Diabetes mellitus and antidiabetic drugs

Balázs Varga Pharm.D., PhD

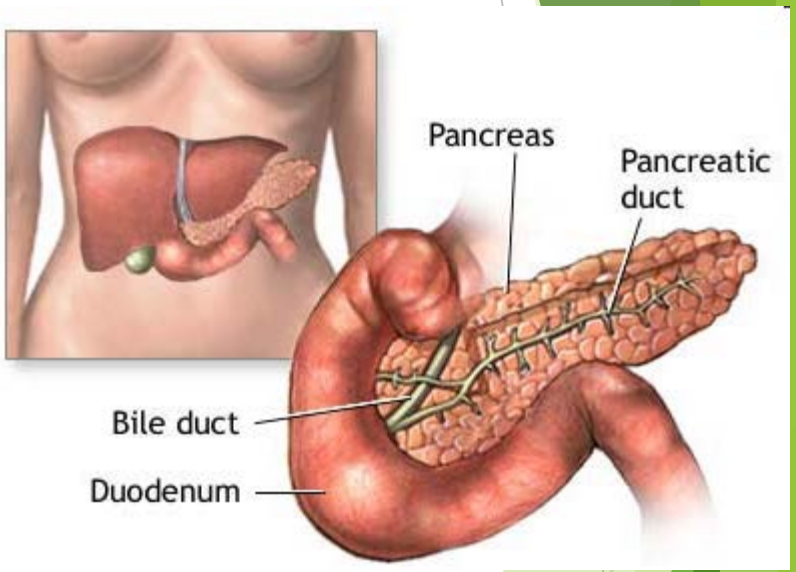
Department of Pharmacology and Pharmacotherapy University of Debrecen

Pancreas and insulin

Pancreas is both an endocrine and an exocrine gland.

- Endocrine hormones (=secreted into the blood): insulin, glucagon and somatostatin

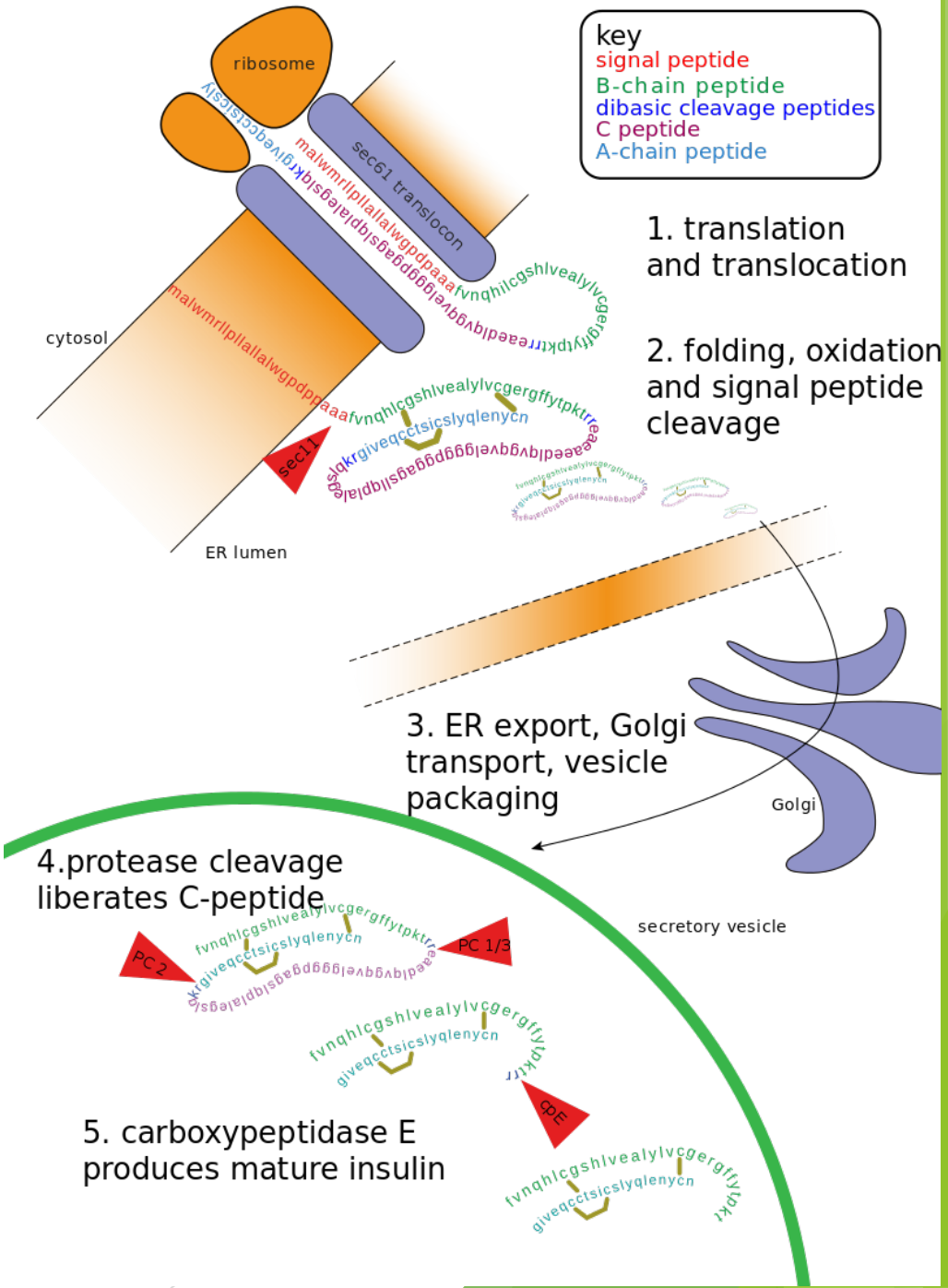
- As exocrine gland (=secreted into gut) it secretes pancreatic juice containing digestive enzymes as lipase, amylase, and proenzymes as trypsinogen and chimotrypsinogen.



Beta cells of Langerhans-islets of Pancreas produce insulin.

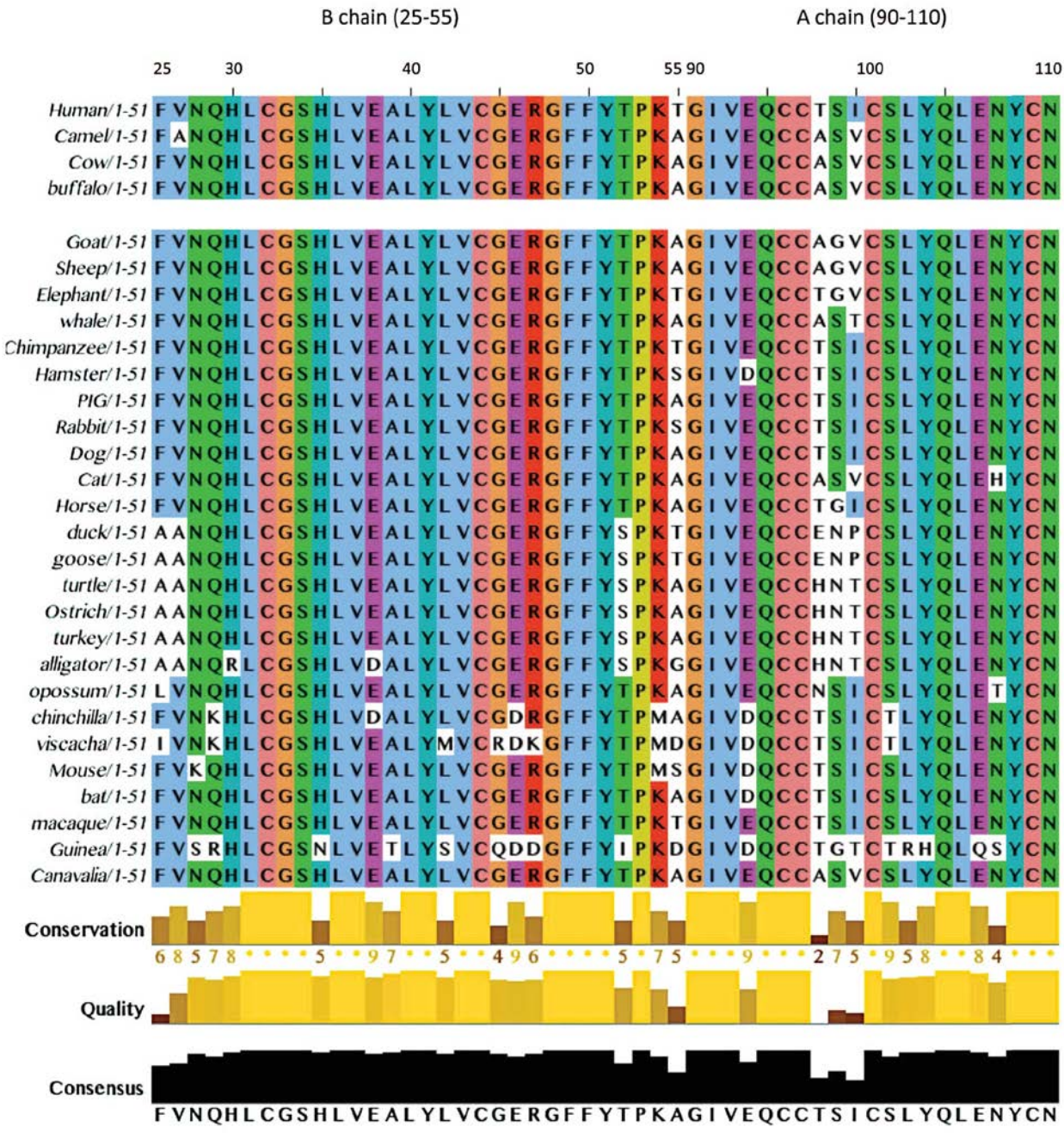
The insulin molecule

- The human insulin protein is composed of 51 amino acids, and has a molecular mass of 5808 Da.
- It is a dimer of an A-chain and a B-chain, which are linked together by disulfide bonds.
- It is synthesized as a single polypeptide called preproinsulin in ER of pancreatic ß-cells.

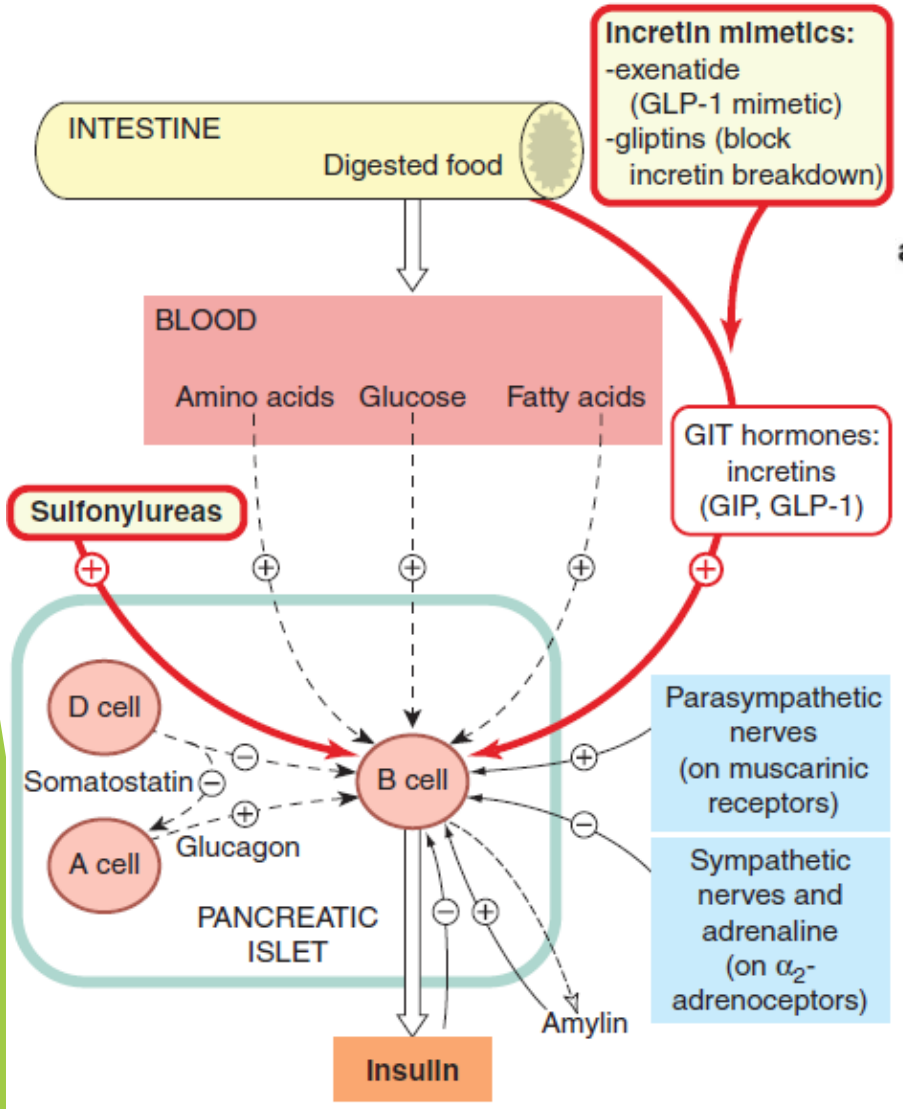


Inter-species variations

- Insulin's structure varies slightly between species of animals.
- Pig, rabbit, dog only differs in 1 amino acid from human.
- Sequence of chimpanzee and macaque is identical to human.



Mechanism of insulin secretion



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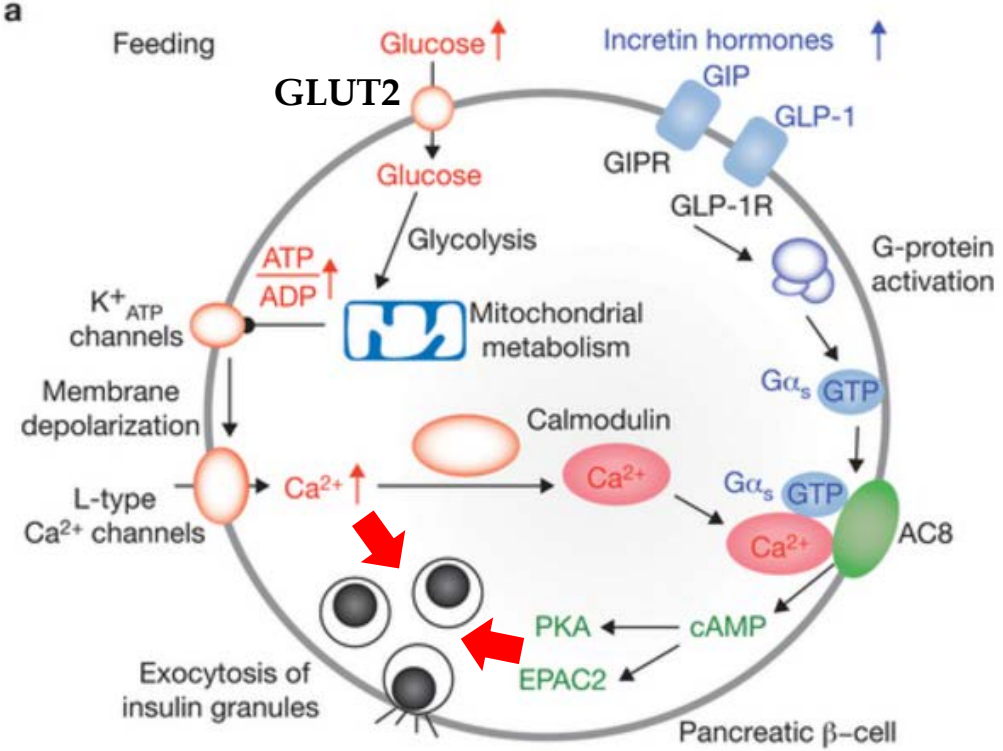
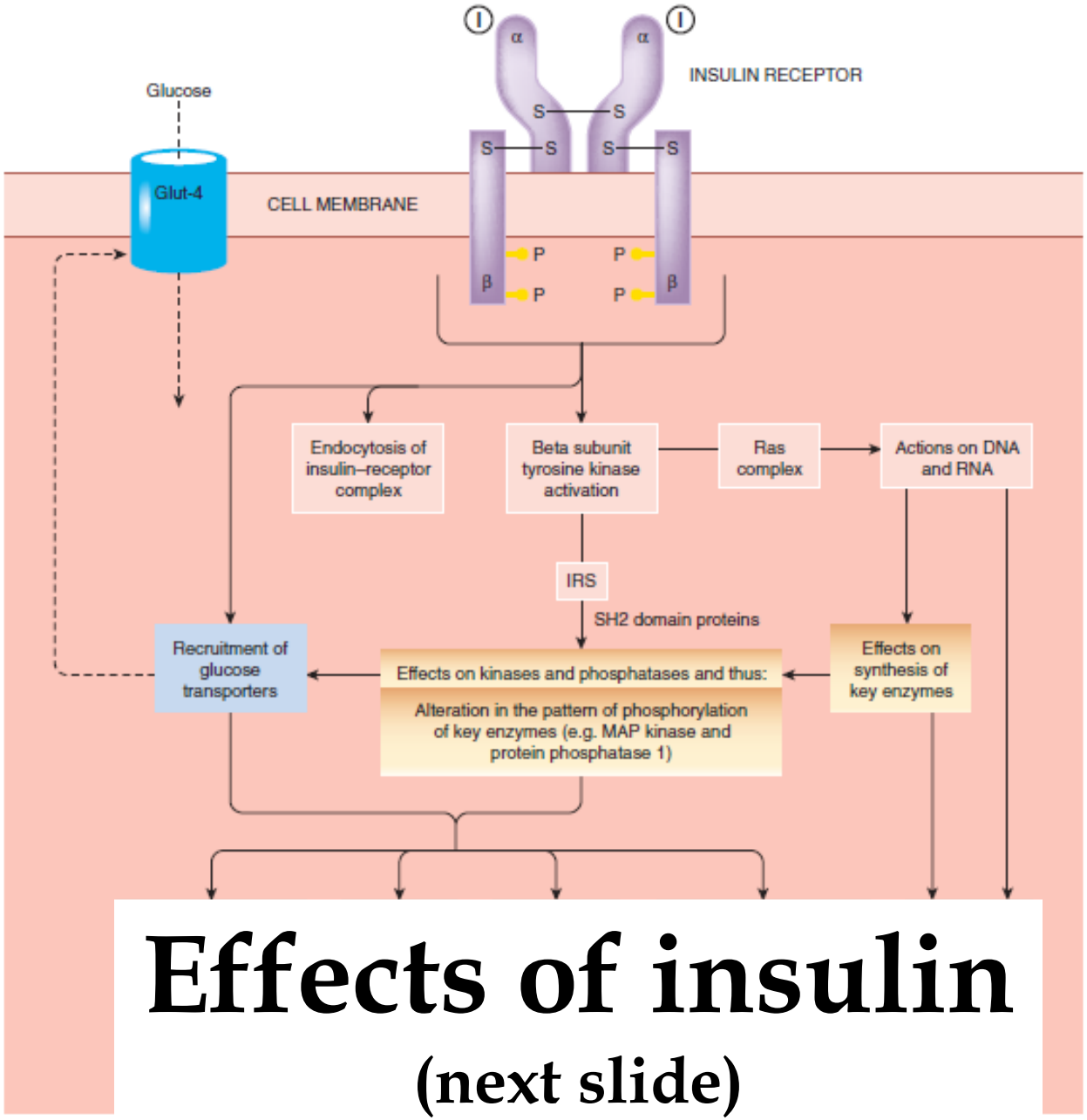


Others can also increase Ca-level e.g.: through Gq pathway acetylcholine and CCK

Nor/adrenaline through α2-rec (Gi) inhibits insulin secretion

Mechanism of action of insulin



Effects of insulin

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The effects of insulin

- Increases glucose uptake

LIVER	MUSCLES	ADIPOSE TISSUE
• glycogen synthesis ↑ • fattyacid synthesis ↑ (from glucose)	• glycogen synthesis ↑ • protein synthesis ↑ • for this aminoacid-uptake ↑	• triglyceride synthesis ↑ • for this glycerin ↑ synthesis from glucose

• Stimulates uptake

• Stimulates anabolic (storaging) processes

- It inhibits the opposites of these

LIVER	MUSCLES	ADIPOSE TISSUE
• glycogenolysis ↓ • glyconeogenesis ↓ • glucose release ↓	• proteolysis ↓ • aminoacid release ↓	• lipolysis ↓ • (thus ketonebody synthesis) ↓ • fattyacid release ↓

• Inhibition of cathabolic (energy-producing) processes

• Inhibition of release

Bloodplasm's Glucose / Aminoacid / Fattyacid levels ↓

- K^+-uptake of muscles ↑ → too much insulin → hypokalaemia

Diabetes mellitus

High blood sugar levels over a prolonged period.

Symptoms include frequent urination, increased thirst, and increased hunger.

There are two types of Diabetes:

- Type 1 or formerly
  Insulin dependent diabetes mellitus (IDDM)

- Type 2 or formerly
  Non-insulin dependent diabetes mellitus (NIDDM)

Type 1 DM

Development:

Usually type 1 diabetes is immune-mediated, where beta cell loss is a T-cell mediated autoimmune attack. (=absolute insuline deficiency)

Characteristics:

- Most likely it appears in childhood or young adulthood.
- Patients are usually thin.
- Insulin is needed for treatment.
- In untreated or badly treated, severe cases ketoacidotic coma may develop which is a life-threatening condition characterised by hyperglycemia and ketosis
- Type 1 diabetes causes approximately 10% of all diabetes mellitus cases.

Type 2 DM

Development:

Ususally develops due to excessive sugar intake for ages.
Due to huge insulin waves after meals insulin resistance develops in the cells sensitive to insulin.
(insulin is secreted but the insulin sensitivity is decreased)
(= relative insuline deficiency)

Characteristics:

- It developes mostly in adulthood but lately it also may occur in childhood as well.
- Patients are usually overweight.
- Treatment:
  - at the beginning lifestlye change (low-CH diet, appropriate nourishment, sports, losing weight)
  - later oral antidiabetic drugs are needed.
  - In the late phase of the disease when insulin secretion depletes, administration of insulin is inevitable – just like in Type 1 Diabetes mellitus.
- 90% of the diabetes patients suffer from Type 2 diabetes.

Complications of DM

- **Macroangiopathy**

  Injury of arteries = accelelrated atherosclerosis; may appear in juvenile

- **Microangiopathy**

  Damage to small arteries and capillaries

  - **Diabetic nephropathy**

    small vessels of kidneys are affected

  - **Diabetic retinopathy**

    Mild form: haemorrhages on the fundus of the eye

    More severe form: macular edema and neoangiogenesis into the vitreous, haemorrhages in front of retina, retinal detachment, blindness

  - **Diabetic neuropathy**

    Most common form: sensory neuropathy ➔ abnormal and decreased sensation, usually in a 'glove and stocking' distribution (pain and numbness)

  - **Diabetic foot syndrome**

    Neuropathy & macroangiopathy complex complications: muscle dystrophy, skin ulcers, infections, necrosis ➔ amputation of fingers

Treatment of Diabetes mellitus

- **Type I Diabetes**
  - insulins
- **Type II Diabetes**
  - agents which increase the sensitivity of target organs to insulin (sensitizers)
    - Biguanides
    - Thiazolidindiones
    - Dual-PPAR agonists
  - agents which increase the amount of insulin secreted by the pancreas (secretogoues)
    - Sulfonylureas
    - Meglitinide-derivatives
    - GLP-1 analogues
    - DPP-4 inhibitors
  - agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract
    - α-glucosidase inhibitors
  - Amylin-analog
  - SGLT2 inhibitors
  - Aldose reductase inhibitor
  - insulins

Insulin and analogs

Insulins

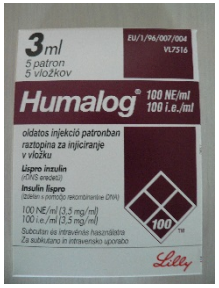
- Insulin is usually given subcutaneously, either by injections or by an insulin pump.

characterized by the rate which they are absorbed/metabolized by the body:

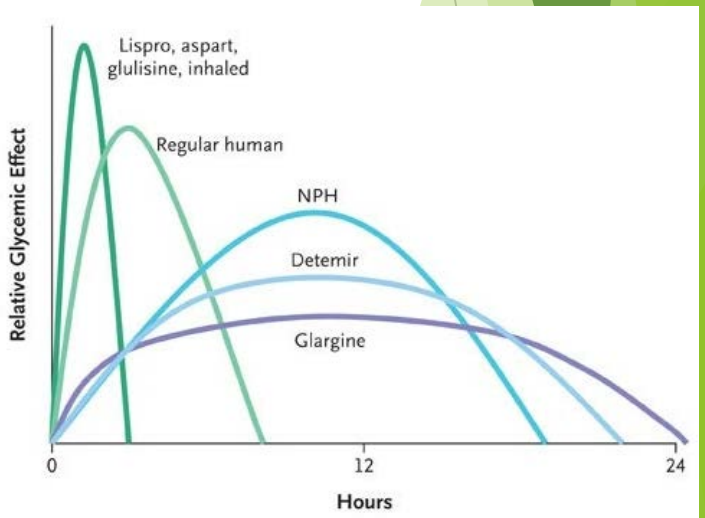
- rapid acting insulins include (from 5-15 mins to 3-4 hours)

  Most insulins form hexamers which delay entry into the blood in active form, these do not.

  - Insulin lispro (Humalog)
  - Insulin aspart (Novorapid)
  - Insulin glulisine (Apidra)
  - Prompt insulin zinc (Semilente, Slightly slower acting) (amorphous state)

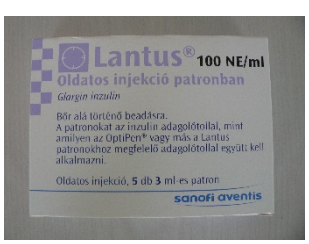


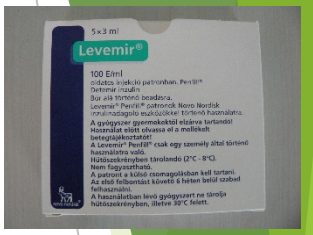
- short acting (from 30 mins to 5-8 hours)
  - Regular insulin (Humulin R, Novolin R, Actrapid)

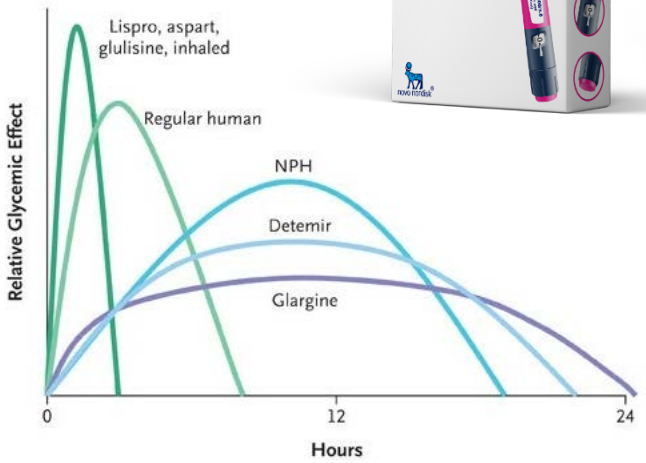


Insulins

- intermediate acting insulins include (from 1-3 hours to 16-24 hours)
  - Isophane insulin = neutral protamine Hagedorn (NPH) (Humulin N, Insulatard)
  - Insulin zinc (Lente) (30% semilente(amorphous) 70% ultra-lente (crystal form))
- long acting insulins (from 1-2 hours to 24 hours)
  - Extended insulin zinc (Ultralente) (crystal form)
  - Insulin glargine (Lantus)
  - Insulin detemir (Levemir)
- Ultra-long acting (from 30-90 mins to more than 24 hours)
  - Insulin degludec (Xultophy)
- Combinations (intermediate/long acting + rapid/short)
  - E.g.: Novolog Mix 70/30 (=70% NPH 30% aspart)
  - Humulin M3 (30/70) (=70% NPH 30% aspart)

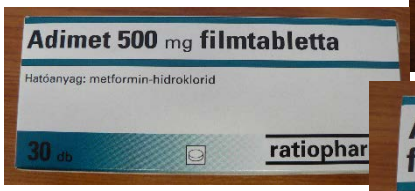






Oral antidiabetic drugs

Insulin sensitizer antidiabetics – Biguanides („-formin”s)



- first line therapy of Type 2 DM
- Metformin (, buformin and phenformin were withdrawn due to impairing lactic acid metabolism ➔ lactic acidosis)
- Mechanism of action:
  - **increases insulin sensitivity** (= ↓insulin resistance) ➔
    - By strenghtening signaltransduction of insulin (e.g. AMPK)
    - By improving insulin binding to insulin receptors
  - **activating AMPK** (AMP activated protein kinase) ➔
    - GLUT4 deployment to the plasma membrane (muscle/adipose tissue) ➔ insulin-independent glucose uptake.
    - **reduce hepatic glucose production** (↓ gluconeogenesis) and glycogen break-down (↓ glycogenolysis)
  - Increases GLUT transport capacity (e.g. through phosphorylation)➔ increases peripheral glucose uptake (liver, muscle)
  - stimulating glycolysis and glycogenesis on the periphery
  - slow glucose absorption from GIT
  - reduction of plasma glucagon levels
  - ↓food intake (appetite lowering effect)
  - ↑HDL ↓LDL

Insulin sensitizer antidiabetics – Thiazolidinediones („-glitazone”s)

- mechanism of action:
  - **increase insulin sensitivity** (= ↓insulin resistance)
    - **Selective agonists of PPAR-γ** (peroxisome proliferator-activated receptor gamma)**, a nuclear regulatory protein** (fat, muscle, liver – endothel, ovarium, imm.cells)
      - PPARs regulate transcription of genes of PPRE (peroxisome proliferator response elements) (=insulin sensitive genes)
        - Stimulate synthesis and deployment of GLUT into cellmembrane
        - **reduce hepatic glucose production** (↓ gluconeogenesis)
  - effects mainly on adipocytes
    - ↑ glucose uptake and utilization
    - ↓ synthesis of resistin
    - ↓ synthesis of cytokines

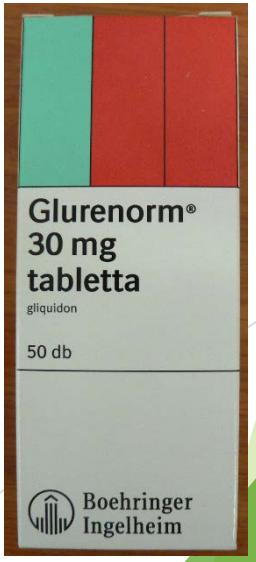
- slow onset – nuclear receptor
- Pioglitazone (Actos) (, rosiglitazone (Avandia), troglitazone (Rezulin) withdrawn from market due to increased risk of heart attack (former) and hepatotoxicity (latter))
- Pharmakokinetics
  - metabolized by CYP2C8, CYP3A4
- triglyceride lowering effect (anti-obesity drug)
- monotherapy in type 2 DM
- coapplication.: biguanides, sulfanylureas

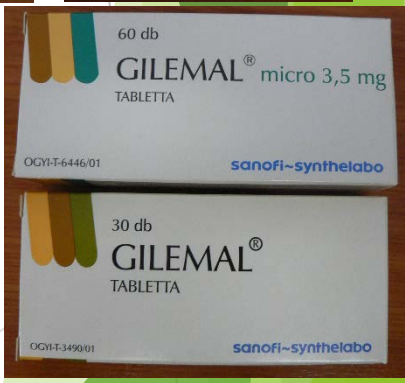
Insulin sensitizer antidiabetics – Dual-PPAR agonists („-glitazar”s)

- A class of "dual", "balanced" or "pan" PPAR ligands, which bind two or more PPAR isoforms
  - Agonist action at PPARα lowers high blood triglycerides, and
  - agonist action on PPARγ improves insulin resistance and consequently lowers blood sugar
- are currently under active investigation for treatment of a larger subset of the symptoms of the metabolic syndrome.
- Saroglitazar (Lipaglyn®) on the market of India
  - aleglitazar failed in Phase III, muraglitazar and tesaglitazar failed before Phase III

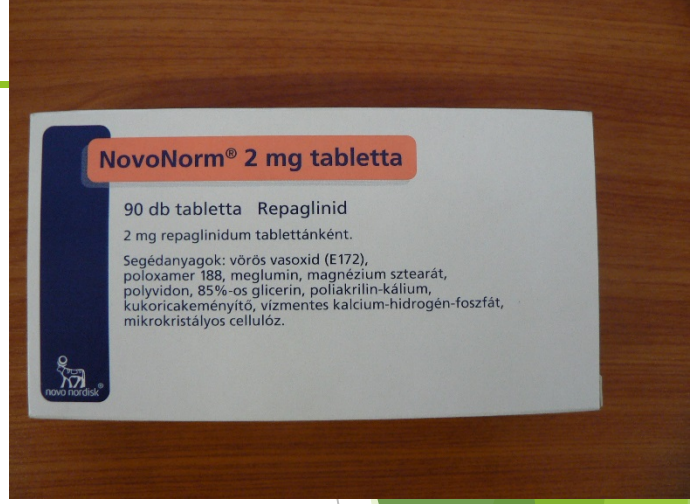
Secretagogue antidiabetics - Sulfonylureas

- mechanism of action
  - ↑ insulin release from pancreatic ß-cells
  - inhibits ATP sensitive K+ channels (as ATP from glucose would) ➔ ß-cell depolarization
  - long term action reduces serum glucagon levels
- first generation sulfonylureas(historical significance)
  - tolbutamide, chlorpropamide, tolazamide
  - Many withdrawn from market due to
    - Increased cardiovascular risk
    - Prolonged hypoglycemia
- second generation sulfonylureas („gli-" agents)
  - glibenclamid (Gilemal), glimepirid (Amaryl, Gliprex), glipizide, gliclazide (Diaprel), gliquidone (Glurenorm) etc.
  - safer, than 1st generation sulfonylureas
    - lower CV risk and hypoglycaemic effect
    - More potent and more effective agents
  - Have extrapancreatic effects as well
    - Reduce microthrombosis
    - Antioxidant effect (decrease plasmal levels of lipidperoxides)
    - Upregulation of GLUT4 in muscle and adipose cells





Secretagogue antidiabetics – Meglitinides („-glinide”s)



- mechanism of action
  - ↑insulin release from pancreatic ß cells
  - inhibits ATP sensitive K+ channels – ß cell depolarization
  - Act on different binding site than sulfonylureas
- Repaglinide, nateglinide, mitiglinide
- Pharmacokinetics
  - rapid onset of action („short acting secretagogues”)
  - metabolized in liver (CYP3A4)
  - dose: before each meal 0,25-4mg
- coapplications: biguanides
- application: if allergy to sulfonylureas

Incretins

- are physiological insulin secretagogues.
  - The amount of insulin secreted is greater when glucose is administered orally than intravenously
- are released from gut after eating.
- glucagon-like peptide-1 (GLP-1 and GLP-2)
- glucose-dependent insulinotropic peptide (formerly gastric inhibitory peptide) (GIP).
  - Inhibitory: decreases the secretion of stomach acid, inhibits the GI motility BUT only in higher-than-physiological concentrations ➔ name-change
- Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).
- Effects:
  - increase insulin secretion
  - increase insulin-sensitivity
  - increase ß-cells mass
  - inhibit acid secretion and gastric emptying in the stomach.
  - decrease glucagon hormone secretion

Secretagogue antidiabetics – GLP-1 analogues („-tide”s)

- Exenatide (Byetta®), Liraglutide (Victoza®), Dulaglutide (Trulicity®), Lixisenatide (Lyxumia®), Semaglutide (Ozempic®)
  (Albiglutide withdrawn from market due to economic reasons), (Taspoglutide failed in Phase III)
- mechanism of action
  - synthetic analogs of GLP-1 = incretin mimetics
  - multiple actions
    - enhance glucose-mediated insulin secretion
    - supression of postprandial glucagon release
    - slow gastric emptying/motility
    - Central: loss of appetite

- application: sc. Injection; oral form of semaglutide in 2019!
- injected 60 min before meal
- Adverse effects: nausea, vomiting, weight loss
- coapplication: biguanides, sulfonylureas (hypoglycaemia!!!)

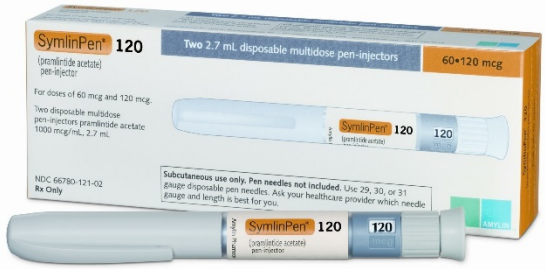
Secretagogue antidiabetics – DPP-4 inhibitors („-gliptin”s)

- Alogliptin, Anagliptin, Evogliptin, Gemigliptin, Linagliptin (Trajenta®), Omarigliptin, **Saxagliptin (Onglyza®)**, **Sitagliptin (Januvia®)**, Teneligliptin, **Vildagliptin (Galvus®)**
- mechanism of action
  - inhibitor of DPP-4 (dypeptidil-peptydase-4) ➔ inhibiting degradation of incretines (GLP-1, GIP↑)
    - increase glucose mediated insulin secretion
    - decrease glucagon levels
- application: orally (OA=85%)
- 100mg/day
- a.e.: headache
- coapplication: biguanides, thiazolidendiones

α-glucosidase inhibitors

- Acarbose (Glucobay), miglitol
- mechanism of action
  - competitive inhibition of intestinal α-glucosidase enzymes (sucrase, maltase, dextranase, glucoamylase)
  - Break-down of Disacharids, oligosacharids is inhibited
  - only monosacharids can be absorbed from the intestinal lumen
  - ↓ monosacharid absorption ➔ ↓ postprandial hyperglycaemia
  - Delay and mitigate postprandial blood sugar levels
  - Balance daytime blood glucose fluctuation
  - Mean blood glucose level decreases
  - They do not inhibit absorption of oral glucose!
- Adverse effects: flatulence, diarrhea, abdominal pain (undigested carbohydr.)

Amylin analogue(s)



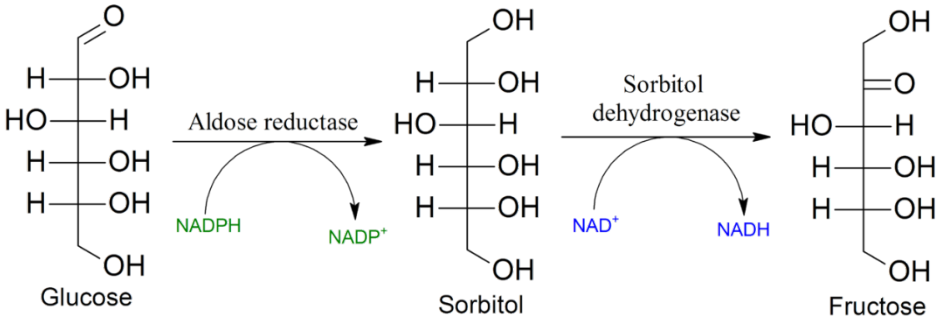
- Pramlintide (Symlin)
- mechanism of action:
  - synthetic analog of amylin (= IAPP-Islets Amyloid Polypeptide)
    - Amylin has all incretin actions except stimulation of insulin secretion
  - suppress glucagon hormone release
  - delay gasric emptying
  - anorectic effects in CNS = promotes satiety
- metabolized by kidneys
- application: sc. (immediat. before eating)
- Type 1 and Type 2 DM
- Adverse effects:
  - hypoglycaemia
  - nausea

Sodium glucose transporter (SGLT2) inhibitors („-gliflozin”s)

- Canagliflozin, Dapagliflozin (Forxiga), Empagliflozin, Ipragliflozin, Tofogliflozin (Remogliflozin, Sergliflozin failed before Phase III)
- mechanism of action:
  - inhibits SGLT2 ➔ decreased glucose reapsorption (excreted with urine)
  - SGLTs are symporters of Na+ and glucose
    - SGLT1 in small intestines,
    - SGLT2 proximal tubule ➔ responsible for 90% of glucose reabsorption
- insulin-independent action
- application: orally
- Adverse effects:
  - due to heavy glycosuria ➔ rapid weightloss, dehydration
  - urinary tract infections and candidiasis
- coapplication: biguanides, sulfonylureas, insulin

Aldose reductase pathway

- aldose reductase catalyzes formation of sorbitol from glucose (= polyol pathway)



- The polyol pathway appears to be implicated in diabetic complications, especially in microvascular damage to the retina, kidney, and nerves.
- Aldose reductase activity increases as the glucose concentration rises in diabetes in those tissues that are not insulin sensitive (lenses, peripheral nerves, glomerulus)
- Sorbitol cannot cross cell membranes, ➔ it accumulates ➔ osmotic stress ➔ drawing water into tissues ➔ retinopathy, neuropathy, nephropathy

Aldose reductase inhibitors („-restat”s)

- Aldose reductase inhibitors are drugs **<u>to prevent eye, kidney and nerve damage</u>** in people with diabetes.
- Epalrestat (, Ranirestat in Phase III)
  (, Fidarestat ,Zenarestat failed before PhaseIII)
  (, Tolrestat withdrawn from market due to hepatotoxicity)
- Mechanism of action:
  - Inhibit aldose-reductase enzyme