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Antidiabetic drugs

Department of Pharmacology MF MU

Antidiabetic drugs

- Insulins
- Drugs used in T2DM

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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 %)

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Clinical picture

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

Randomly detected glycemia above 11.1 mmol / L
Fasting glycaemia above 7.0 mmol / L

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

T2DM - less noticeable symptoms, evolving from months to years

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

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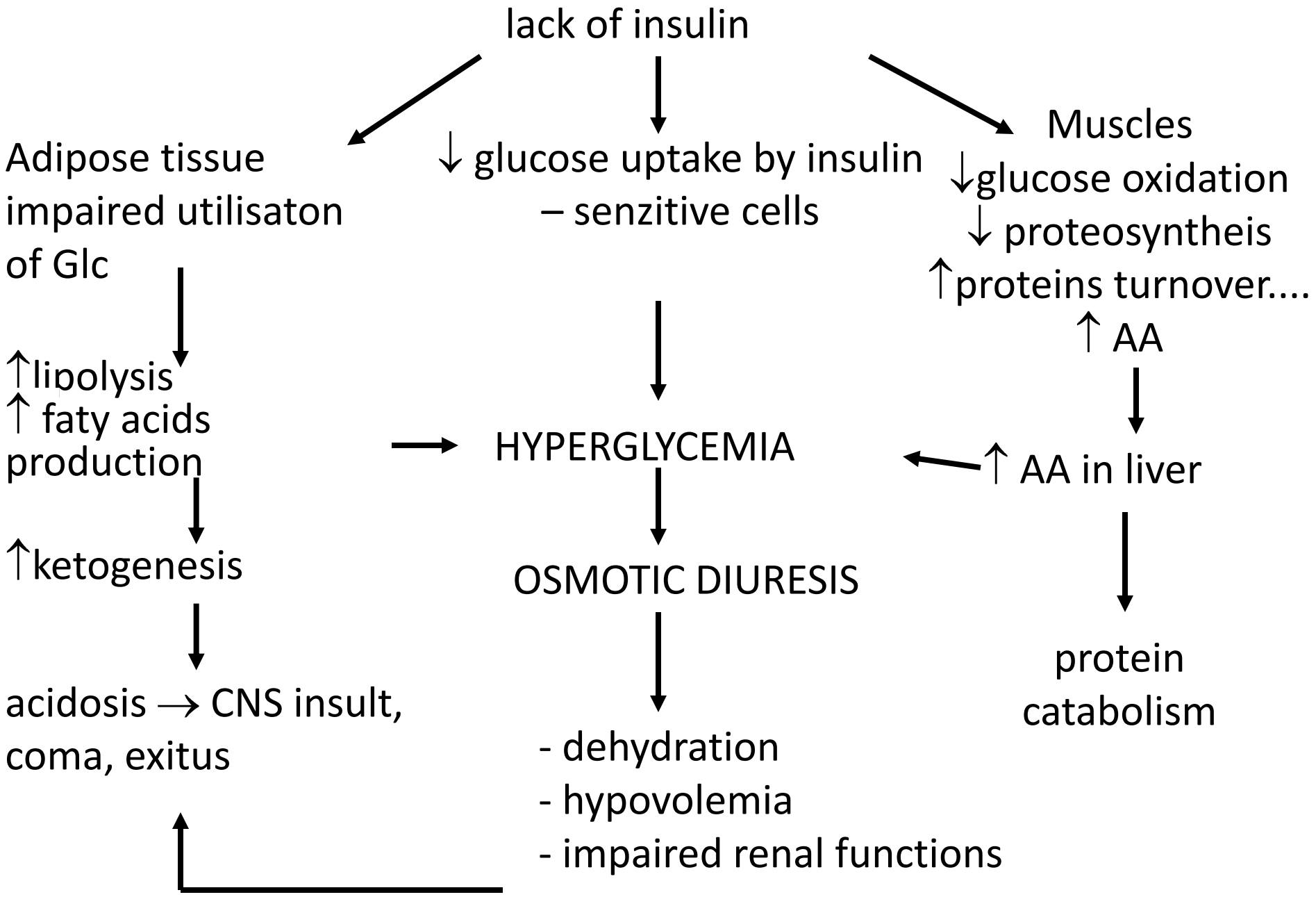

lack of insulin
Adipose tissue
impaired utilisaton
of Glc
↓ glucose uptake by insulin
– senzitive cells
Muscles
↓glucose oxidation
↓ proteosyntheis
↑proteins turnover....
↑ AA
↑lipolysis
↑ faty acids
production
HYPERGLYCEMIA
↑ AA in liver
↑ketogenesis
OSMOTIC DIURESIS
protein
catabolism
acidosis → CNS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

METABOLIC SYNDROME

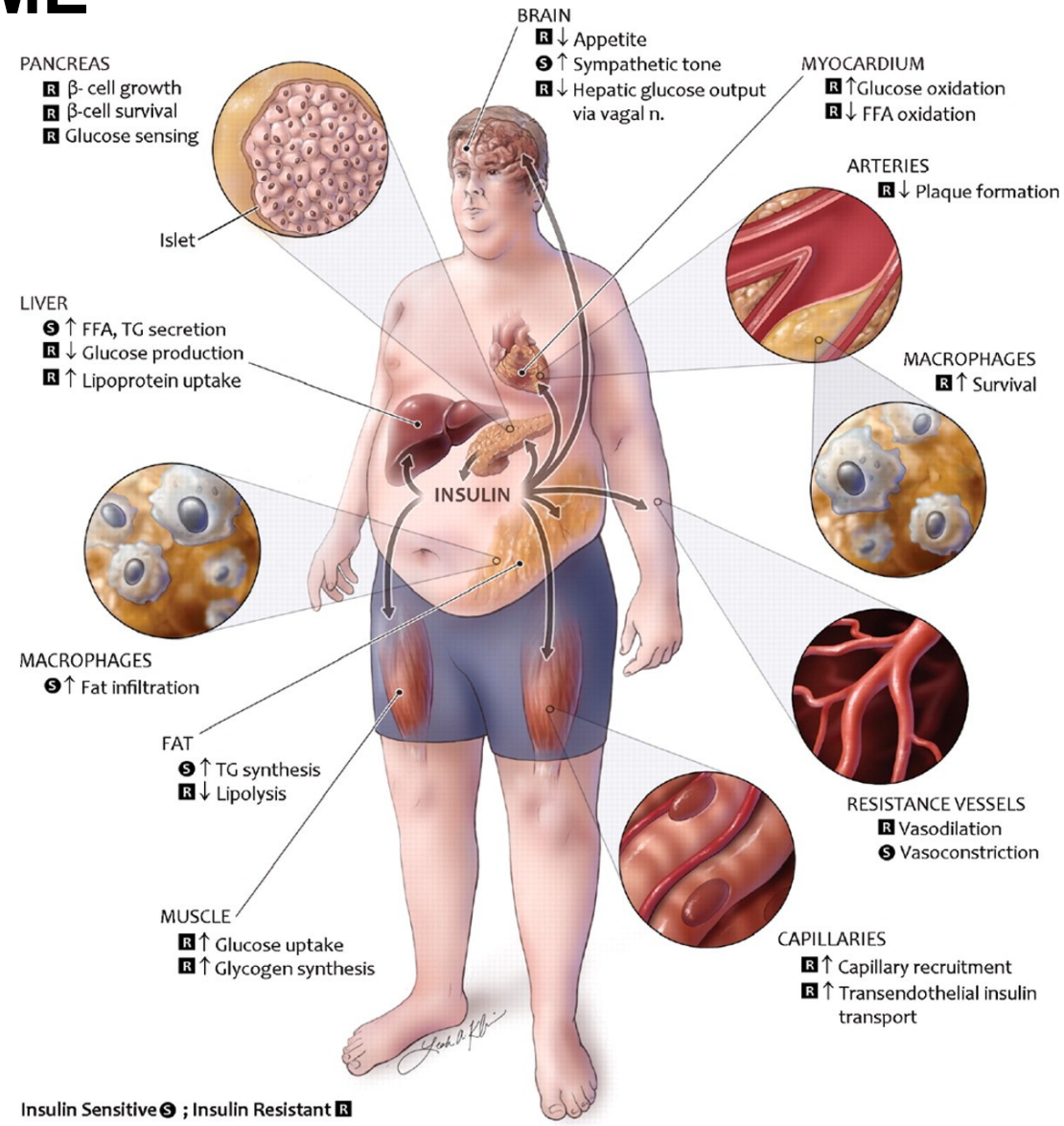
Insulin resistance

Hypertension (high blood pressure)

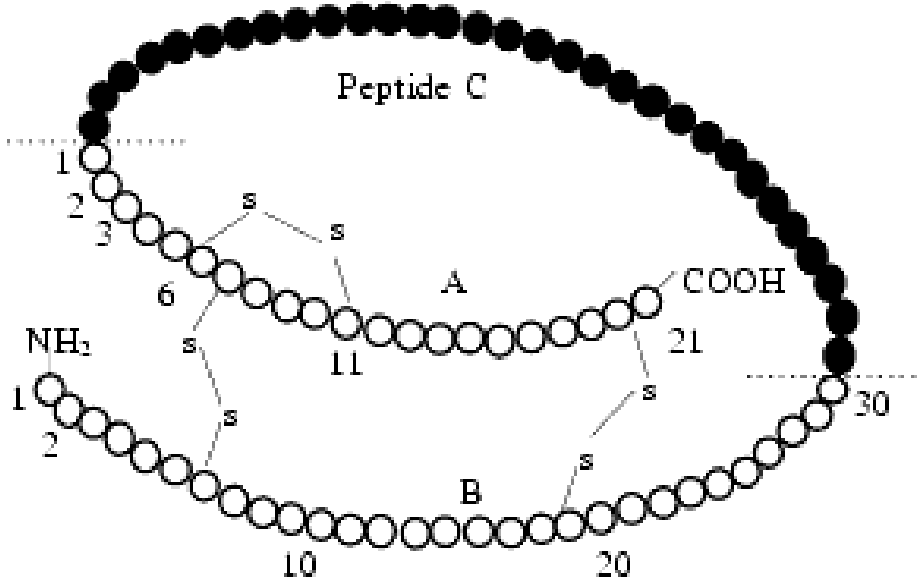
Hypertriglyceridaemia (elevated TAG)

Disorders of glucose tolerance or diabetes

Obesity type of apple (male type of obesity)



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



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

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

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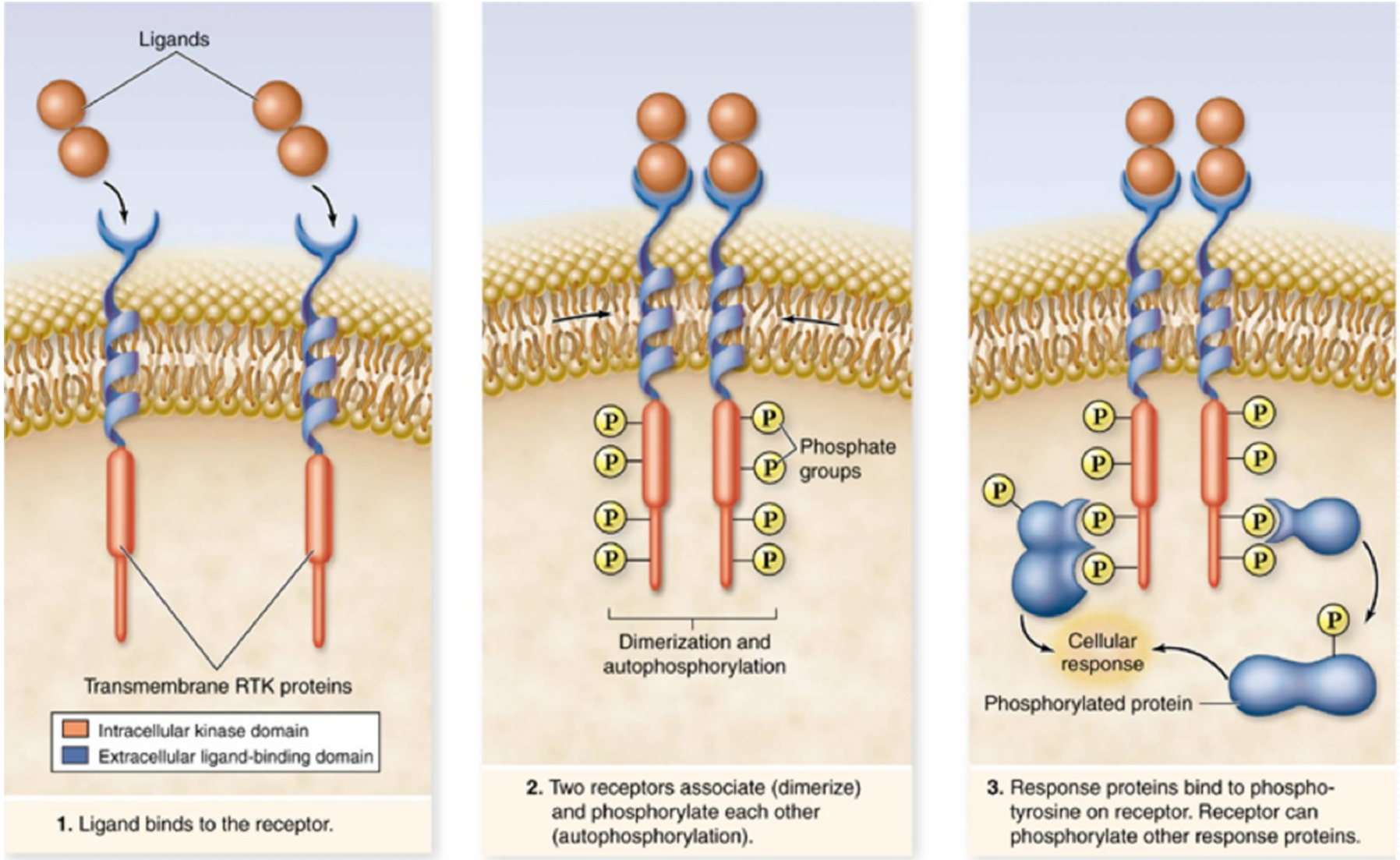
Factors decreasing insulin secretion

somatostatin

insulin (negative feedback)

α - activation of sympathetic n.s. (adrenalin)

Insulin receptor



Lincová a kol. 2002

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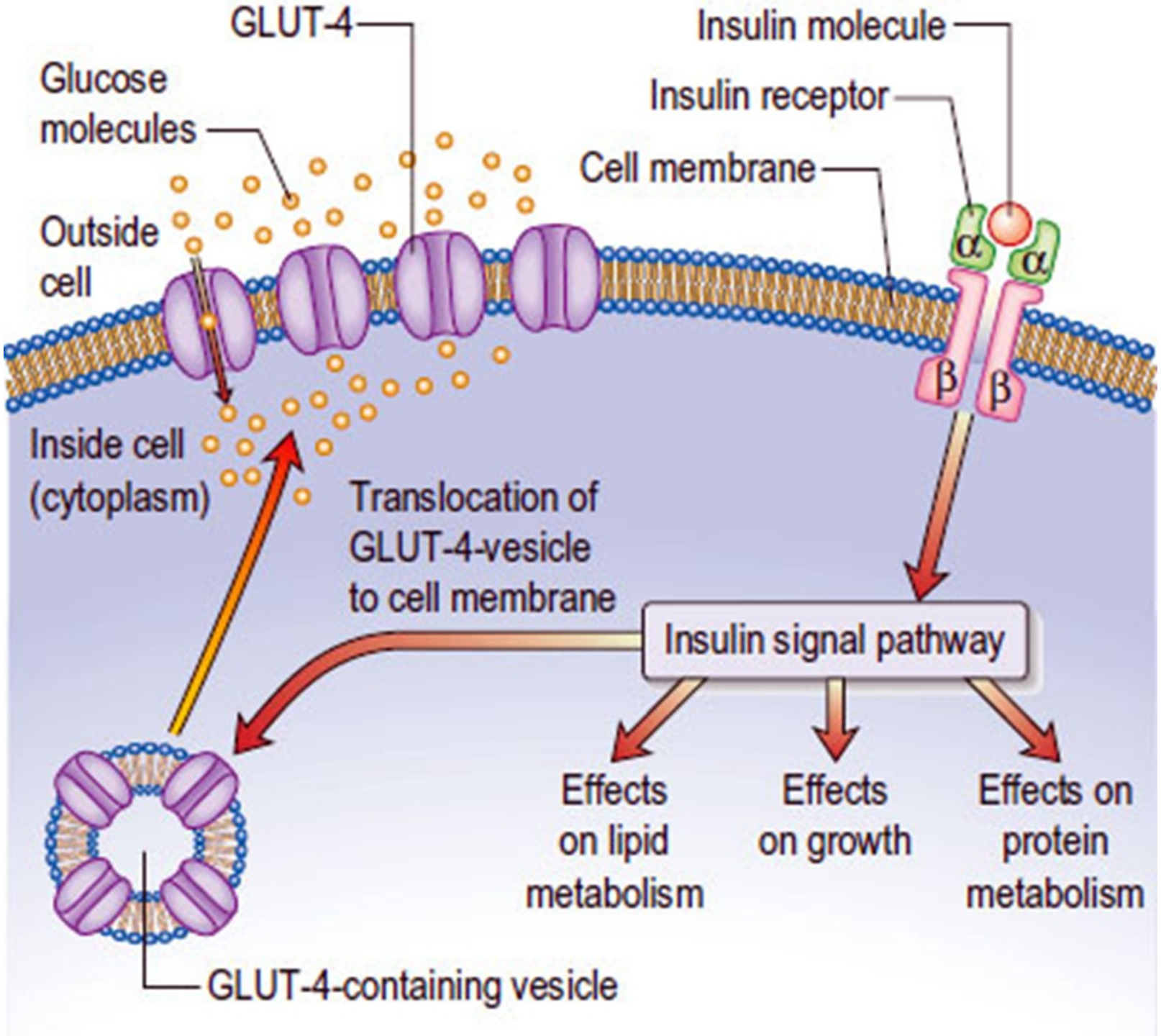
GLUT-4
Insulin molecule
Glucose molecules
Insulin receptor
Cell membrane
Outside cell
α
α
β
β
Inside cell (cytoplasm)
Translocation of GLUT-4-vesicle to cell membrane
Insulin signal pathway
Effects on lipid metabolism
Effects on growth
Effects on protein metabolism
GLUT-4-containing vesicle

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

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Terapeutical use of insulin

- DM I. Type
- ketosis, ketonuria or ketoacidosis
- patients with serious infetion/gangrene

- DM II where blood Glc. not normalized with POAD, diet
- DM II patients, use corticosteroids, liver or kidney impairment

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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

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Insulin preparations

Short acting

A) insulin analogues: insulin lispro, aspart, glulisine
Can be administered intravenously
Start of operation 0-15 min.
Maximum of efficacy 30-45 min after admin.
Effective for 2 - 5 hours.

B) neutral aqueous solutions of insulins
(Crystalline insulin, soluble insulin)
Can be administered intravenously
Start of action 30 min.
Maximum 1 - 3 hours.
Effective for 4 - 6 hours.

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Intermediate acting

NPH (Neutral Protamine Hagedorn)

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

Start of operation 1 - 2.5 hours

Maximum 4 - 8 hours.

Working time 12 - 24 hours.

Almost no longer used

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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

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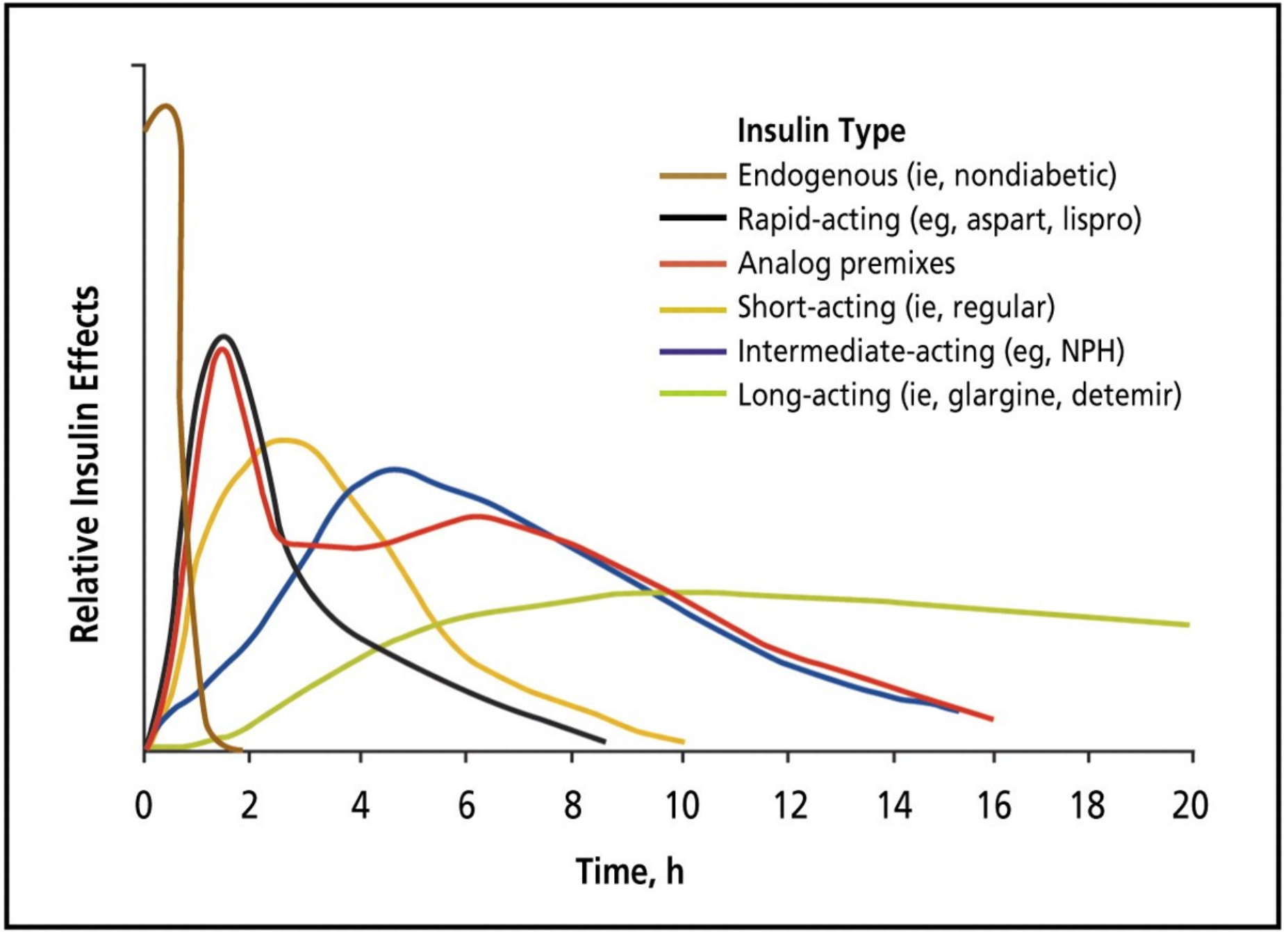
Insulin Type
Endogenous (ie, nondiabetic)
Rapid-acting (eg, aspart, lispro)
Analog premixes
Short-acting (ie, regular)
Intermediate-acting (eg, NPH)
Long-acting (ie, glargine, detemir)
Relative Insulin Effects
0
2
4
6
8
10
12
14
16
18
20
Time, h

Complications of insulin therapy

- hypoglycaemia

- allergy

- lipodystrophy

insulin resistance - spec. antibodies

weight gain

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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 ?

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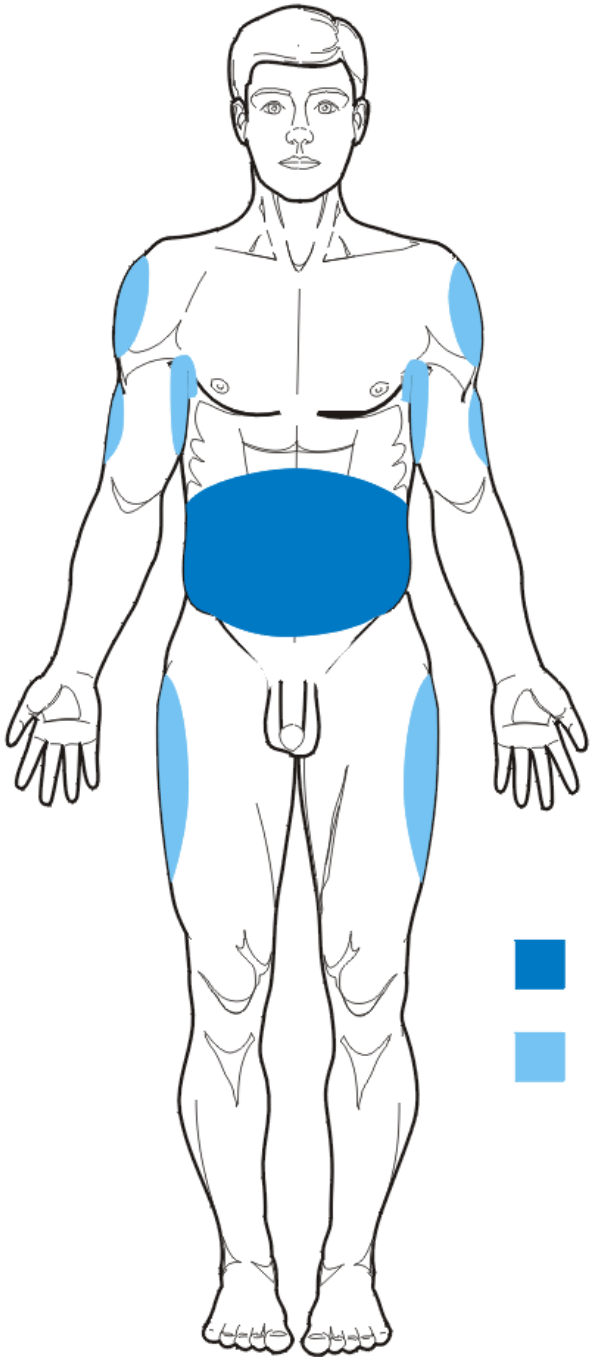
Insulin administration sites



preferred

acceptable

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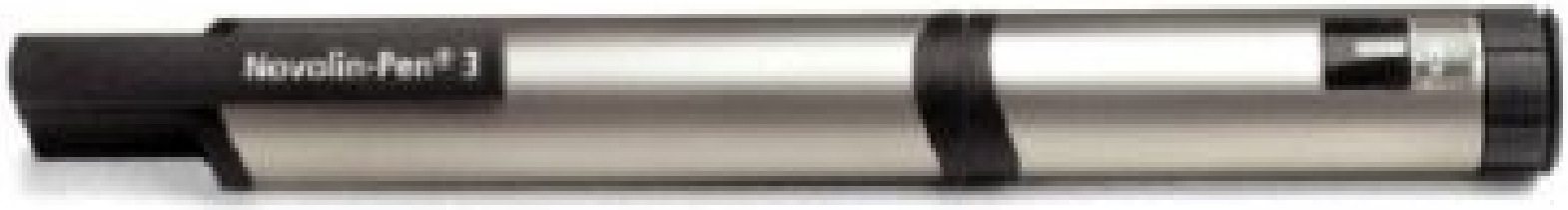

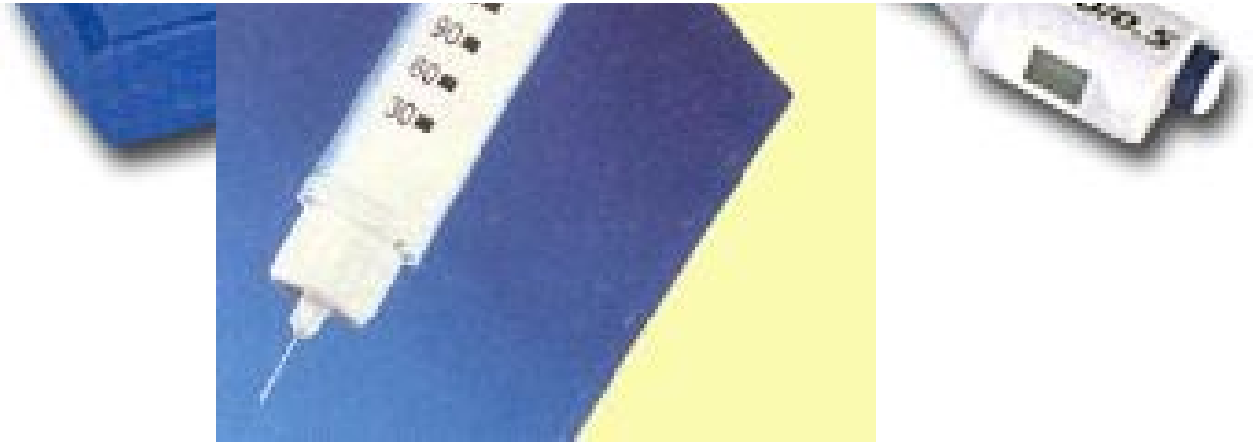

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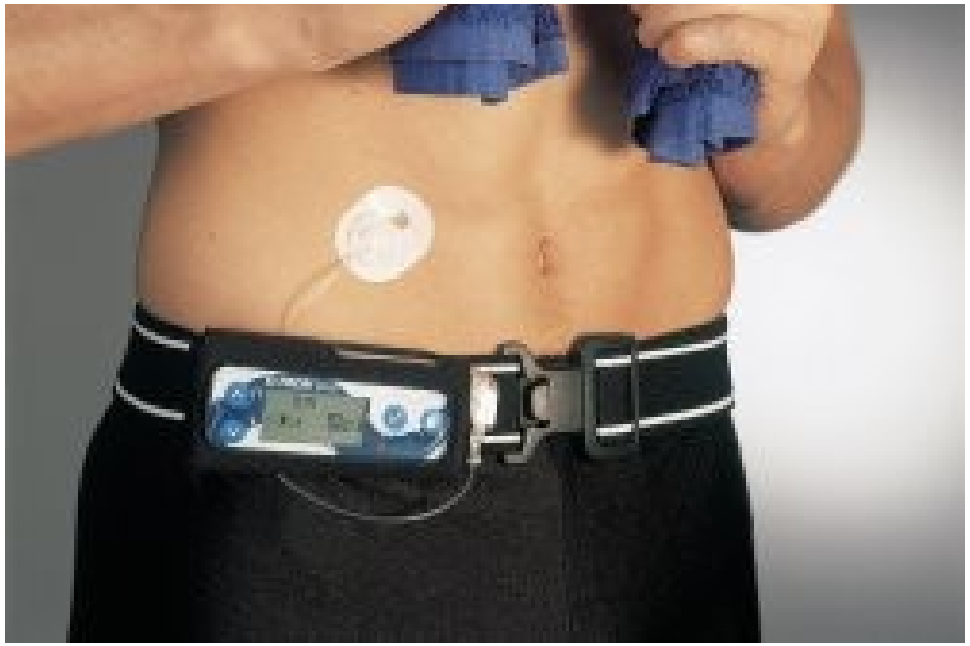

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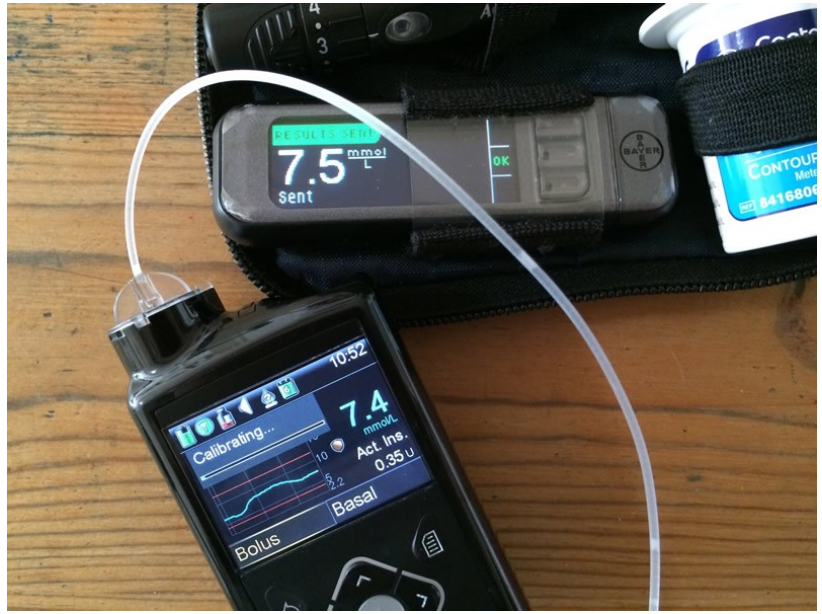
7.5
mmol
L
sent
OK
CONTOUR
10:52
Calibrating...
7.4
mmol/L
Act. ins.
0.35 u
Basal
Bolus

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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

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Antidiabetics

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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

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(Oral) antidiabetics

The effect is linked to the ability of insulin secretion

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

- indication:

- T2DM - if not properly compensated with diet

- T1DM with a high insulin resistance, when insulin does not lead to a sufficient decrease in blood glucose

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Antidiabetics

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

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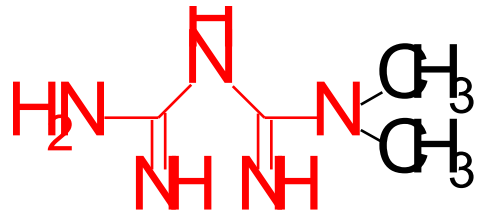
Biguanides



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“

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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

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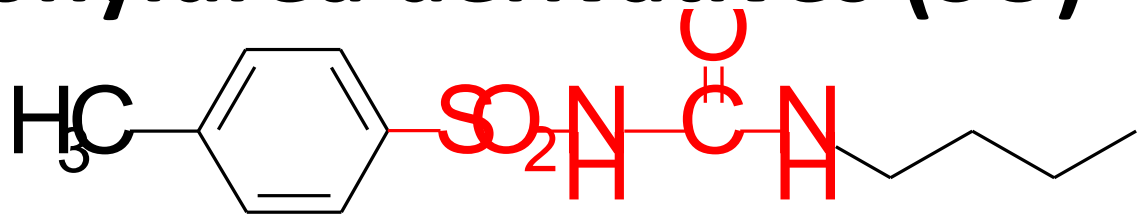
sulfonylurea derivatives (SU)



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

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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

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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

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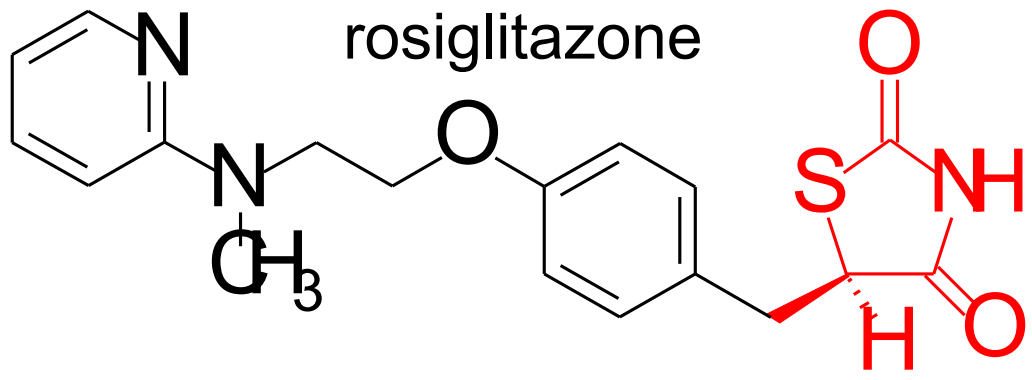
Thiazolidinediones

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

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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

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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

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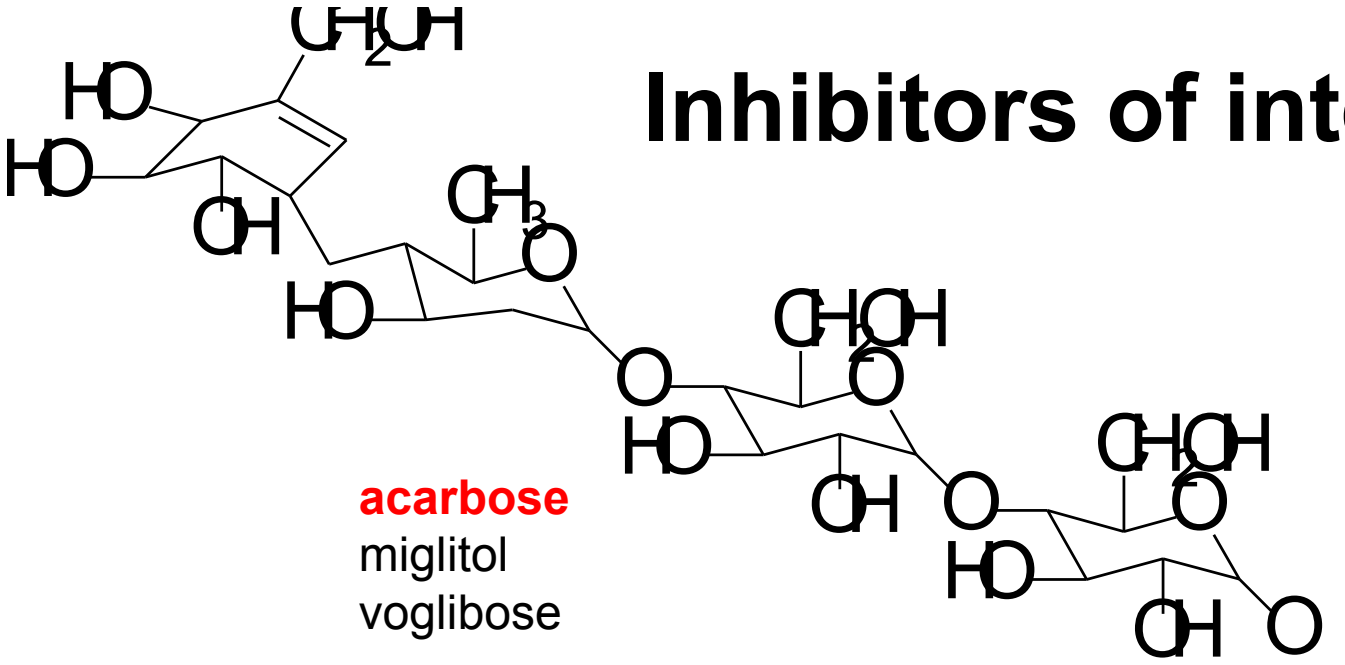
Inhibitors of intestinal glucosidase



acarbose
miglitol
voglibose

acarbose

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)

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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

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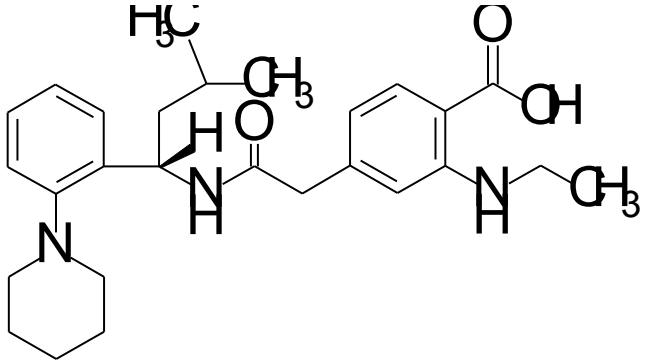
Meglitinides

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

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Clinical use

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

Contraindications:

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

AE:

Hypoglycemia, nausea, diarrhea, joint pain

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DM - Complications

1) hypoglycemia

consciousness - sweet (sacharide) drink, meal

unconsciousness - i.v. Glu 20-40%

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

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DM - Complications

2) allergy (hypersensitivity IgE) - corticosteroids, adrenalin i.v.

3) insulin resistance - IgG against insulin (animal insulins), change insulin preparation, POAD

4) lipodystrophy - change application sites (scheme), esthetic surgery

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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..

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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

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DM - Complications

relapse of infections, mycosis

hypertension

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