Hormonal drugs

Lecture 1

- HORMONES are biologically active substances, which are produced by the cells of the endocrine system and regulate the functions of organs and systems of the body, support homeostasis.
- For the treatment doctors can use:

1. Preparations of natural hormones
2. Synthetic analogues of natural hormones
3. Synthetic substitutes derived from natural hormones but with additional properties
4. Antagonists of hormones (antihormone) or blockers of specific hormone receptors.

Types of hormone therapy

1.Specific:

- Substitutive (replacement therapy)
- Stimulating
- Inhibitory (suppressive)

2.Non-specific: glucocorticoids as anti-inflammatory and anti-allergic agents

Thyroid hormone

1. Calcitonin
2. Iodine-containing hormones:
   tetraiodothyronine (thyroxine, T4),
   triiodothyronine (T3).

- T3, T4 are formed in the follicles of the thyroid gland by iodination of tyrosine. Peroxidase takes part in the activation of iodine.
- The formation of T3 and T4 is regulated by Thyrotropic hormone of the pituitary gland according to the principle of negative feedback.

❖ Hypothyroidism: myxedema, cretinism –

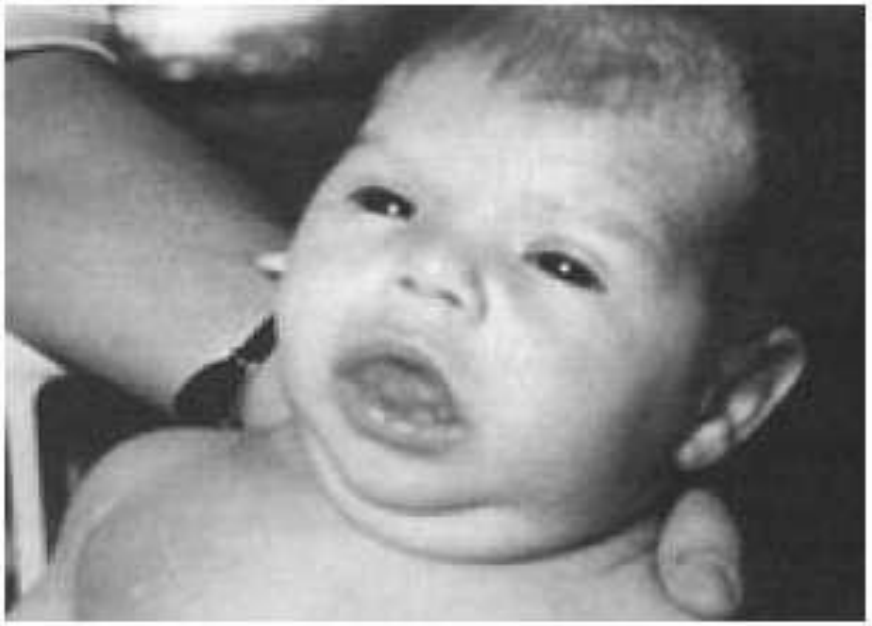
Drugs of T3, T4

❖ Hyperthyroidism: thyrotoxicosis –

antithyroid drugs

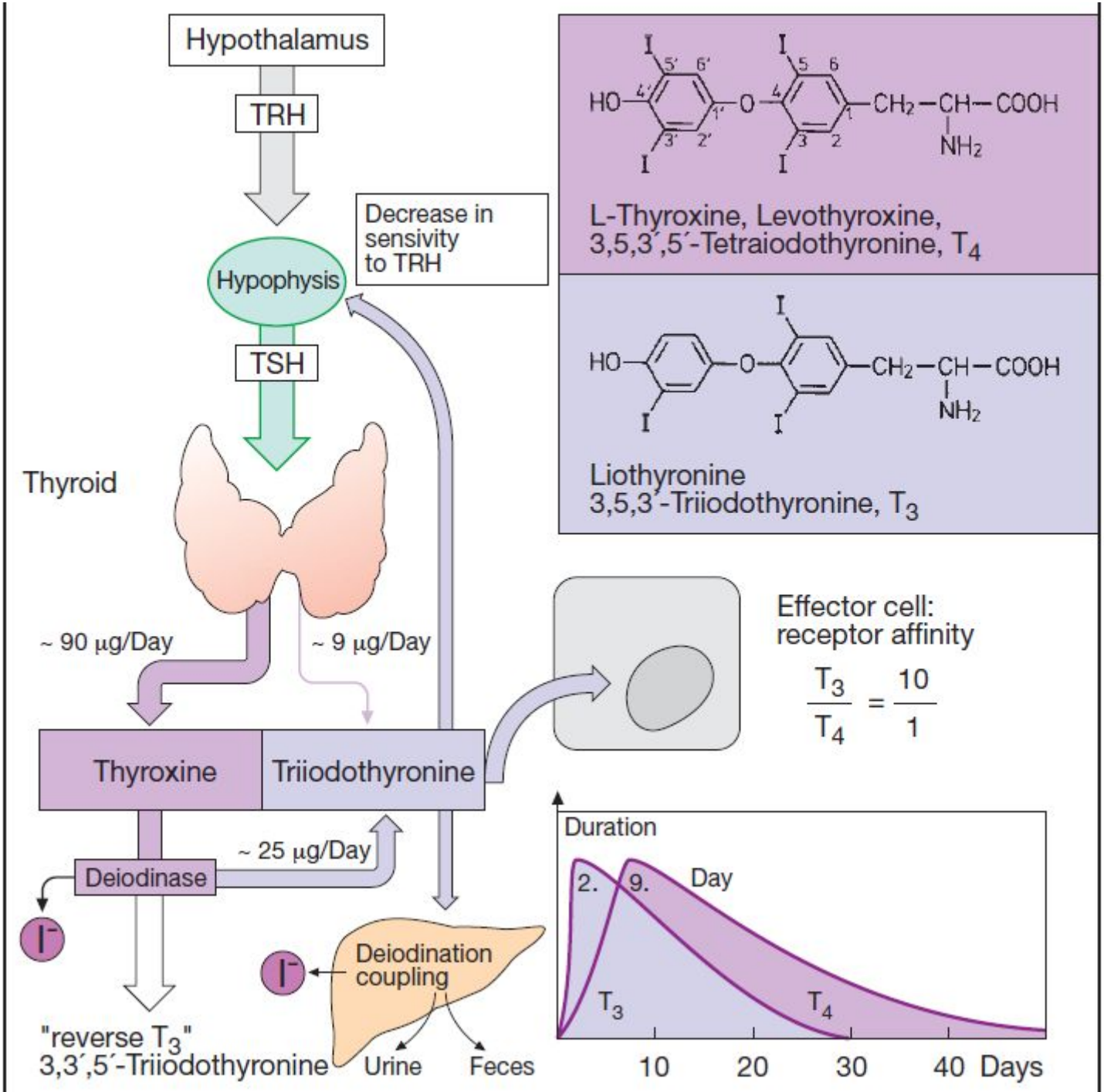
myxedema

cretinism



- Myxedema (mucosal edema): asthenia, apathy, drowsiness, decreased blood pressure, bradycardia, weight gain, decreased mental and physical activity.
- Cretinism is the physical and mental underdevelopment of children.
- These hormones affect the formation of brain, bones, regulation of growth and development of the body.
- For treatment and prevention of hypothyroidism we use: Liothyronine (Triiodothyronine) Levothyroxine (L-thyroxine)
- Route of administration-orally (tab.)

- They penetrate through the membranes of the cells. T4 is converted to T3 → penetrate into the nucleus and enhance its matrix activity.
- They increase the absorption of glucose, its use by cells;
- They increase the synthesis of dehydrogenases, tissue respiration (indicator-increase the consumption of O2 by cells and increase the release of CO2).
- They increase the synthesis of enzymes regulating metabolic processes of anabolism and catabolism.
- They elevate the synthesis of bioreceptors, including adrenergic receptors, restore the response of tissues to catecholamines.

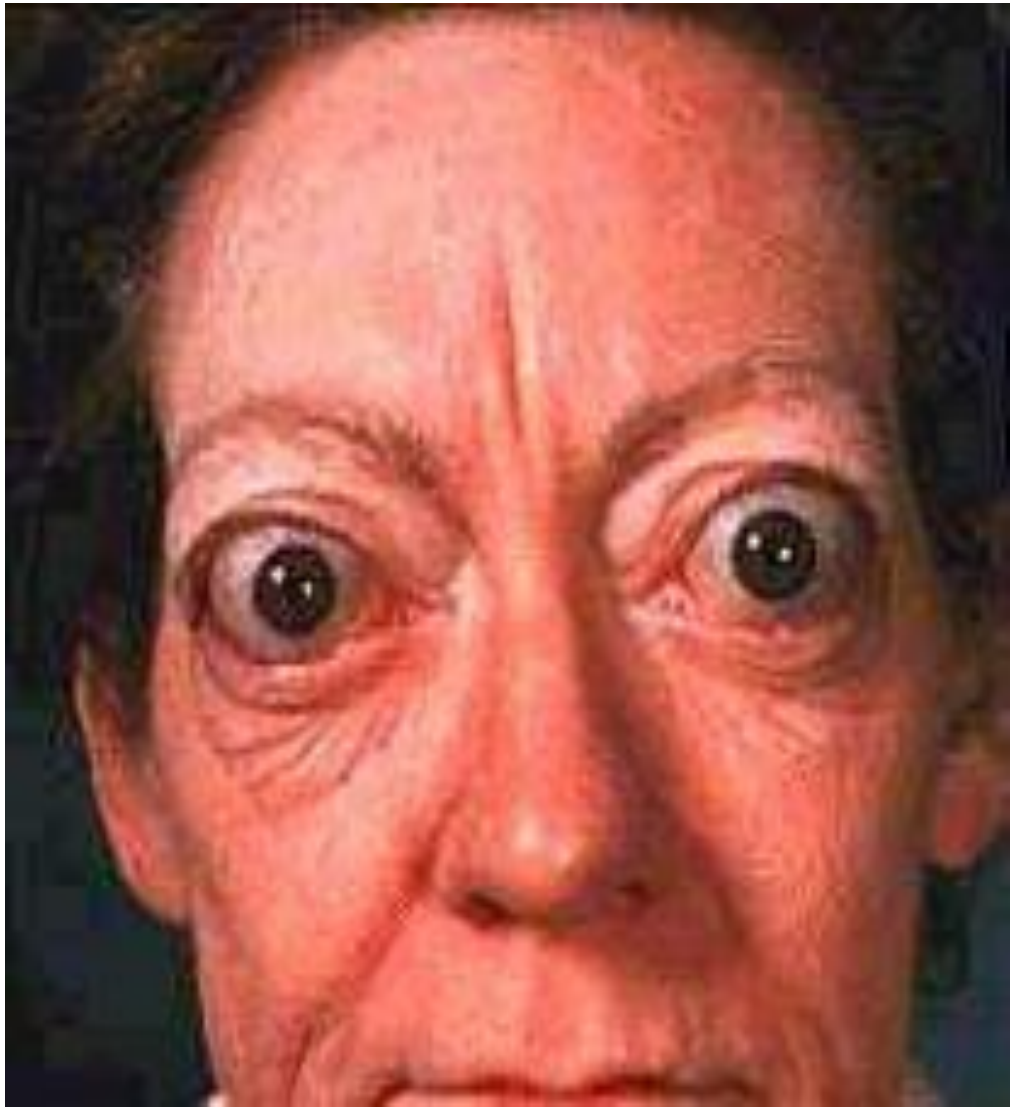

Hypothalamus
TRH
Hypophysis
TSH
Decrease in sensivity to TRH
Thyroid
~ 90 µg/Day
~ 9 µg/Day
Thyroxine
Triiodothyronine
~ 25 µg/Day
Deiodinase
I⁻
"reverse T3"
3,3´,5´-Triiodothyronine
I⁻
Deiodination coupling
Urine
Feces
L-Thyroxine, Levothyroxine,
3,5,3´,5´-Tetraiodothyronine, T4
Liothyronine
3,5,3´-Triiodothyronine, T3
Effector cell:
receptor affinity
T3/T4 = 10/1
Duration
2.
9.
Day
T3
T4
10
20
30
40 Days

- Thyroxin effect develops gradually and reaches its maximum after 8-10 days. The effect lasts for several weeks. Thyroxin is mainly converted into triiodthyronine.
- Triiodothyronine has more rapid onset. It is completely absorbed from intestine. Its maximal effect is observed between 24-48 h and lasts for several days.

 Application: prevention of cretinism, myxedema, myxedematous crisis.

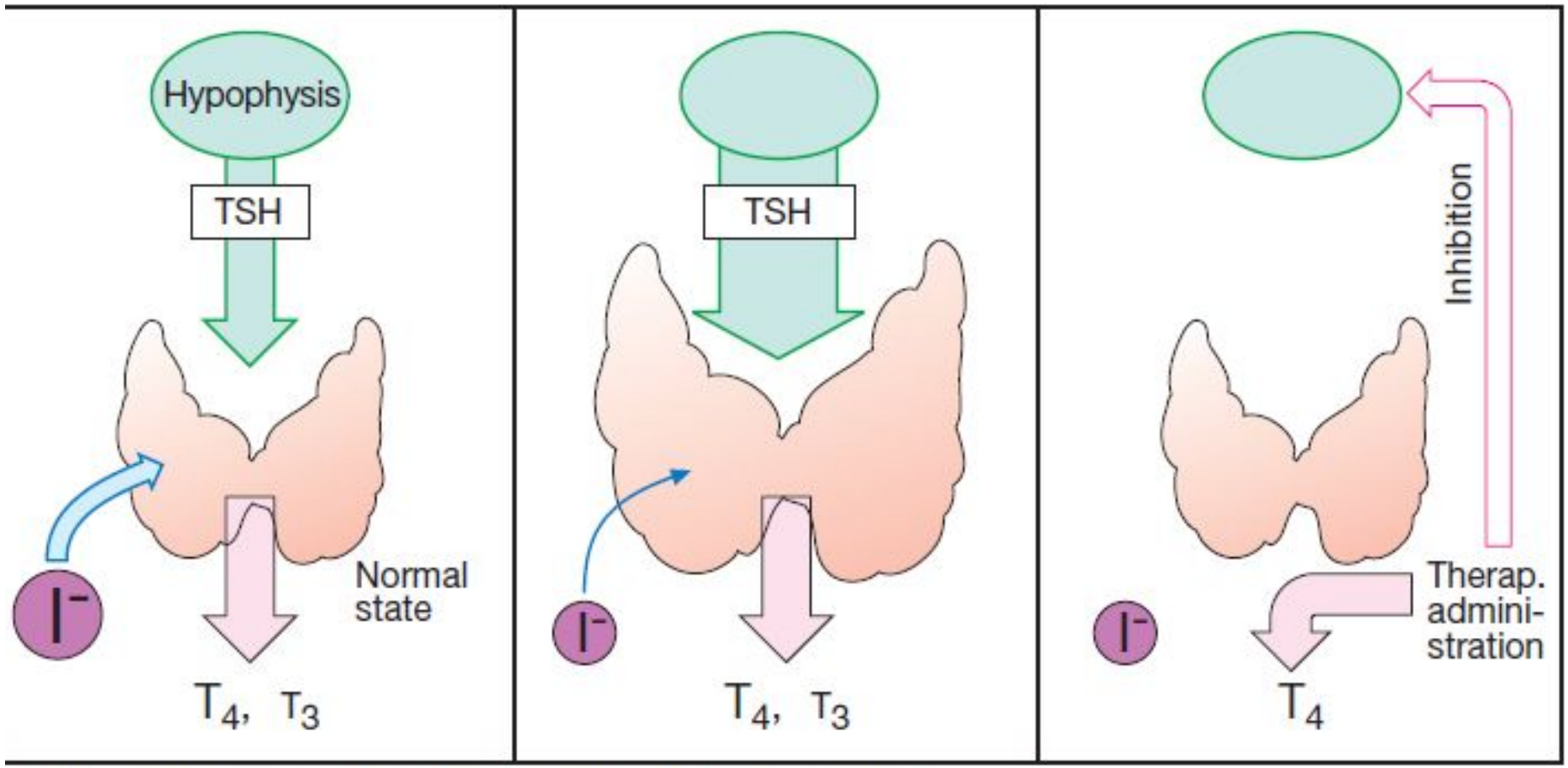
 In case of overdose: signs of hyperthyroidism.

- Hyperthyroidism: hyperexcitability, sleep disturbance, asthenia, fervescence, tachycardia, exophthalmus, enlargement of the thyroid gland.



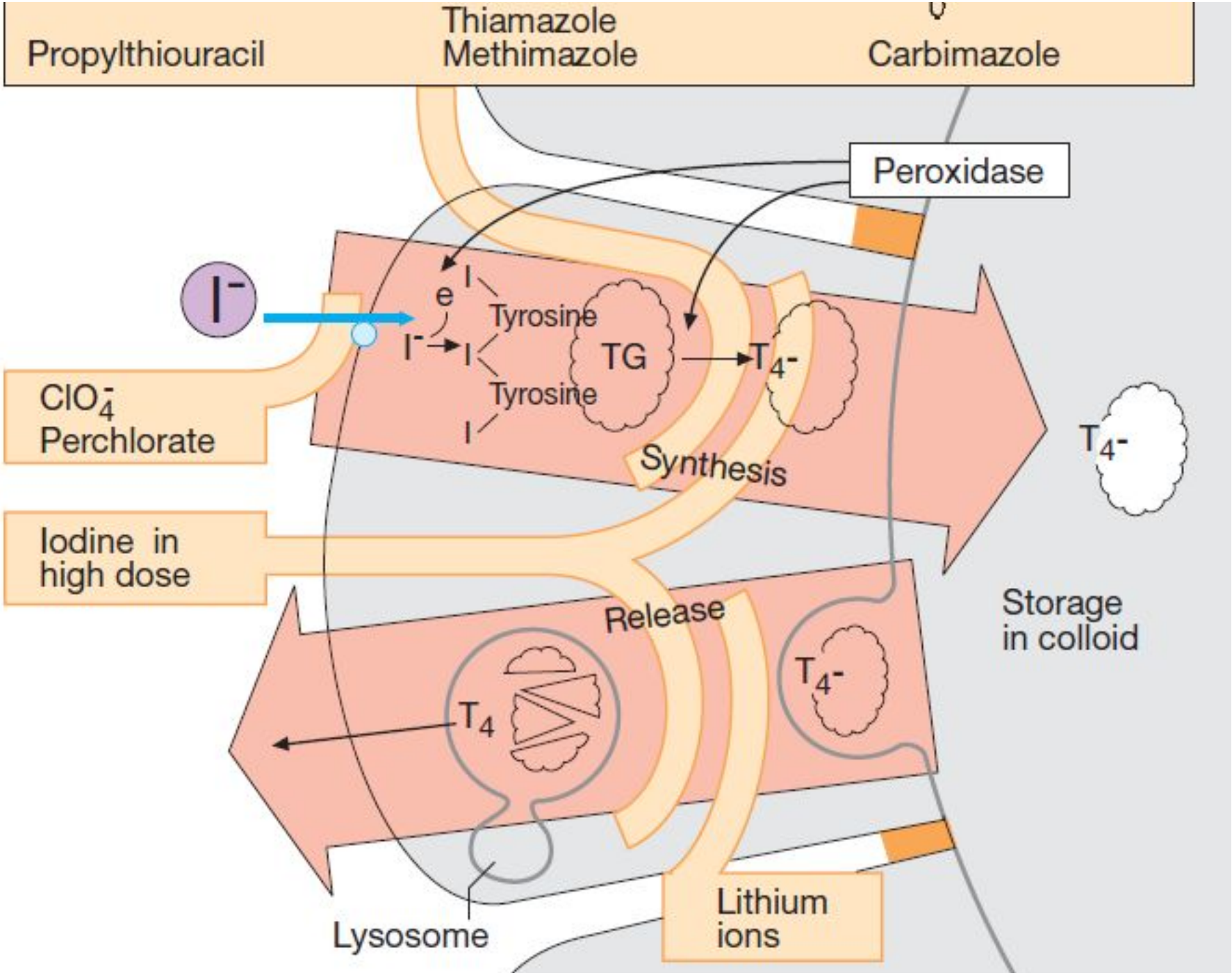
Antithyroid drugs

- Inhibiting thyrotropic hormone production in the anterior pituitary lobe: iodine, diiodotyrosine
- Inhibiting thyroid hormone synthesis in the thyroid gland: thiamazole, propylthiouracil
- Preventing iodine absorption by the thyroid gland: potassium perchlorate
- Destruction the follicular cells of the thyroid gland: radioactive iodine
- Endemic goiter: KI (Iodomarin)



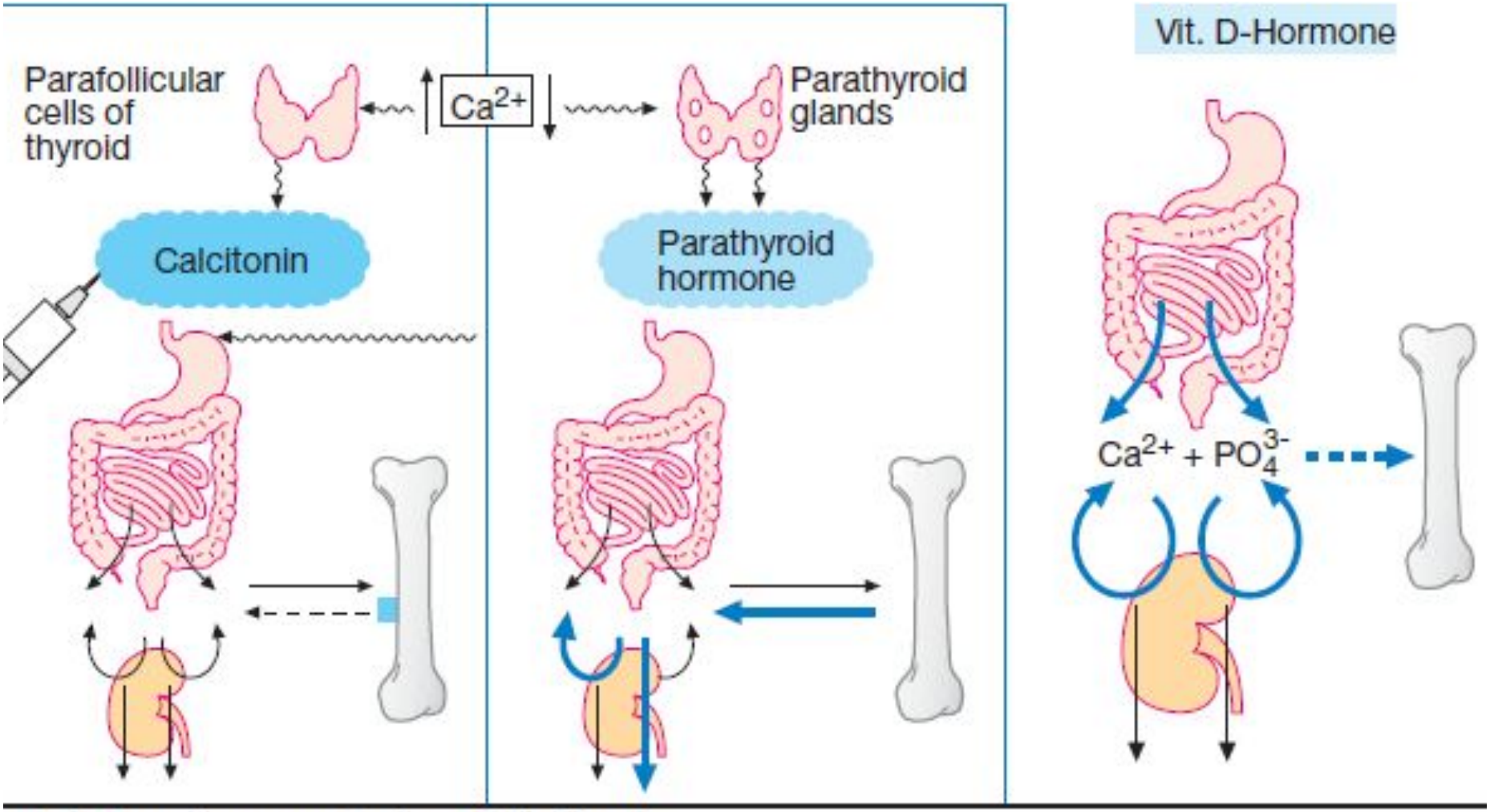
3. Endemic goiter and its treatment with thyroxine

- Thiamazol and carbimazole block peroxidase, reduce iodization of tyrosine, reduce the formation of mono-, diiodtyrosin, their condensation with formation of T3, T4.
- They are appointed orally. The drugs reduce the pulse rate, reduce blood pressure, normalize sleep, improve metabolism, eliminate the phenomenon of neurosis.
- Side effect: leukopenia, agranulocytosis, thrombocytopenia, dyspepsia, allergy. A goiter can develop. Iodine preparations can be used.


Propylthiouracil
Thiamazole
Methimazole
Carbimazole
Peroxidase
I⁻
e
I
Tyrosine
I⁻
I
TG
T4-
Tyrosine
I
ClO4-
Perchlorate
Synthesis
T4-
Iodine in
high dose
Release
Storage
in colloid
T4
T4-
Lysosome
Lithium
ions

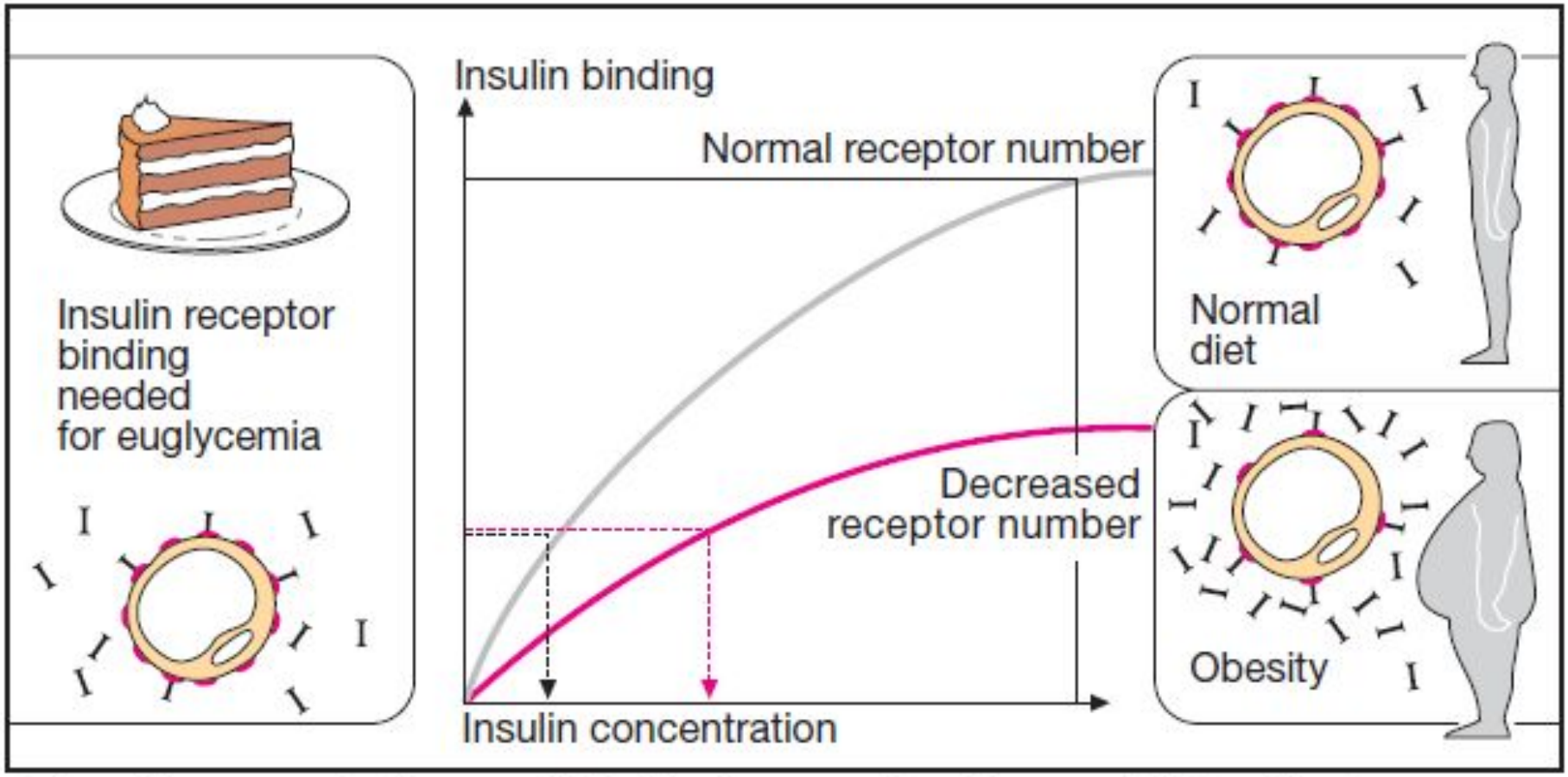
- **Calcitonin** inhibits bone resorption by direct action on osteoclasts and promotes calcium deposition by osteoblasts. It inhibits proximal tubular reabsorption of Ca and phosphates. Plasma concentration of Ca is reduced. The action of calcitonin lasts ~8 hours. Calitonin has anti-inflammatory action also.
- Indications: osteoporosis (long-term immobilization, old age, long-term glucocorticoid therapy), Paget's disease .
- Side effects: allergic reactions, irritant effect at the injection site.
- Drugs: synthetic human calcitonin, synthetic salmon calcitonin.

- **Parathormone** is a polypeptide**.**
- It increases the palsma calcium level.
- It activates hydroxylase, which converts calcidiol to calcitriol (the most active metabolite of vit. D).
- P. increases the activity of osteoclasts, reduces the activity of osteoblasts. It causes decalcification of the bones and Ca release into the blood.
- P. promotes Ca absorption from the GIT.
- P. increases the reabsorption of Ca ions in the renal tubules.
- Preparation: teriparatide (active fragment of P. 1-34)
- Uses: spasmophilia and tetany.



Calcium homeostasis of the body

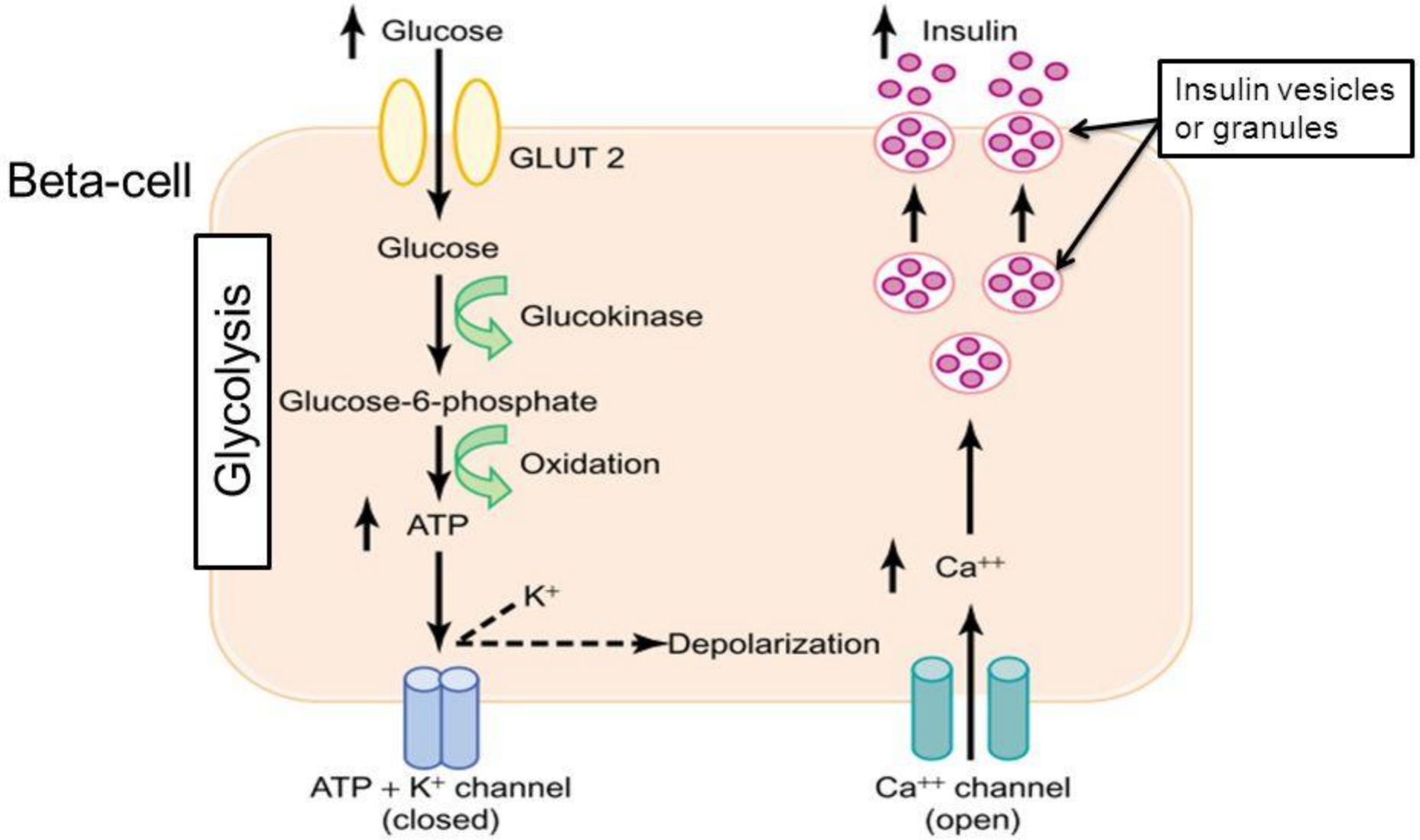
- Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia, glycosuria, hyperlipidaemia, negative nitrogen balance and sometimes ketonaemia.
- Type I Insulin-dependent diabetes mellitus (**IDDM**) - juvenile onset diabetes mellitus (β cell destruction, circulating insulin levels are low or very low),
- Type II Noninsulin-dependent diabetes mellitus (**NIDDM**) - maturity onset diabetes mellitus (insulin in circulation is low, normal or even high, but abnormality in gluco-receptor of β cells and reduced sensitivity of peripheral tissues to insulin).



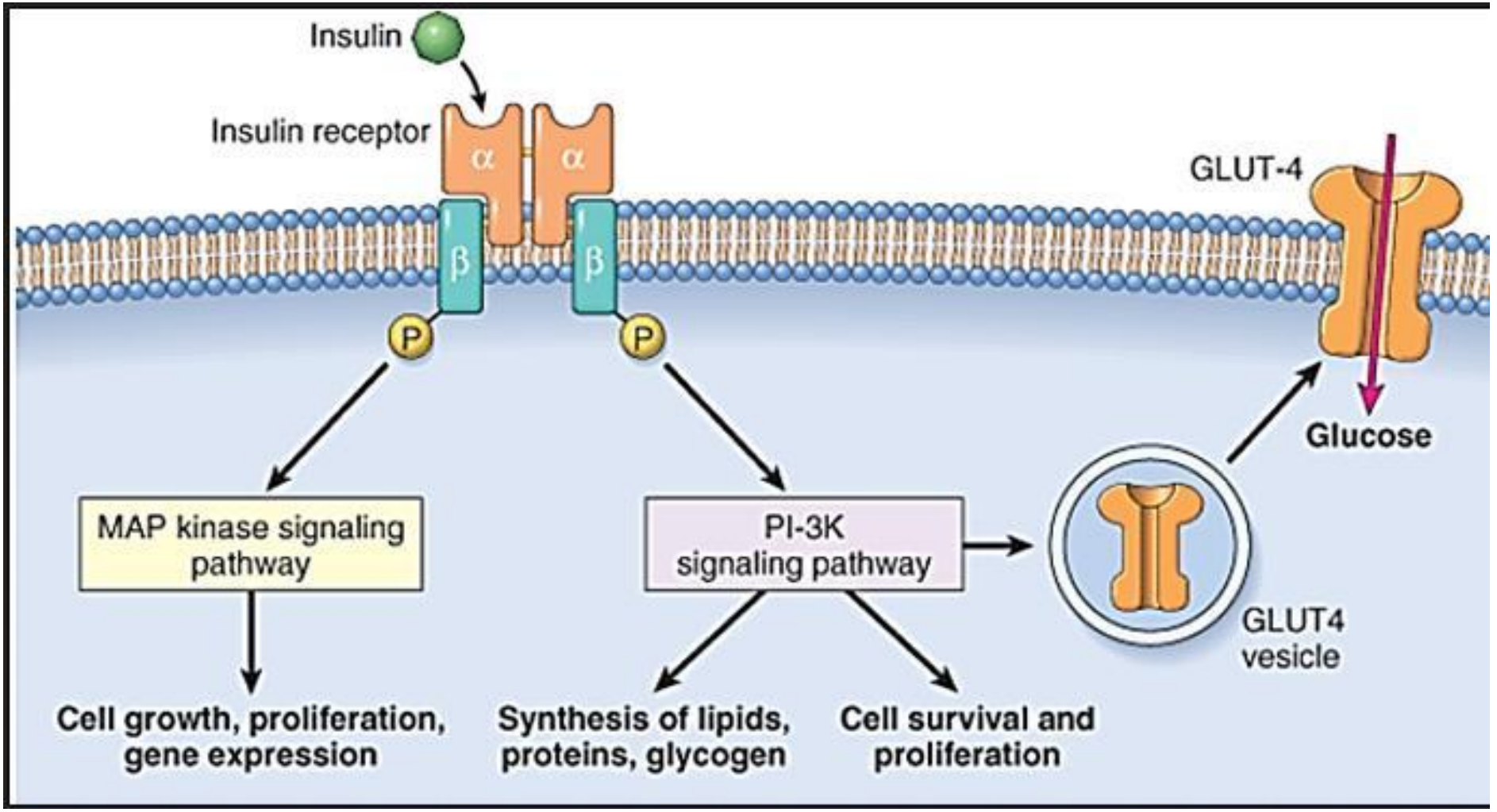
A. Insulin concentration and binding in normal and overweight subjects

- Insulin is a two chain polypeptide. It is synthesized in the β cells of pancreatic islets.
- Under basal condition ~1U insulin is secreted per hour by human pancreas. Much larger quantity is secreted after every meal. Secretion of insulin from β cells is regulated by mechanism:
- chemical - glucose stimulates **insulin release**.
- hormonal - somatostatin inhibits release of both insulin and glucagon; glucagon evokes release of insulin as well as somatostatin.
- and neural - adrenergic α2 receptor activation decreases insulin release; adrenergic β2 stimulation increases insulin release.

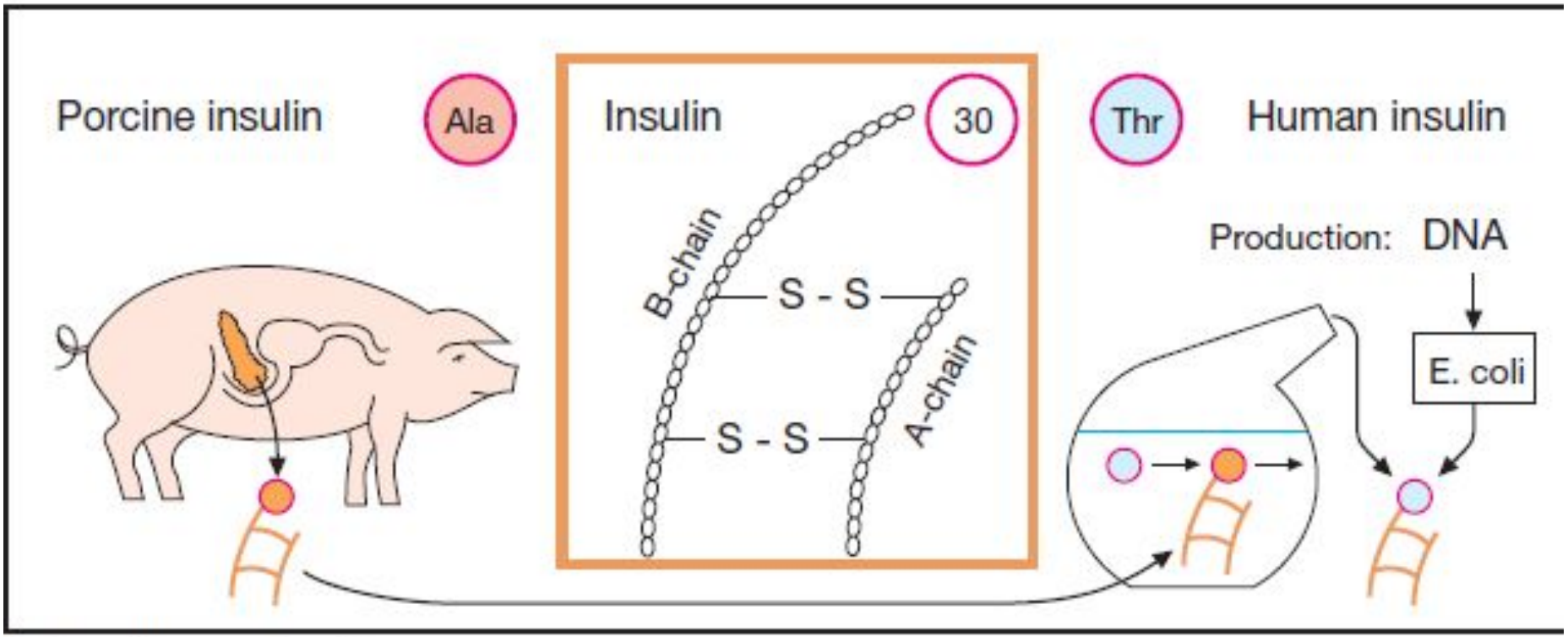
Mechanisms of Insulin Secretion



- Insulin acts on specific receptors located on the cell membrane. There are many receptors in liver and fat cells. The specific receptors have two α and β subunits. The α subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity.
- Insulin activates glucose transport through the cellular membranes by the special transport system (Glut 4).
- Insulin activates utilization of glucose by the muscles and fatty tissues.
- Glycogenogenesis increases but insulin reduces glycogenolysis in the liver and sceletal muscles.


Insulin
Insulin receptor
α
α
β
β
P
P
GLUT-4
Glucose
MAP kinase signaling pathway
PI-3K signaling pathway
GLUT4 vesicle
Cell growth, proliferation, gene expression
Synthesis of lipids, proteins, glycogen
Cell survival and proliferation

- Insulin inhibits the conversion of aminoacids into glucose (gluconeogenesis).
- It stimulates protein synthesis and promotes storage of triglycerides in the fatty tissues, inhibits lipolysis in adipose tissue.
- Insulin exerts major long-term effects on multiplication and differentiation of many types of cells.
- Insulin decreases blood sugar levels, eliminates glucosuria, polyuria, thirst (polydipsia).
- Ketone bodies (acetone, acetoacetic acid) disappear from urine and blood.
- Weight loss and excessive hunger (bulimia) are stopped.



A. Insulin production

- **Preparations of insulin:** highly purified pork/beef insulins; recombinant human insulins; insulin analogues.

Ultra-short-acting insulin: I. Lispro, Aspart I.

- Onset of action (S.C.) - 10-20 min.
- Max effects - 1-3 hours,
- Duration of action - 3 -5 hours.

Short-acting insulin: Actrapid HM, Humulin-Regular; Actrapid MC (pork monocomponent).

✔ Onset of action - 30 – 60 min.

✔ Max effect - 2 – 4 hours;

✔ Duration of action - 6-8 hours.

Average duration of action:

Isophane (contains protamine)

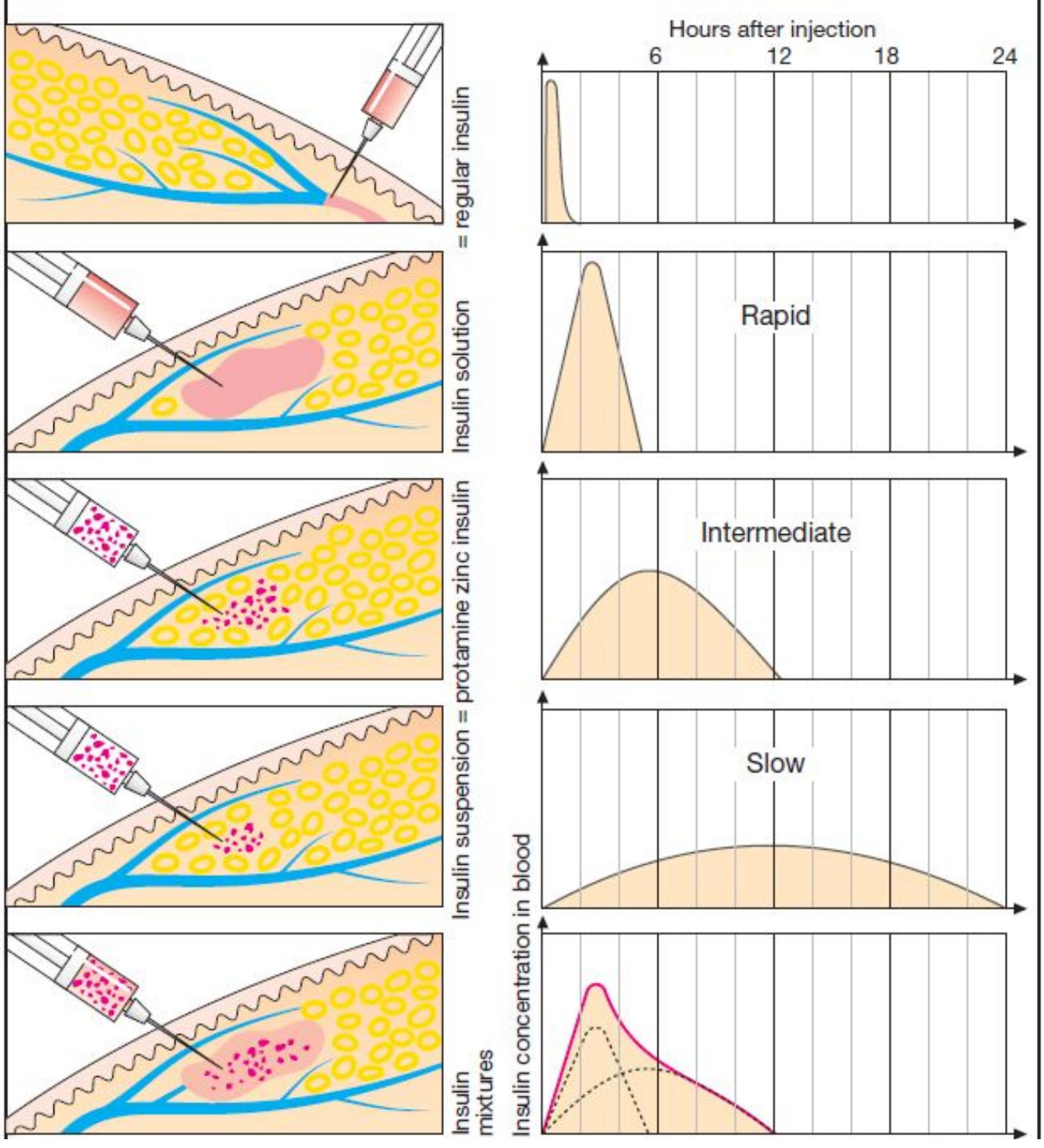
Monotard MC (contains Zn)

- The beginning of the effect - 1.5-2 hours,
- Max effect - 3-12h.,
- Duration - 8-12 hours.

Long-acting:

The beginning of the effect - 4-8 hours,

- Max effect - 8-18 hours,
- Duration - 20-30 hours.



Insulin preparations and blood level-time curves

- Combined preparation. HUMAN MIXTARD: Human soluble insulin (30%) and isophane insulin (70%), 40 U/ml. and 100 U/ml vials
- Start of action - after 30 min. (S.C.),
- Max. effect - 2 -8 hours,
- Duration of action up to 18-20 hours.

- ❑ Insulin preparations are used S.C., I.M., I.V. (water soluble).
- ❑ Most drugs are produced in special portable pen-sized injectors.

Indications for use

- **IDDM**, hyperglycemic coma,
- **NIDDM** (ineffectiveness of oral drugs, special conditions - pregnancy, operations, severe concomitant diseases,
- Cachexia,
- Psychiatry (insulin coma),
- Arrhythmias (polarizing mixture).

Side effects: hypoglycemia, allergic reaction, insulin resistance, lipodystrophy.

Oral hypoglycaemic drugs (They are used for the treatment of type 2 diabetes mellitus)

A. Enhance Insulin secretion

1. Sulfonylureas (K_{ATP} Channel blockers): Glibenclamide, Glipizide, Gliclazide, Glimepiride
2. Postprandial hypoglycemic substances: Repaglinide, Nateglinide
3. Glucagon-like peptide-1 (GLP-1) receptor agonists (Injectable drugs) - Exenatide
4. Dipeptidyl peptidase-4 (DPP-4) inhibitors: Sitagliptin, Vildagliptin

B. Overcome Insulin resistance

1. **Biguanide (AMP_K activator)-** Metformin
2. **Thiazolidinediones (insulin sensitizers)**
   -Pioglitazone

C. ***Miscellaneous antidiabetic drugs***

1. **α-Glucosidase inhibitors** - Acarbose
2. **Amylin analogue** -Pramlintide
3. **Sodium-glucose cotransport-2 (SGLT-2) inhibitor** -Dapagliflozin

Derivatives of sulfonylureas. Mechanism of action:

Blockade of ATP-sensitive K+-channels

↓

Depolarization of the β-cells membranes

↓

Opening of the voltage-dependent

Ca^{2+} channels

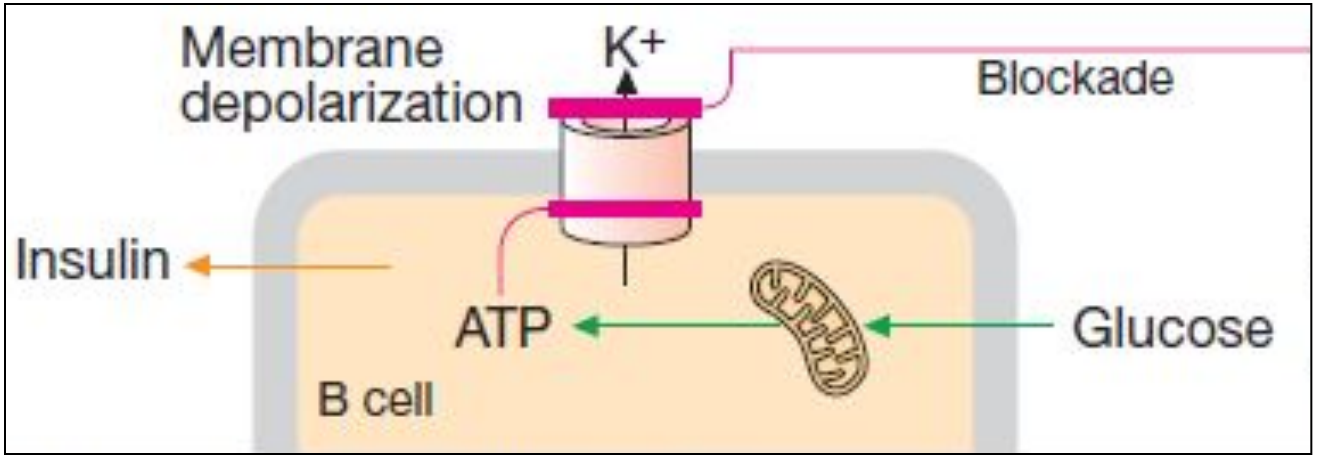
↓

Ca^{2+} enters

B-cells

↓

Insulin release



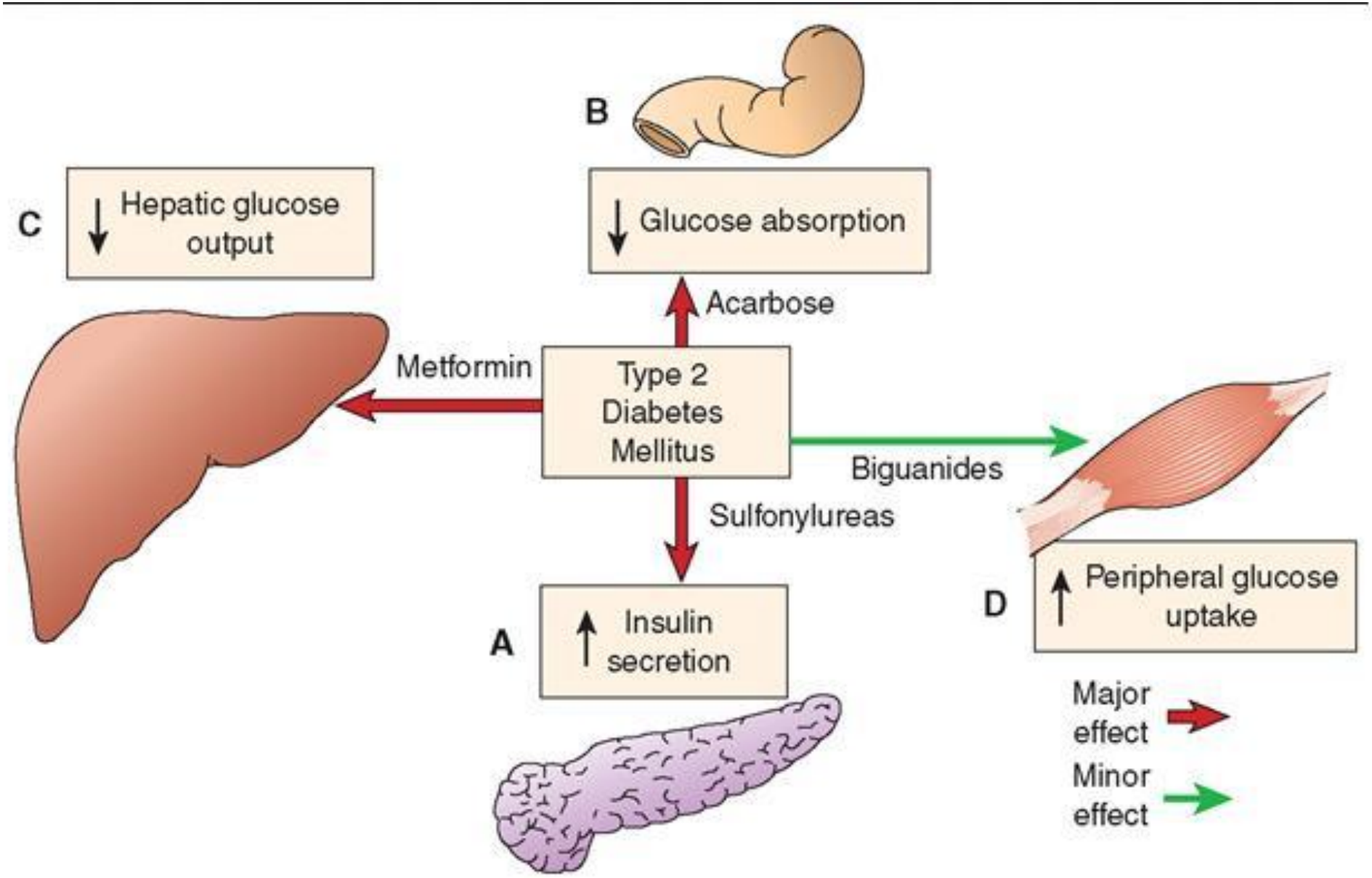
- They promote the regeneration of ß cells, ↑ their number.
- They potentiate the action of insulin: ↑synthesis of insulin receptors, ↑their sensitivity to insulin. ↓synthesis of insulin antibodies, ↓ glucagon production.
- Gliclazide improves microcirculation.
- Glimepiride acts more selectively on the K + channels of the gland, less affects the heart.
- Side effects: hypoglycemia, dyspepsia, allergy, leukopenia, agranulocytosis, thrombocytopenia, cholestasis, jaundice, heart failure.

- **Repaglinide and Nateglinide are** K_{ATP} channel blockers with a quick and short lasting insulinemic action.
- They induce fast onset short-lasting insulin release. They are administered before each major meal to control postprandial hyperglycaemia.
- Side effects: dizziness, mild headache, dyspepsia, nausea and joint pain.

Metformin

- ↓absorption of glucose from the intestine,
- ↑ its uptake by the muscles,
- ↑ glycolysis, ↓gluconeogenesis,
- ↑ number of insulin receptors,↑action of insulin, ↑lipolysis, ↓ lipogenesis,
- ↓body weight, appetite,
- ↓the content of atherogenic lipoproteins, cholesterol.

❖ **Side effects:** metallic taste in the mouth, nausea, abdominal pain, hypoglycemia, ketoacidosis, malabsorption of Vit. B12 and folic acid (anemia).


B
C
↓ Hepatic glucose output
↓ Glucose absorption
Acarbose
Metformin
Type 2 Diabetes Mellitus
Biguanides
Sulfonylureas
D
↑ Peripheral glucose uptake
A
↑ Insulin secretion
Major effect
Minor effect

- **Glucagon-like peptide-1 (GLP-1)** is an important incretin released from the gut in response to ingested glucose. It induces insulin release from pancreatic β cells, inhibits glucagon release from α cells, slows gastric emptying and suppresses appetite by activating specific GLP-1 receptors.
- GLP-1 itself is not suitable for clinical use because of rapid degradation by the enzyme **dipeptidyl peptidase-4 (DPP-4)** which is expressed on the luminal membrane of capillary endothelial cells, kidney, liver, gut mucosa and immune cells.
- Incretin **glucose-dependent insulinotropic peptide (GIP)** also induces insulin release.

- **Exenatide** is a synthetic DPP-4 resistant analogue of GLP-1 and activates its receptors. It is injected S.C.
- **Vildagliptin and sitagliptin** block DPP. They increase concentration of incretins and production of insulin. They are taken orally, but they can cause acute pancreatitis.
- **Pioglitazone, rosiglitazone** increase the sensitivity of insulin receptors (insulin sensitizers).

- Acarbose is a blocker of α-glucosidase.
- It ↓digestion and absorption of carbohydrates in the small intestine.
- In the large intestine, carbohydrates are broken down to form gases.
- It is taken orally.
- Side effects: diarrhoea, meteorism.

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