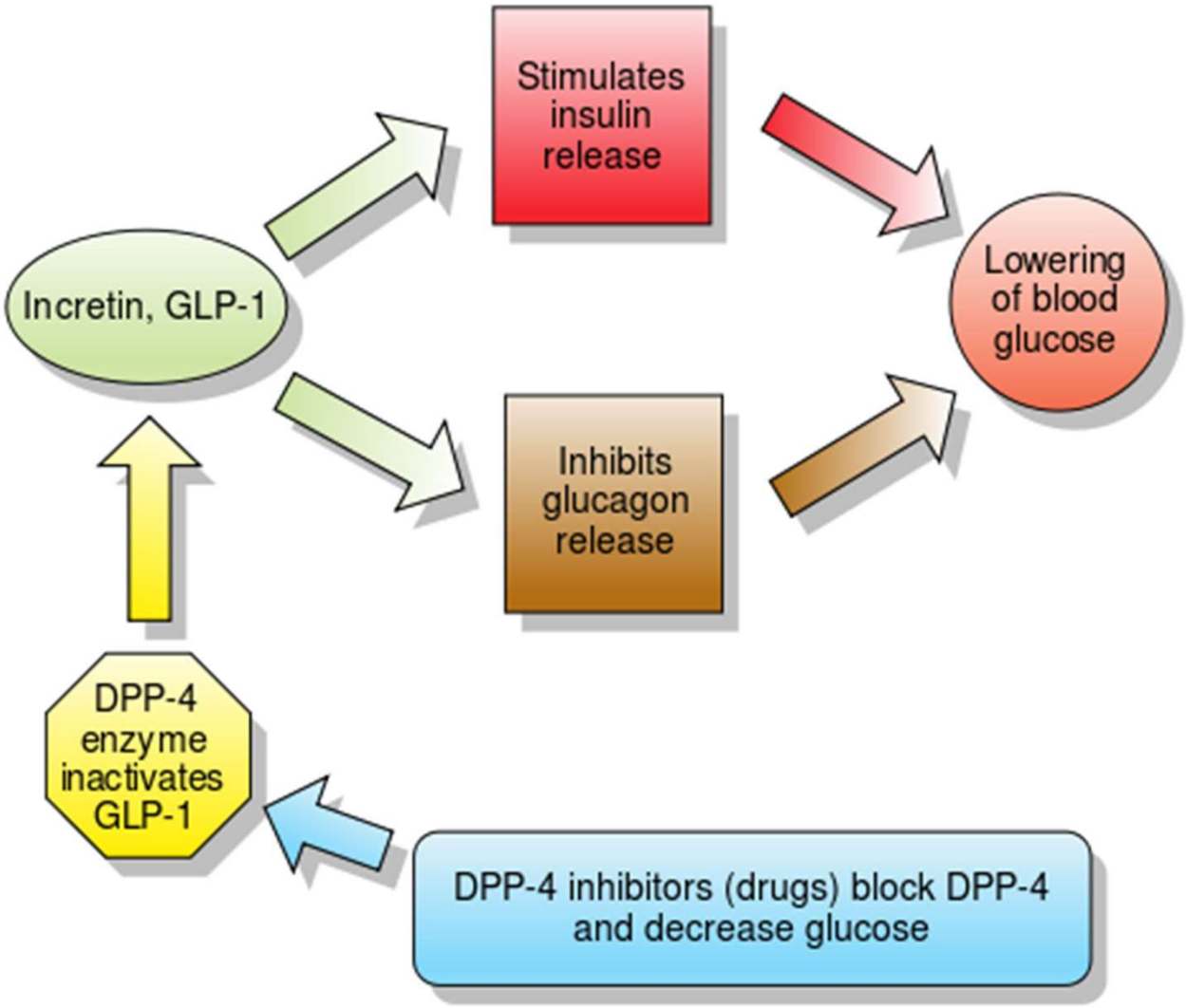
5. Meglitinides

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:

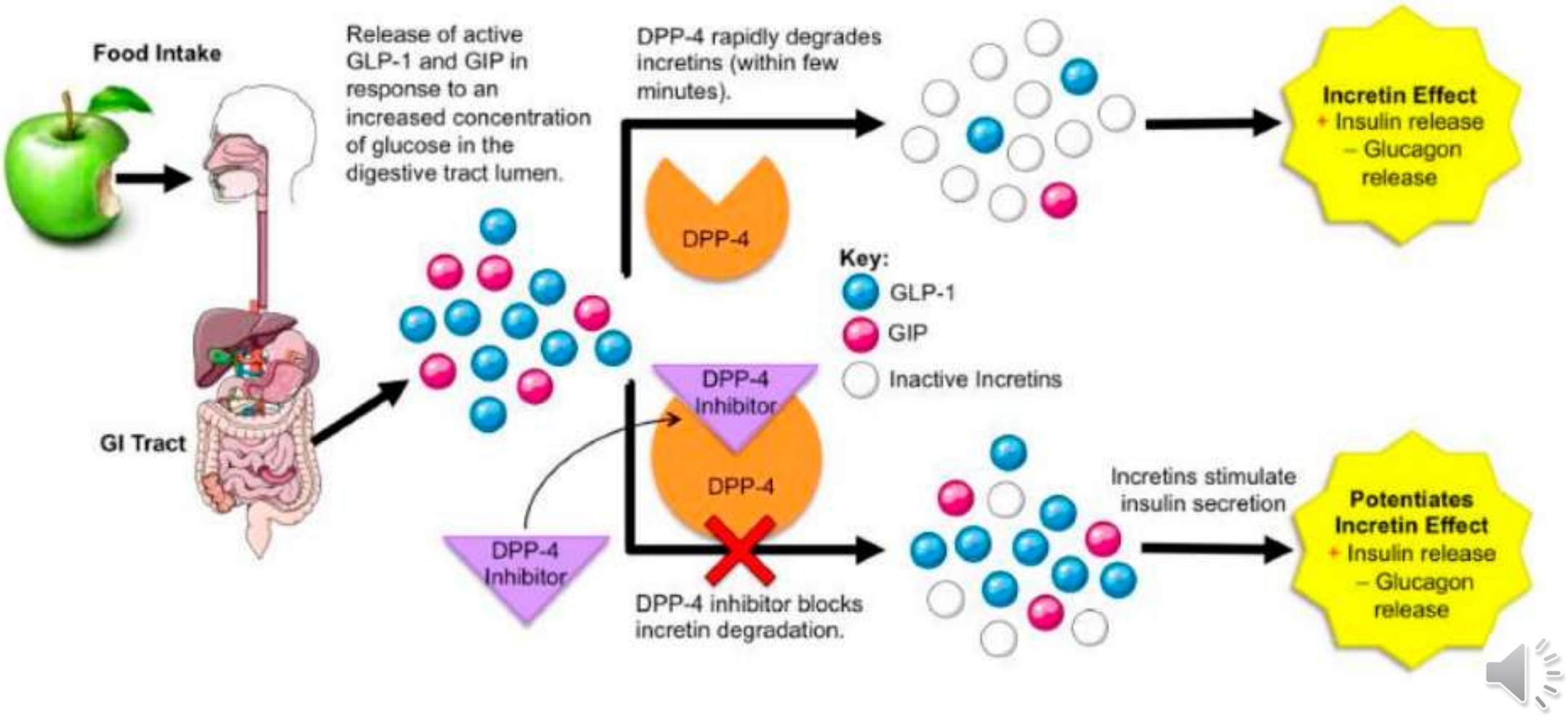
- ↑ insulin secretion (dependent on glycemia)
- ↓ glucagon secretion,
- prolong stomach content evacuation

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):

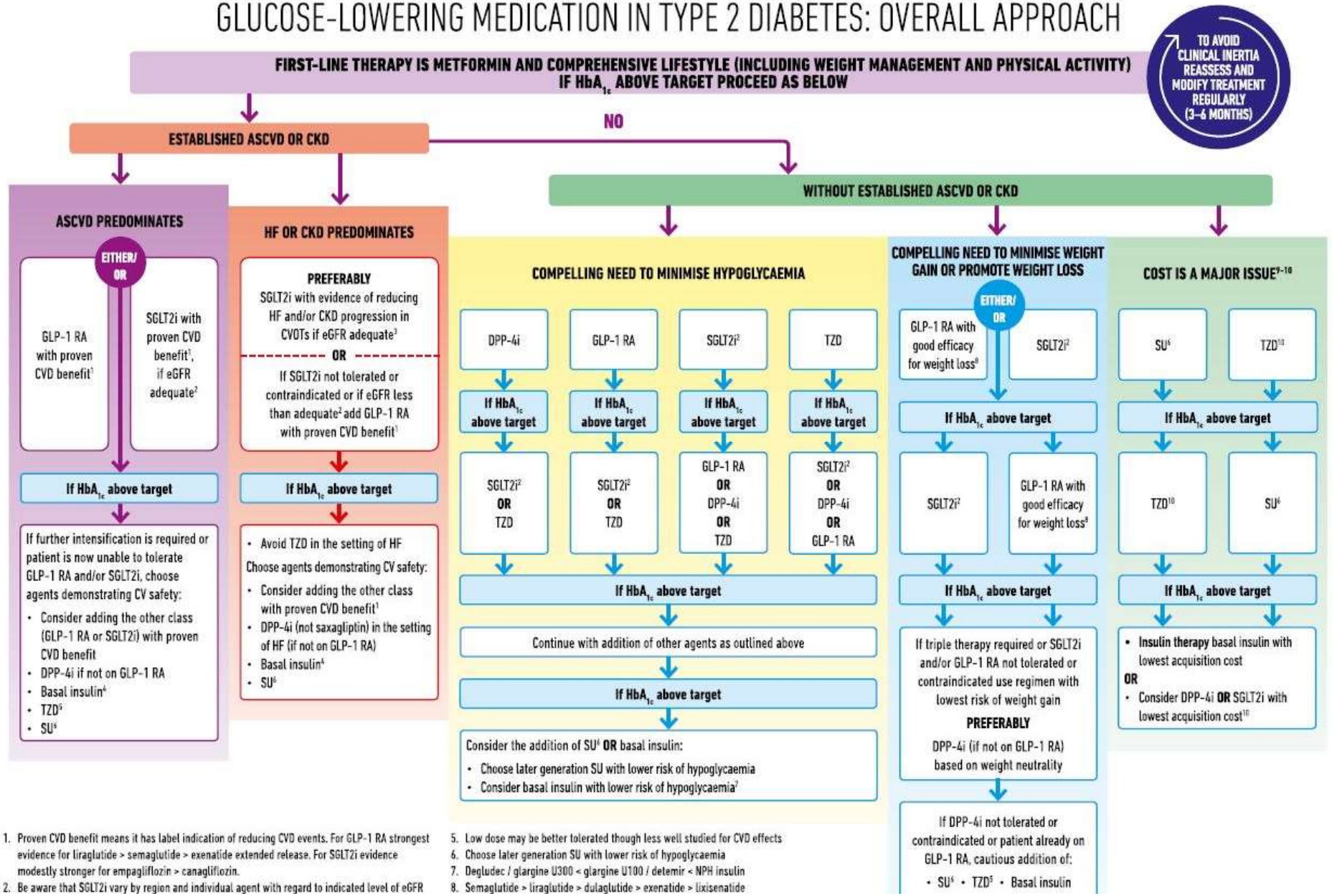
Triple Therapy — Metformin + — Lifestyle Management

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).

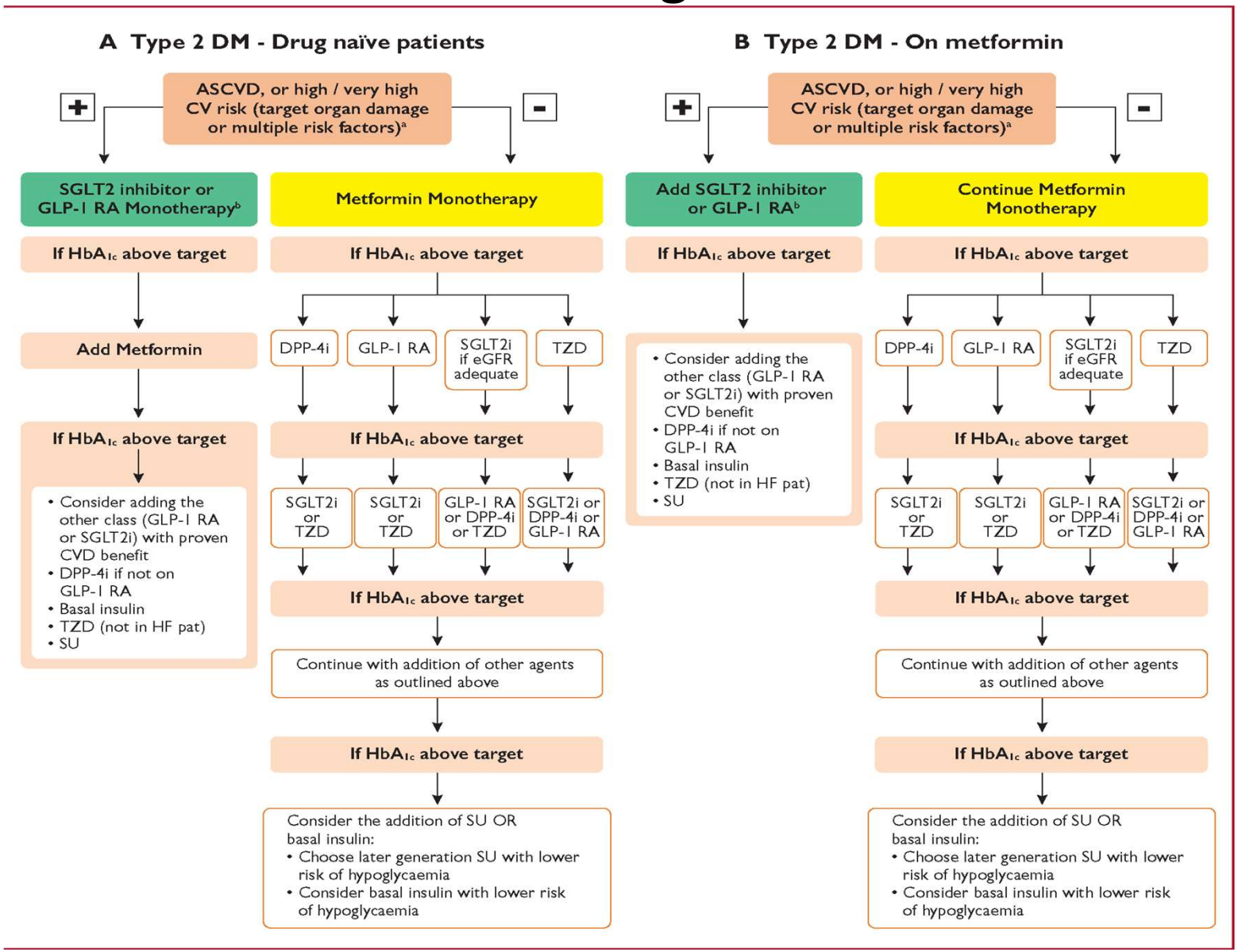
Combination Injectable Therapy (See Figure 8.2)

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



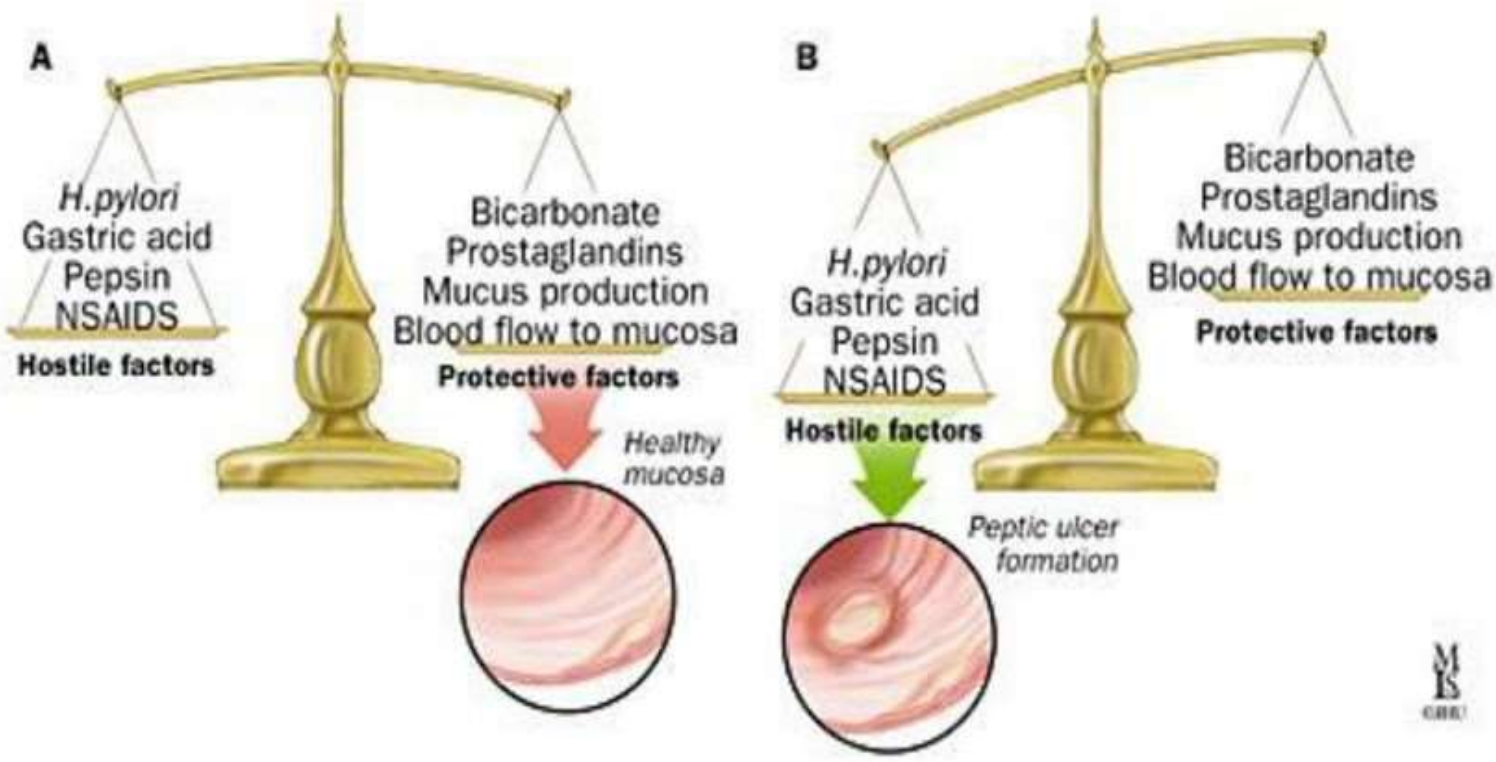
Useful links

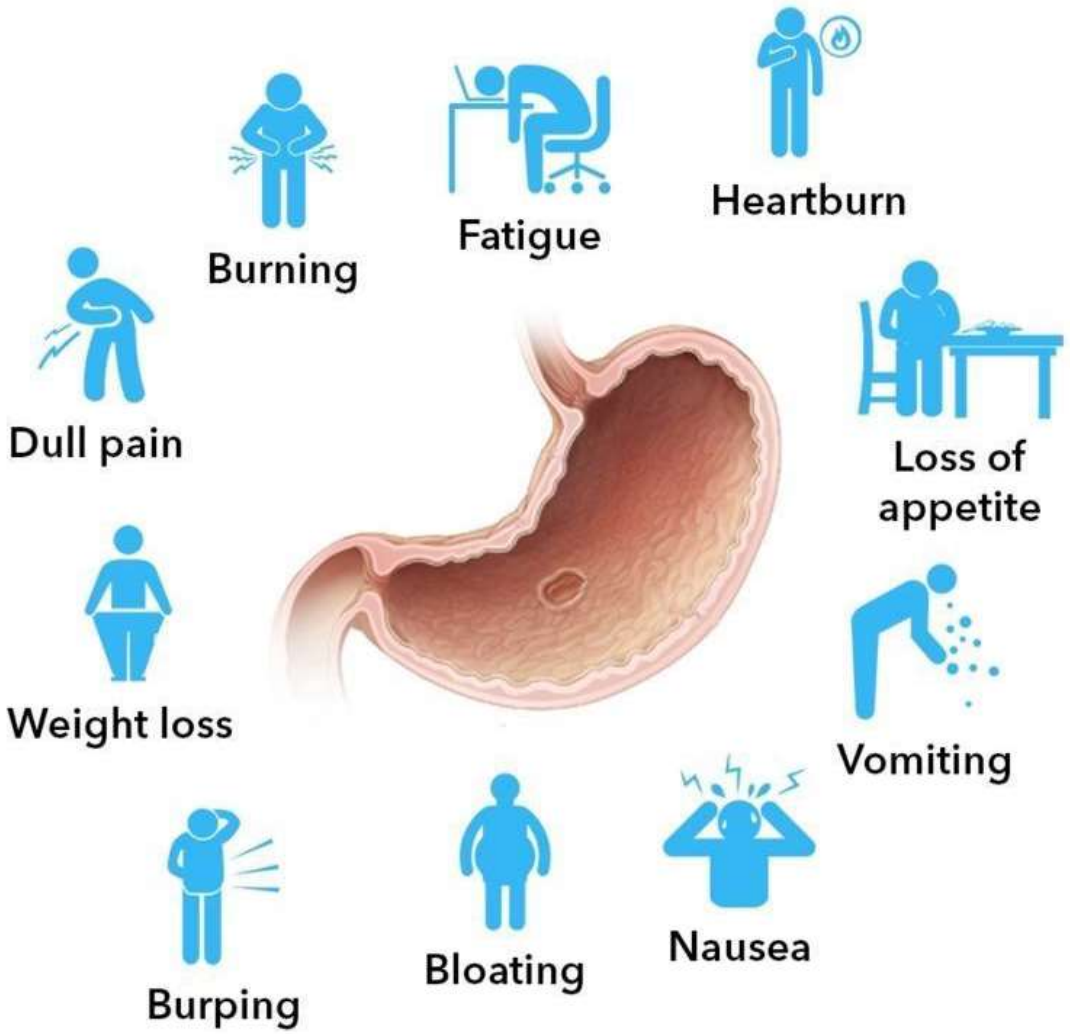
American Diabetes Association
http://www.diabetes.org/

Drugs used in gastric ulcer disease

Gastric ulcer disease

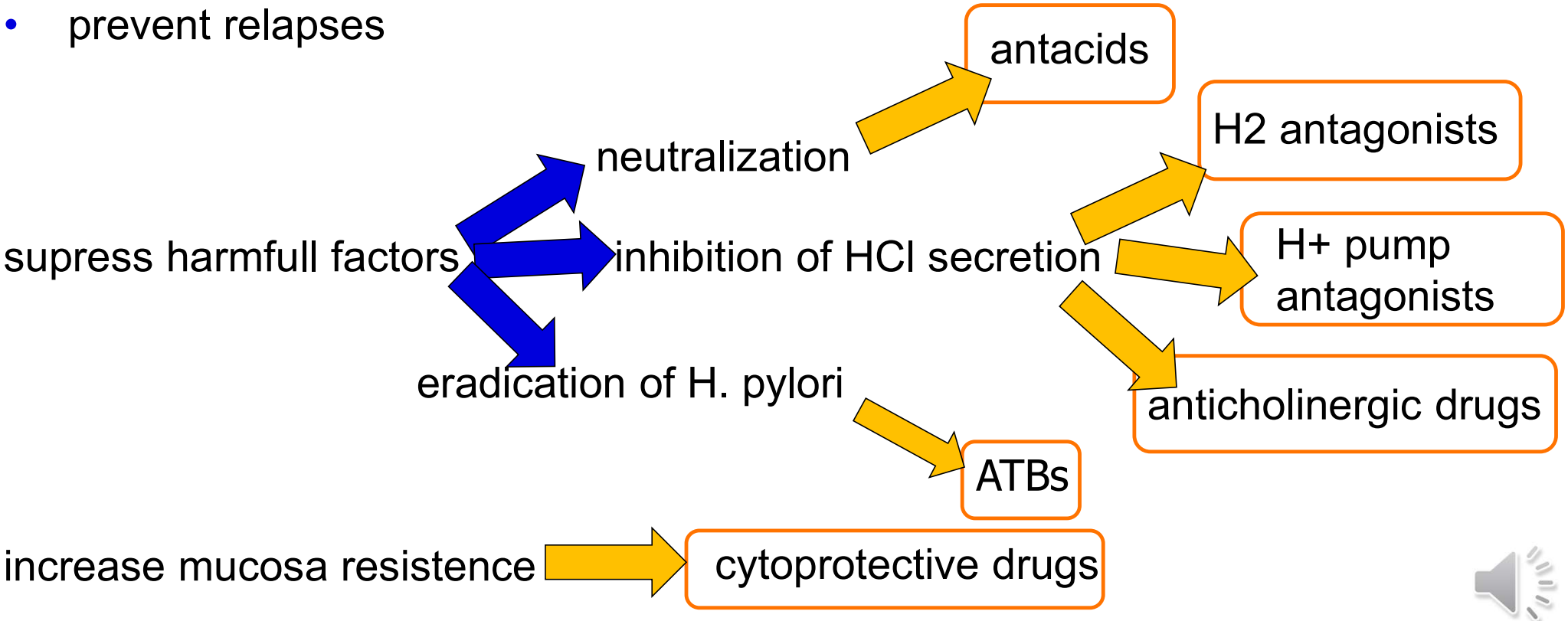
Peptic ulcers – result of dysbalance between protective and harmfull factors




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 Minor: CYP3A4	High
Esomeprazole	Major: CYP2C19 Minor: CYP3A4	Moderate
Pantoprazole	Major: CYP2C19 Minor: CYP3A4	Low
Lansoprazole	CYP2C19 CYP3A4	Moderate
Rabeprazole	Major: Non-enzymatic Minor: CYP2C19 Minor: CYP3A4	Low

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

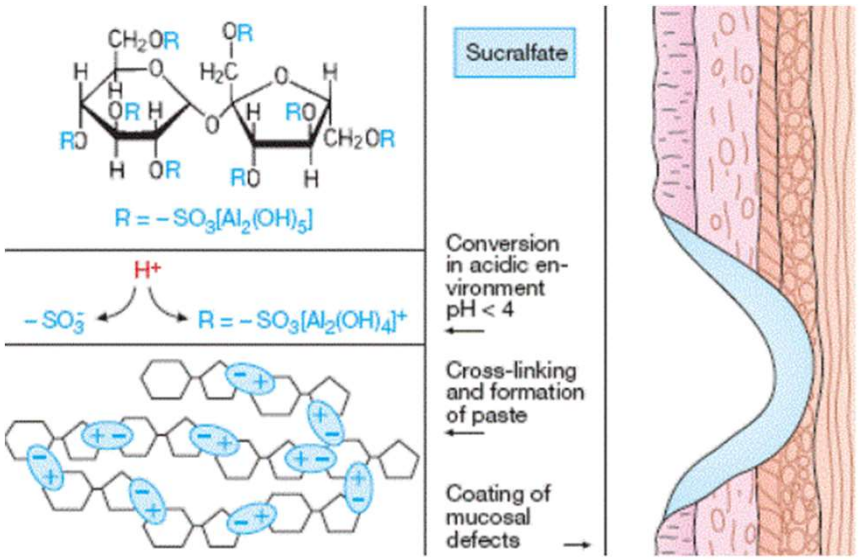
Cytoprotectives

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