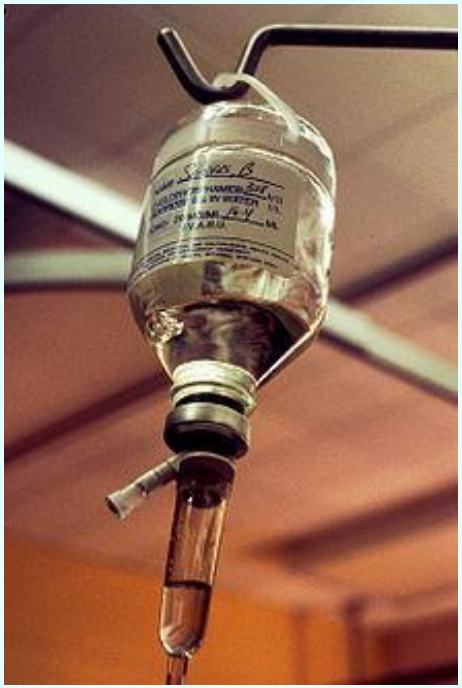
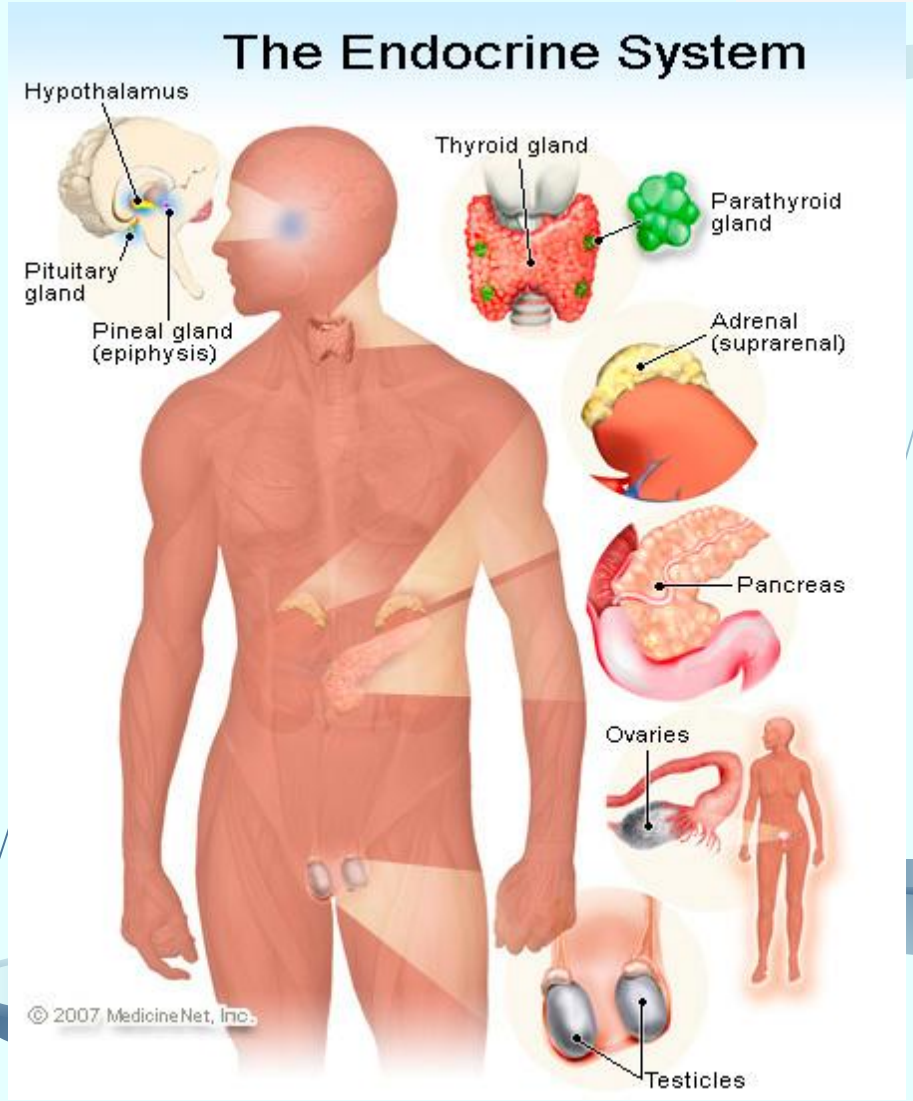
ZSMU Pharmacology Department

Lecture № 5

DRUGS USED IN ENDOCRINE DISORDERS





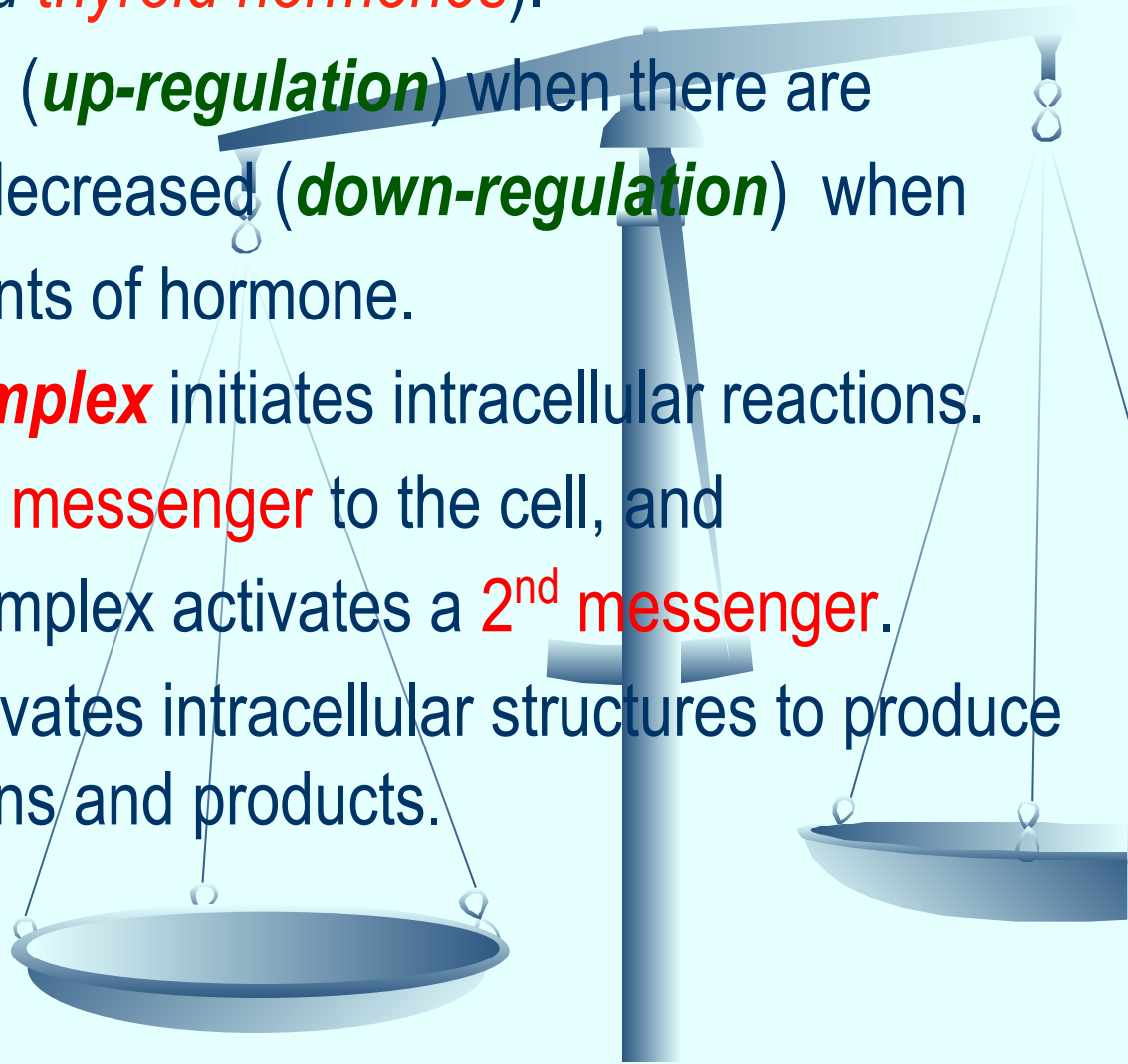
Classification of hormones

By the chemical structure:

- Peptides - hormones of hypothalamus, pituitary and parathyroid glands, pancreas, calcitonin.
- Aminoacid derivatives - hormones of the thyroid gland.
- Steroids - hormones of the adrenal and gonadal glands.

Mechanism of action

- Once hormones reach a responsive cell, they bind with receptors in the cell membrane (*protein hormones*) or inside the cell (*steroid and thyroid hormones*).
- Receptors may be increased (***up-regulation***) when there are low levels of hormone or decreased (***down-regulation***) when there are excessive amounts of hormone.
- The ***hormone–receptor complex*** initiates intracellular reactions.
- Many hormones act as a 1st messenger to the cell, and the hormone–receptor complex activates a 2nd messenger.
- The 2nd messenger then activates intracellular structures to produce characteristic cellular functions and products.



Second Messenger Systems

- **Cyclic AMP** is the **2nd messenger** for many hormones, including **Corticotropin, Glucagon, Thyroid stimulating hormone, Follicle stimulating hormone, Luteinizing hormone, Parathyroid hormone** and **Antidiuretic hormone**.
- It is formed by the action of the enzyme **adenyl cyclase** on **ATP**.

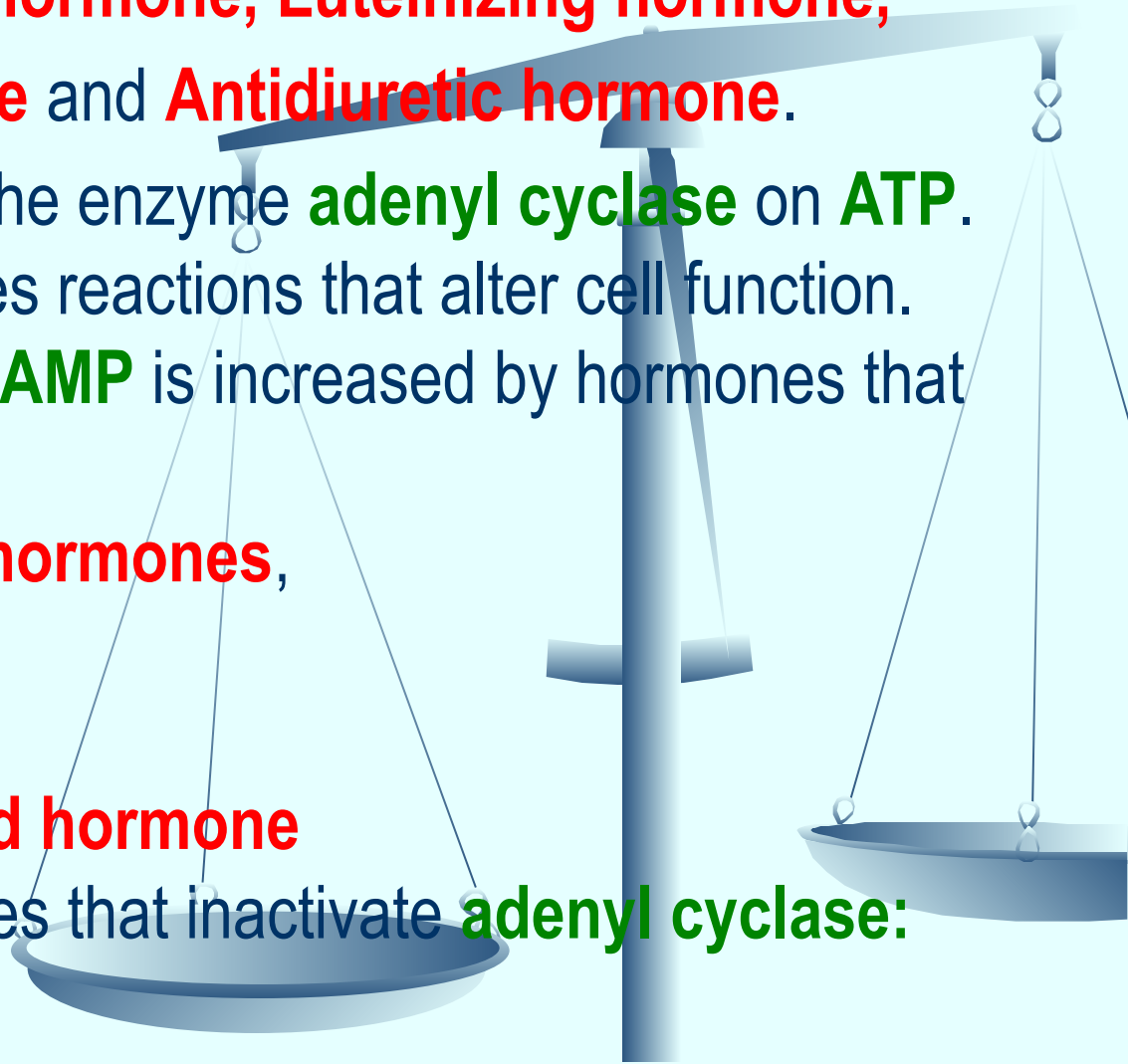
Once formed, **cAMP** activates reactions that alter cell function.

The amount of intracellular **cAMP** is increased by hormones that activate **adenyl cyclase:**

the **Pituitary hormones**,
Calcitonin,
Glucagon,
Parathyroid hormone

and decreased by hormones that inactivate **adenyl cyclase:**

Somatostatin



- **Ca^{2+}** is the 2^{nd} messenger for Gonadotropin-releasing hormone. This hormone binds to receptors to increase intracellular Ca^{2+}.

  The Ca^{2+} binds with an intracellular protein *Calmodulin*.
- The Ca^{2+} – Calmodulin complex activates ***Protein kinases***, which:

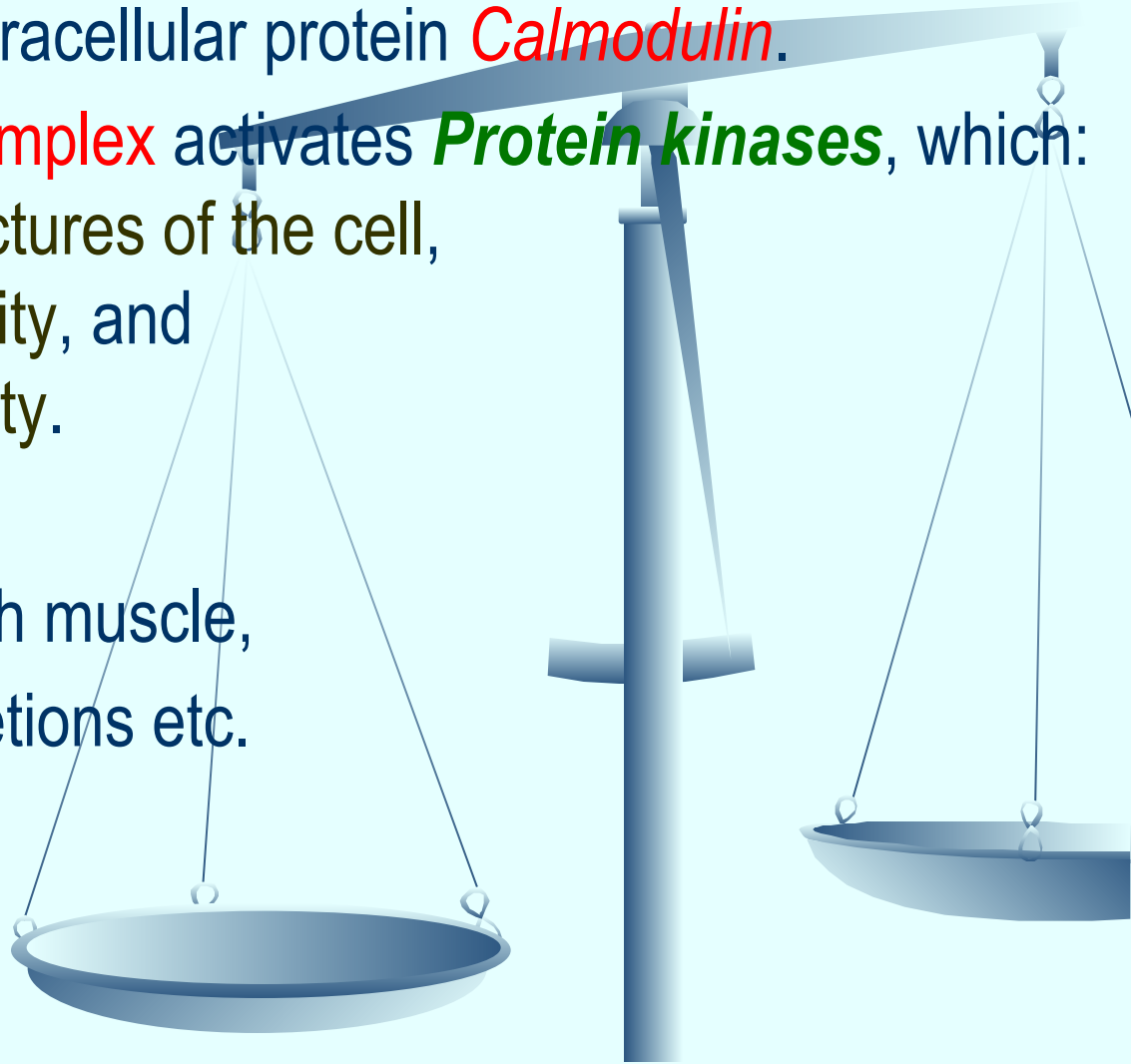
  Regulate contractile structures of the cell,

  Cell membrane permeability, and

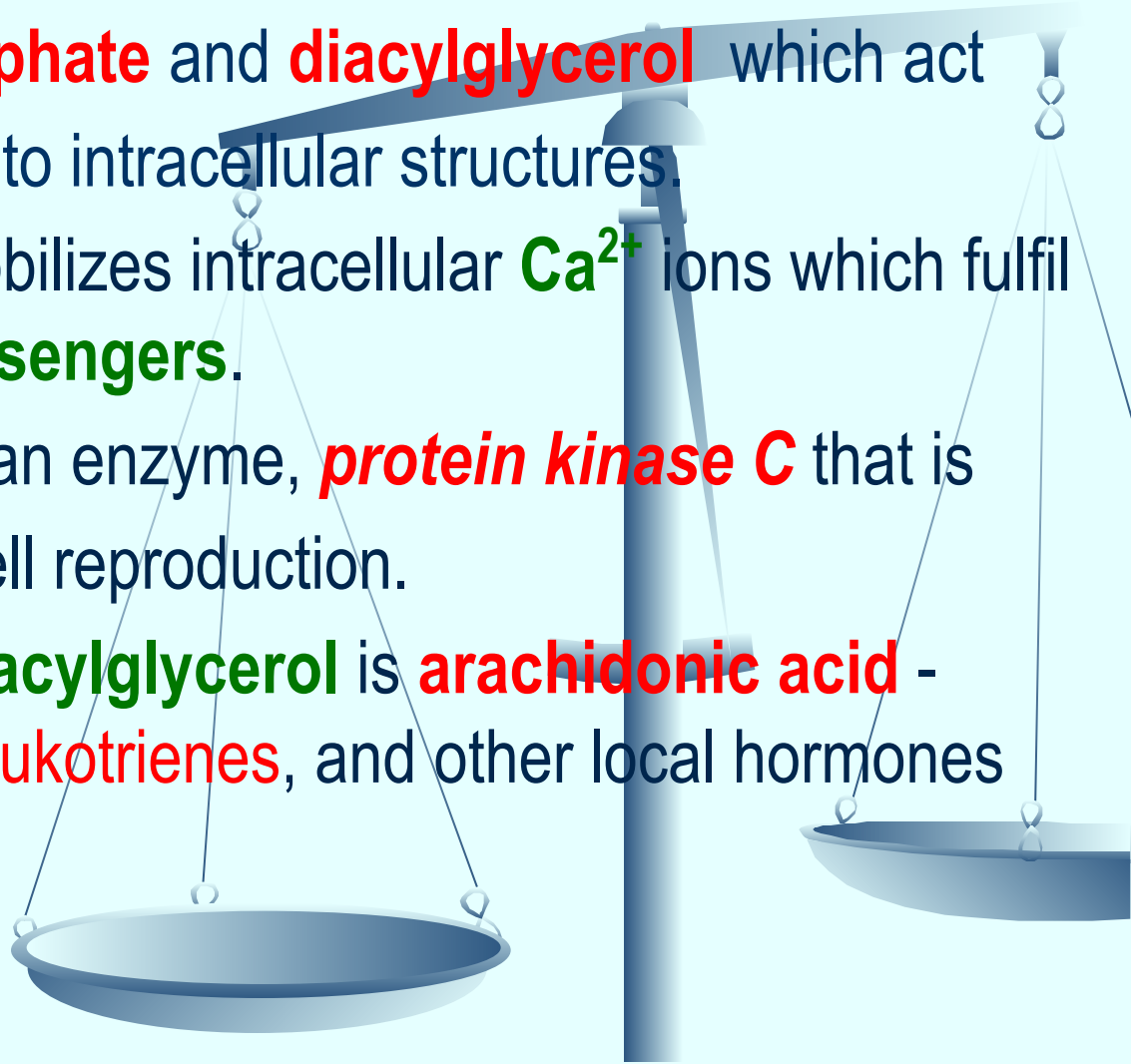
  Intracellular enzyme activity.
- **Specific effects** include:

  Contraction of smooth muscle,

  Changes in the secretions etc.



- Some hormones activate cell membrane receptors and transform them into ***phospholipase C***, an enzyme that causes some of the **phospholipids** in cell membranes to split into smaller molecules: **inositol triphosphate** and **diacylglycerol** which act as 2nd **messengers** to intracellular structures.
- **Inositol triphosphate** mobilizes intracellular **Ca^{2+}** ions which fulfil their functions as 2nd **messengers**.
- **Diacylglycerol** activates an enzyme, ***protein kinase C*** that is important in cell reproduction.
- The lipid component of **diacylglycerol** is **arachidonic acid** - the precursor for PGs, leukotrienes, and other local hormones



Steroid Regulation of Protein Synthesis

- Steroid hormones are lipid soluble and cross cell membranes easily.
- Once inside the cell, the hormone molecules bind with specific receptor proteins.
- The hormone–receptor complex enters the **nucleus** of the cell where it activates **Gene Expression –** nucleic acids (DNA and RNA) and the Genetic Code to synthesize new proteins.

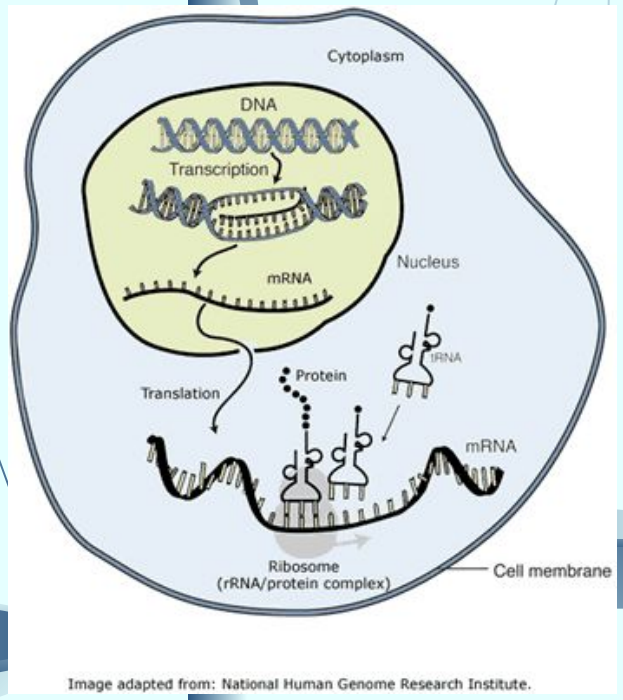


Image adapted from: National Human Genome Research Institute.

Hormones of hypothalamus and pituitary gland

Growth group:

→ **Anterior lobe of pituitary gland:**

- **Growth hormone (GH, somatotropin).** → **Somatomedines**

Somatropin, Somatrem.

Applications: pituitary dwarfism (nanism)

Receptors in organs and tissues

► **Increase of protein synthesis, increase of glucose level (antagonism with insuline), stimulation of lipolysis, decrease of secondary sexual attributes (antagonism with sex hormones).**

- **Inhibitor of Growth hormone production - Bromocriptine (D_2-dopaminemimetic).**

Thyroid group:

→ **Hypothalamic hormones:**

- Thyrotropin-releasing hormone (TRH) - Thyroliberin.

Rifathyroin [Protirelin].

Applications: diagnostics of hypothyroidism level.

→ **Anterior lobe of pitultary gland hormones:**

- Thyroid stimulating hormone (TSH) - Thyrotropin:

Thyrotropin.

Applications: thyroid gland insufficiency (as additional to thyroid gland hormones).

Sex hormones group:

→ **Anterior lobe of pituitary gland hormones (drug preparations):**

- **Follicle-stimulating hormone (FSH)**

Menopausal gonadotropin

Applications: treament of pituitary or hypothalamic hypogonadism.

- **Luteinizing hormone (LH)**

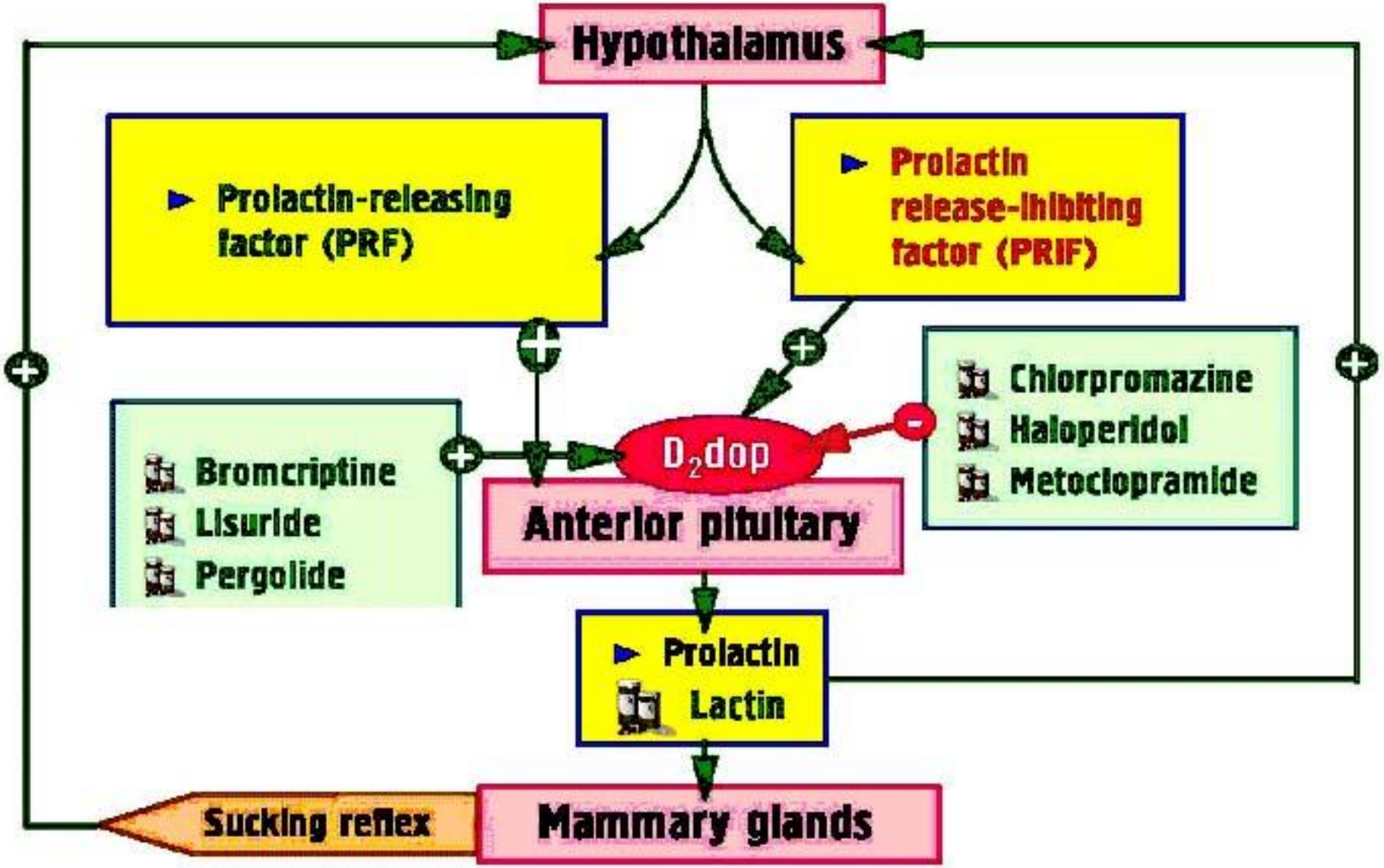
Human chorionic gonadotropin.

Applications: together with FSH preparations to promote ovulation and implantation in women and testosterone production in man.

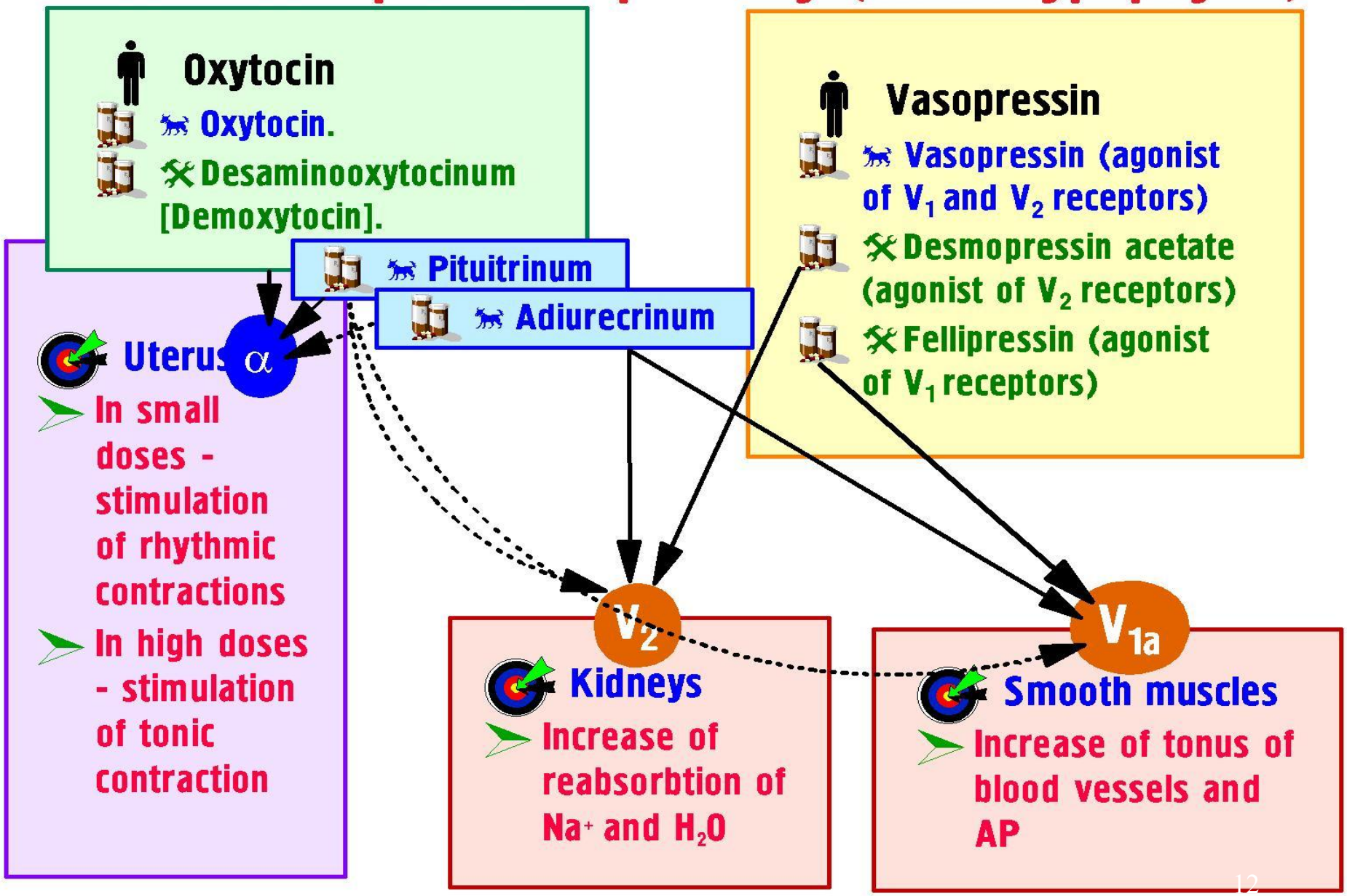
Antagonist of gonadotopins release - Danazol.

Applications: endometriosis, gynecomastia, menorragia.

Prolactin Group



Hormones of posterior pituitary (neurohypophysis)

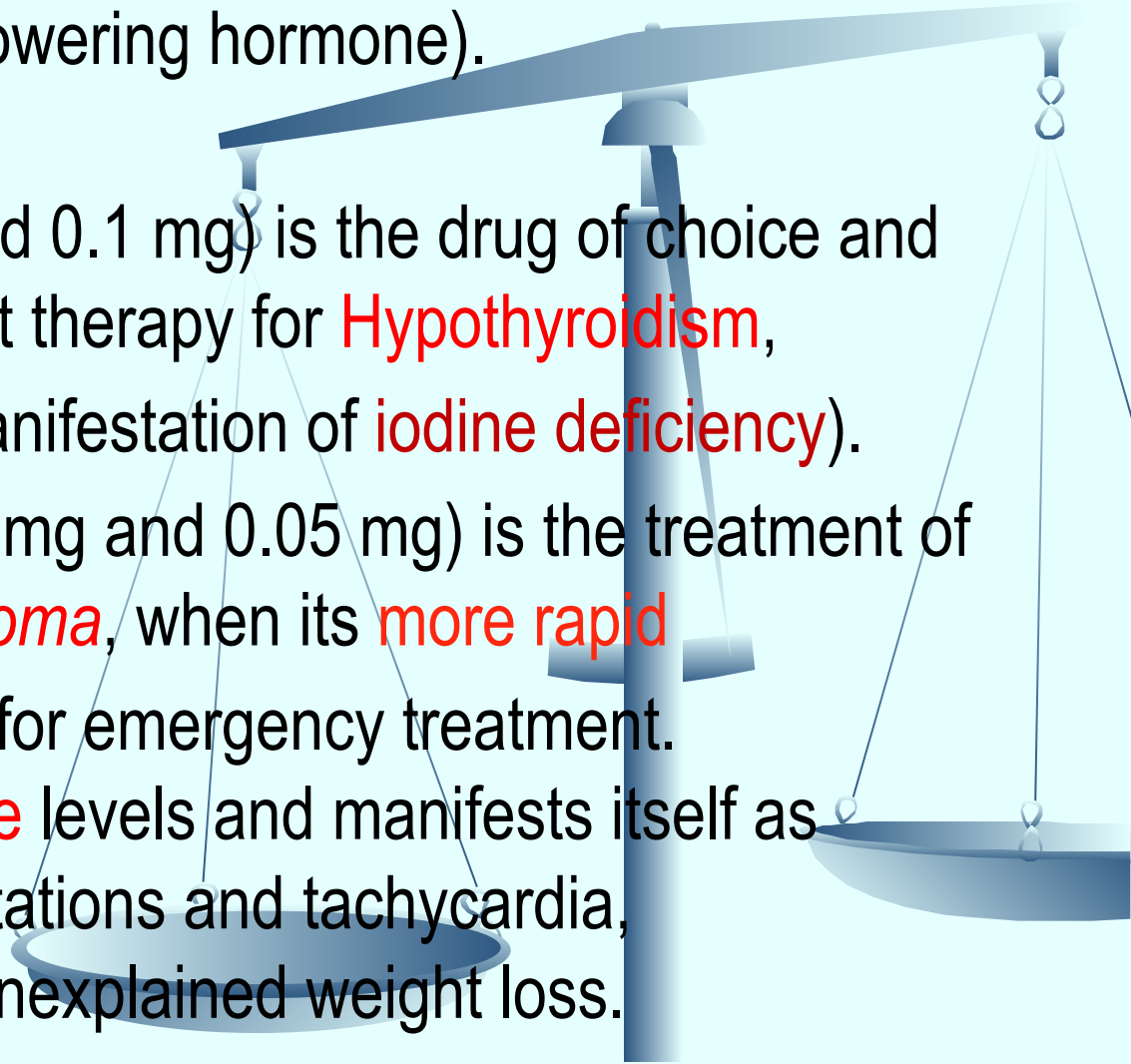


Thyroid Hormones:

Thyroxine (Tetraiodothyronine,T4 -contains 4 atoms of iodine)

Triiodothyronine (T3 - contains 3 atoms of iodine) is > potent and has a **more rapid onset** but **shorter duration** of action

Calcitonin (a plasma Ca^{2+} lowering hormone).



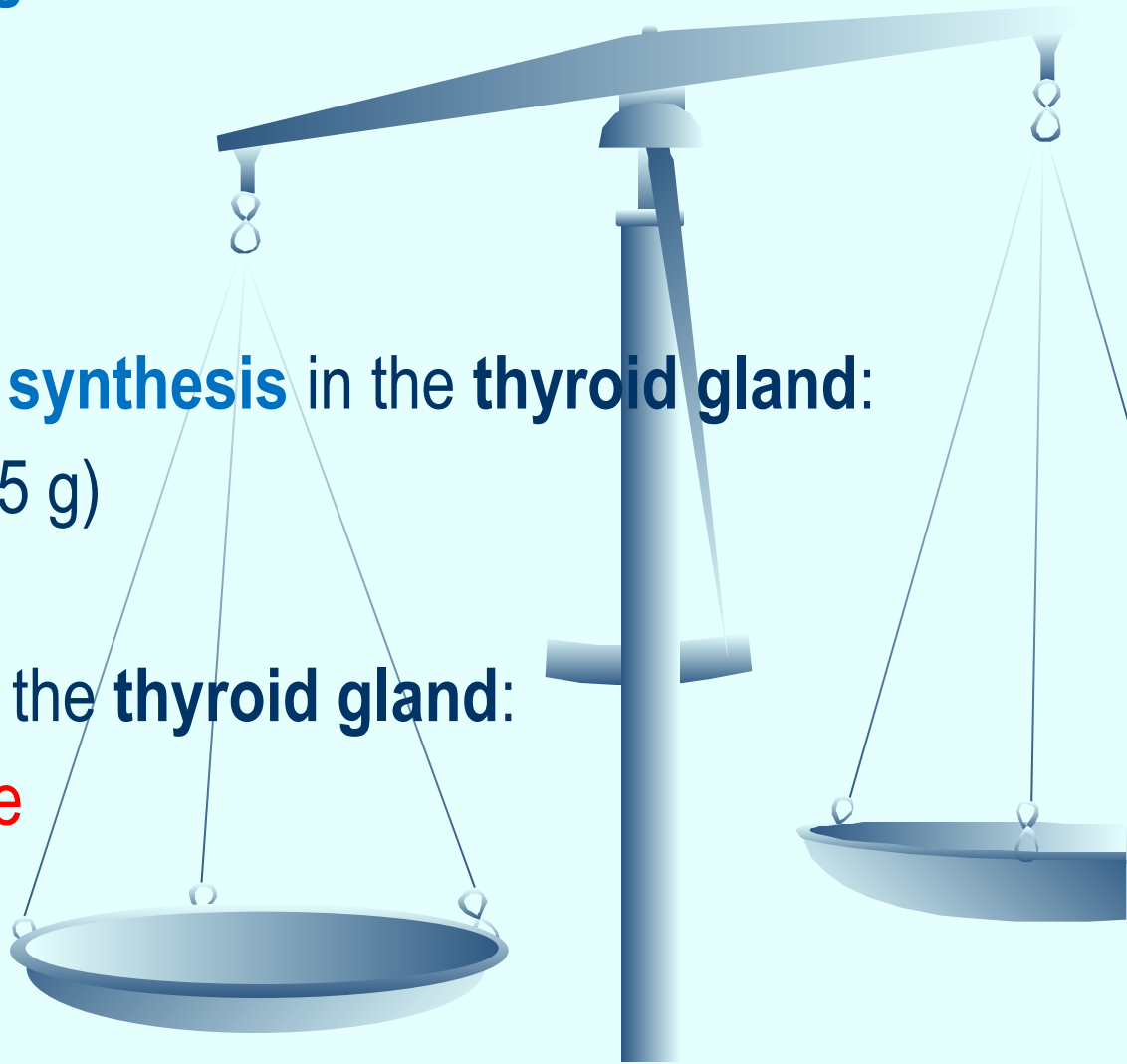
- **L-Thyroxin** (tab. 0.05 mg and 0.1 mg) is the drug of choice and the standard replacement therapy for Hypothyroidism, Endemic Goiter (a manifestation of iodine deficiency).
- **Triiodothyronine** (tab. 0.02 mg and 0.05 mg) is the treatment of choice for *myxoedema coma*, when its more rapid action is required for emergency treatment.

Toxicity is related to thyroxine levels and manifests itself as nervousness, heart palpitations and tachycardia, intolerance to heat and unexplained weight loss.

Antithyroid drugs:

are used to lower the functional capacity of the hyperactive thyroid gland and have the following directions of action:

- 1. Inhibit **thyroid-stimulating hormone secretion** by **anterior pituitary**:
  - Iodine
  - Diiodthyrosine
- 2. Inhibit **thyroid hormones synthesis** in the **thyroid gland**:
  - Mercazolyl (Tab. 0.005 g)
  - Propylthiouracil
- 3. Inhibit **iodine trapping** by the **thyroid gland**:
  - Potassium perchlorate
- 4. Destroy **thyroid tissue**:
  - Radioactive iodine



INSULIN PREPARATIONS

A. **Rapid Acting Insulin -** max effect per 1-4 hours

short duration of action 4-8 hours

- Regular **Insulin** - *vial* 5 and 10 ml – 40 U/ml
- **Insulin Lispro**
- **Actrapid -** *vial 10 ml - 40 and 100 IU/ml SC* or IV

B. **Intermediate Acting Insulin -** max effect per 6-12 hours

Intermediate duration of action 18- 24 hours

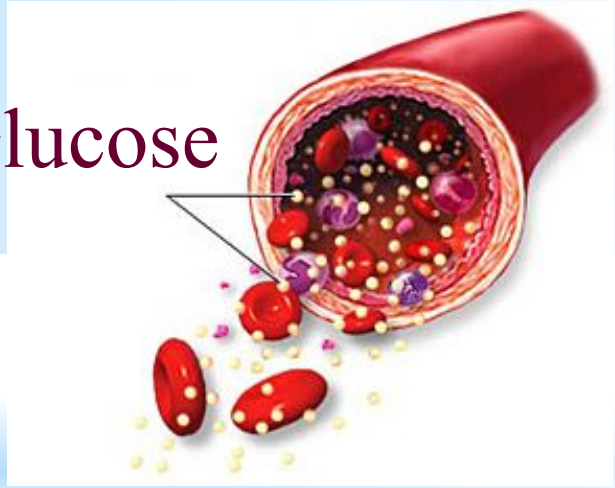
- **Semilente Insulin** suspension
- **Lente Insulin**: a mixture of 30% Semilente Insulin and 70% Ultralente Insulin

C. Prolonged acting insulin:

· Ultralente Insulin

max effect per 12-18 hours

prolong duration of action 24-40 hours



MECHANISM OF ACTION of INSULIN

- Insulin binds to receptor on the surface of its target cells.

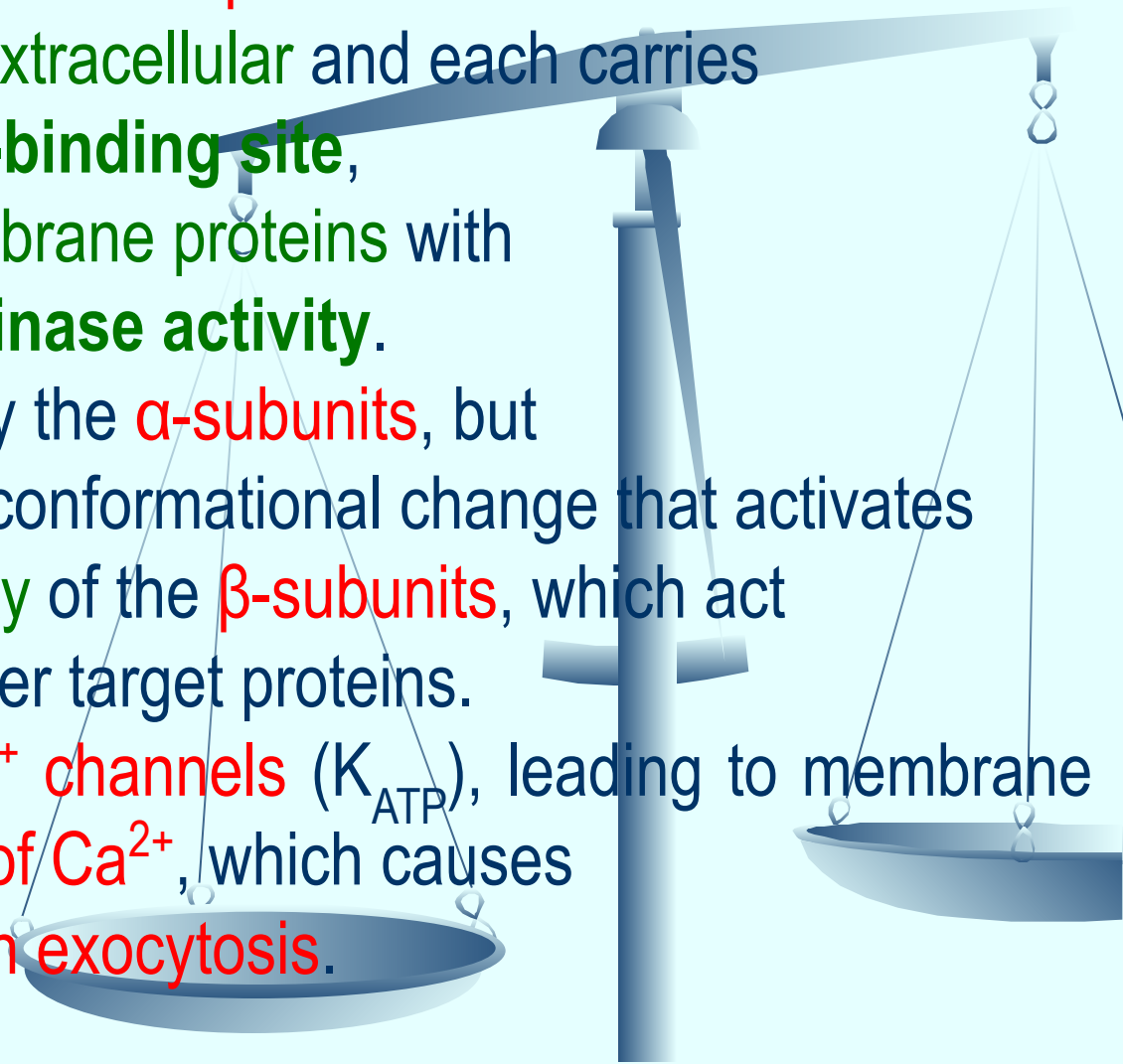
The receptor is a transmembrane glycoprotein complex consisting of two α- and two β-subunits.

The α-subunits are entirely extracellular and each carries an **insulin-binding site**,

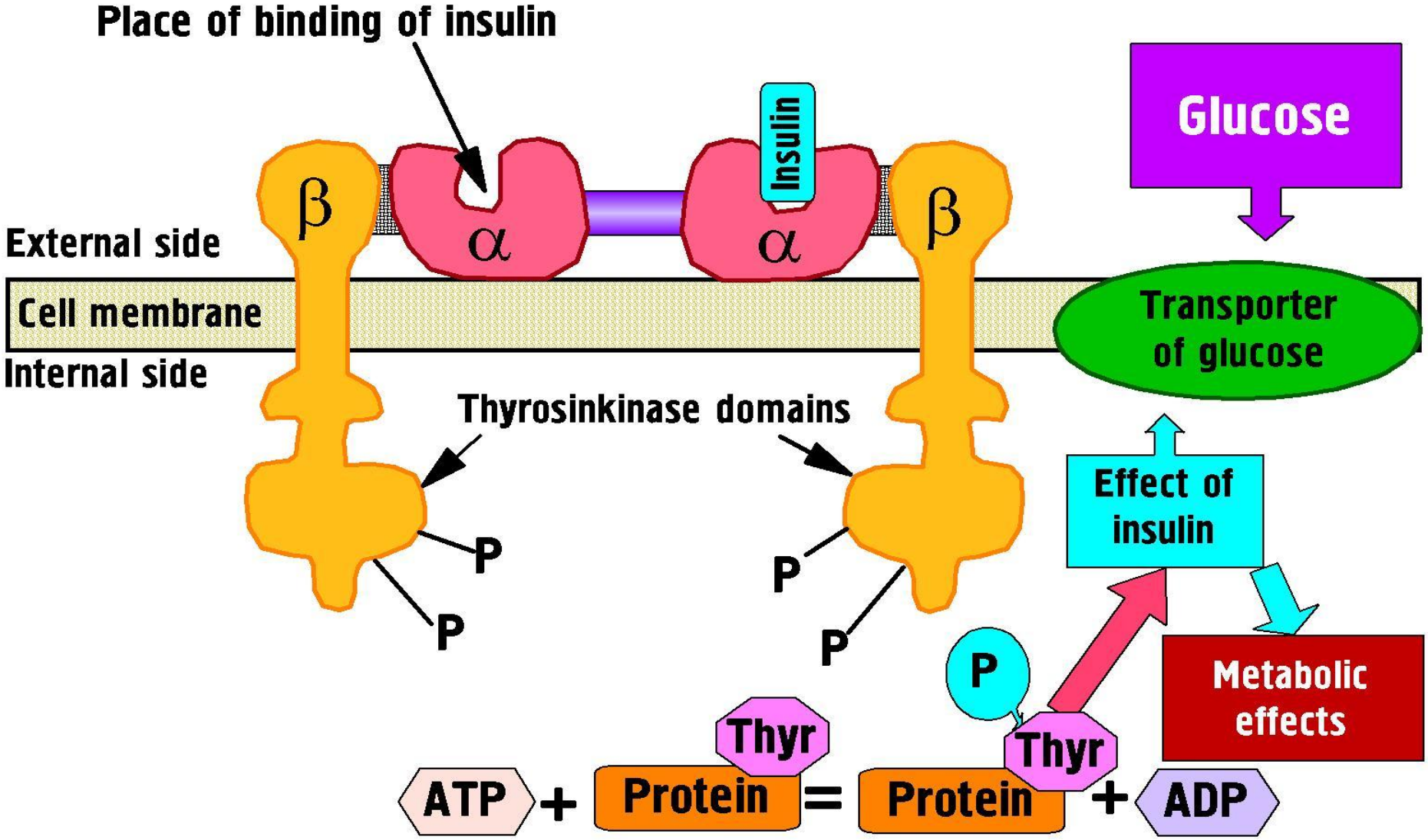
the β-subunits are transmembrane proteins with **tyrosine kinase activity**.

This activity is suppressed by the α-subunits, but insulin binding causes a conformational change that activates the *tyrosine kinase* activity of the β-subunits, which act on each other and on other target proteins.

ATP levels rise and block K^+ channels (K_{ATP}), leading to membrane depolarization and an influx of Ca^{2+}, which causes pulsatile insulin exocytosis.



Insulin - hormon of pancreatic β-cells



Types of glucose transporters

Trans-porters	Tissue	Glucose concentration (mmol/l)	Function
GLUT 1	All tissues, especially erythrocytes and brain.	1-2	Basal glucose capture and transport through hematoencephalic barrier.
GLUT 2	Pancreatic β-cells, liver, kidneys, intestine.	15-20	Regulation of insuline release, other aspects of insulin metabolism.
GLUT 3	Brain, kidneys, placenta and other tissues.	< 1	Glucose capture into neurones and the cells of other tissues.
GLUT 4	Muscles, fatty tissue.	5	Insuline-dependent glucose capture.
GLUT 5	Intestine, kidneys.	1-2	Absorbtion of fructose in intestine.

Insulin is a *fuel-storage* hormone and affects *cell growth* and *differentiation*.

Insulin ↓*Blood Glucose* by:

- Glucose uptake into *muscle* and *fat* via a transporter Glut-4
- Glycogen synthesis
- Glycogen breakdown
- Gluconeogenesis

Adrenaline Blood Glucose by:

- **Inhibiting Insulin Release** (via α_2-Receptors)
- **Promoting Glycogenolysis** (via β_2-Receptors in **Striated Muscle** and **liver**)

Somatostatin inhibits Insulin Release.

Actrapid (*vial 10 ml* : *40 and 100 IU/ml for SC* or IV) - is a fast acting **human insulin** produced in *Saccharomyces cerevisiae* by recombinant DNA technology. It may be used in combination with *intermediate* or *long-acting insulin*.

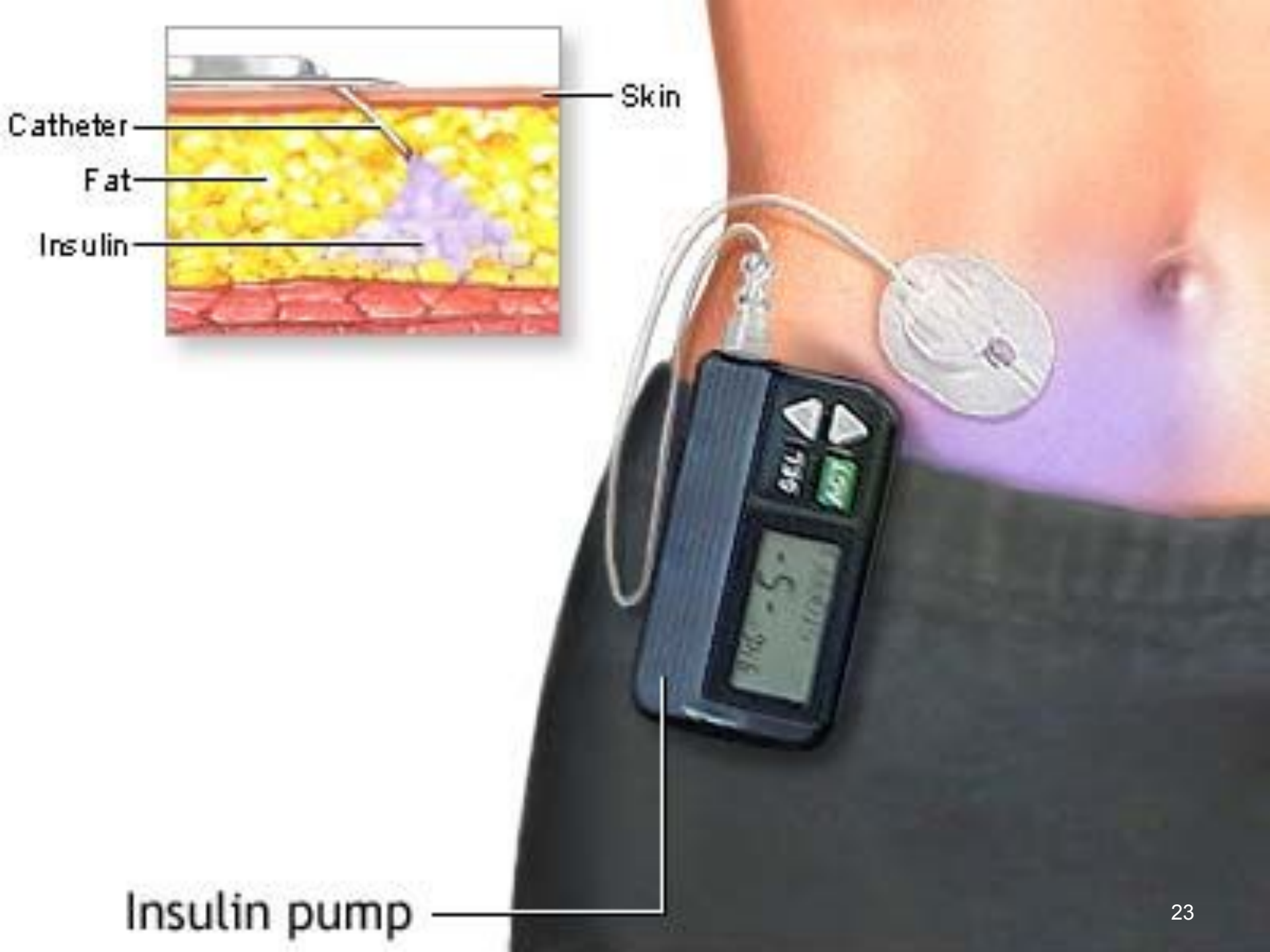
It is administered SC by injection in the abdominal wall, the thigh, the gluteal region or the deltoid region.

Injection into a lifted skin fold minimizes the risk of unintended IM injection. The needle should be kept under the skin for at least 6 sec to make sure the entire dose is injected.

Injection sites should always be **rotated** within the same region in order to reduce the risk of **lipodystrophy**.

SC injection into **the abdominal wall** ensures a faster absorption than other injection sites. The duration of action will vary according to the **dose**, **injection site**, **blood flow**, **temperature** and **level** of **physical activity**.

Insulin Pens


Skin
Catheter
Fat
Insulin
Insulin pump

Insulin Inhaling Device (Exubera)

CLINICAL USES of INSULIN:

Type 1 Diabetes:

- Diabetic Ketoacidosis
- Short-term treatment of patients with Type 2 diabetes during intercurrent events: Operations, Infections, AMI
- During pregnancy, for Gestational Diabetes not controlled by diet alone.

Emergency treatment of hyperkalaemia:

- insulin is given with glucose to lower extracellular K^+ via redistribution into cell

Oral *(Synthetic)* Hypoglycemic Agents:

I. Stimulators of insulin release by beta cells:

1. Sulfonylurea derivatives:

I. Generation – moderate duration of action (8-24 hours):

Butamide (*Tolbutamide*)

II Generation – Long duration of action (24-60 hours):

Chlorpropamide (*tab. 0.1 and 0.25 g*)

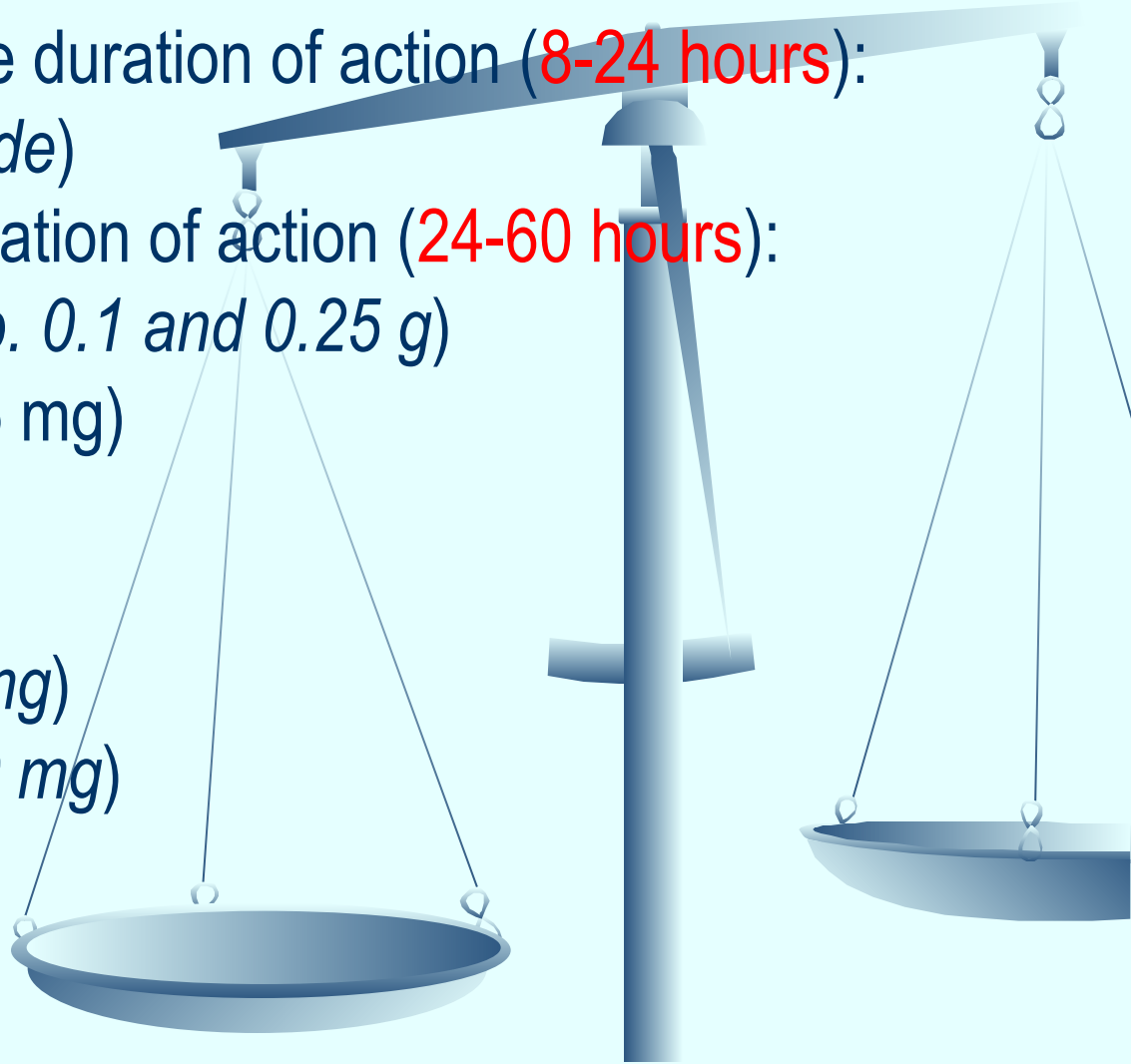
Glibenclamide (*tab.*5 mg)

Glipizide (*tab. 5 mg*)

2. Meglitinides:

Repaglinide (*tab. 1 mg*)

Nateglinide (*tab. 120 mg*)



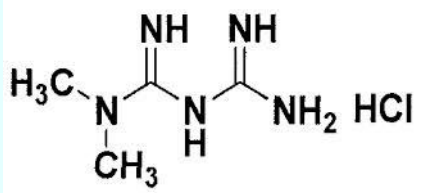
Repaglinide and **Nateglinide** are *non-sulfonylureas* meglitinides that lower blood sugar by stimulating pancreatic secretion of insulin.

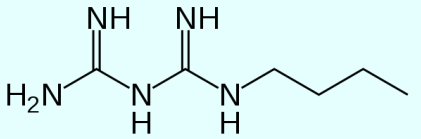
- can be used as monotherapy with diet and exercise or in combination with *Metformin*.
- well absorbed from the GIT; peak plasma level occurs within 1 hour.
- have a plasma half-life of 1–1.5 hours and are highly bound (>98%) to plasma proteins.

Image courtesy of: Novo Nordisk

Repaglinide (***NovoNorm***) is metabolized and removed from the bloodstream within **3–4 hours** after a dose, ***Nateglinide*** within **~6** hours. This decreases the workload of pancreatic β cells (i.e., decreases duration of β-cell stimulation), allows plasma insulin levels to return to normal before the next meal, and decreases risks of hypoglycemic episodes.

II. Inhibitors of hepatic gluconeogenesis:



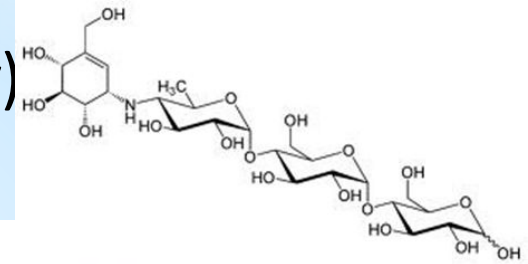


Biguanids: **Metformin** (*Tab 0.5 g*)

Buformin

- **Stimulate Anaerobic Glycolysis** in peripheral tissues
  - **Glucose Utilization**
  - **Gluconeogenesis** in the **liver**
  - **Glucose Absorption** from the **GIT**
- **Inhibit intestinal α-glucosidases**
  - **Enzyme degradation** of **di-, oligo-** and **polysaccharides** (***glycans***) to **monosaccharides**
    - Appetite
    - insulin resistance

III. Alfa-glucosidase inhibitor Acarbose (*Glucobay*)



inhibits **alpha-glucosidases** in the brush border of the small intestines and **pancreatic alpha-amylase**.

Pancreatic alfa-amilase hydrolyzes **complex starches** to **oligosaccharides** in the lumen of the small intestine.

The membrane-bound intestinal **α-glucosidases** hydrolyze **oligosaccharides**, **trisaccharides**, and **disaccharides** to **glucose** and other **monosaccharides** in the small intestine.

- ↓ **the rate of digestion** of **complex carbohydrates**.
- The **carbohydrates** are not broken down into glucose molecules.
- The long-term effect is a reduction in glycated Hb (Hb_{A1c}).

Side effects: diarrhea, flatulation.

Classification of Glucocorticoids:

1. Short-acting: Hydrocortisone acetate, Cortisone
2. Intermediate-acting: Prednisolone , Triamcinolone
3. Long-acting: Betametasone,

   Dexametasone
4. Ointments for local use - Fluorine-containing:

   Synaflan, Flumethasone
5. Aerosols or powders for inhalations:

   Beclometasone

   Fluticasone

Action on mediators of inflammatory and immune response:

GCs change Gene Expression:

- Production of prostanoids owing to Decreased Expression of COX-2
- Generation of cytokines –

IL 1-6, IL-8, TNF-α and cell adhesion factor – through inhibition of transcription of the relevant genes

- Complement components in the plasma
- Generation of induced NO
- Histamine release from basophils
- IgG production.

Clinical uses of Glucocorticoids:

1. Replacement therapy for patients with adrenal failure -

Addison's disease

2. Anti-Inflammatory Immunosuppressive Therapy:

- Asthma
- Inflammatory conditions of skin, eye, ear or nose:

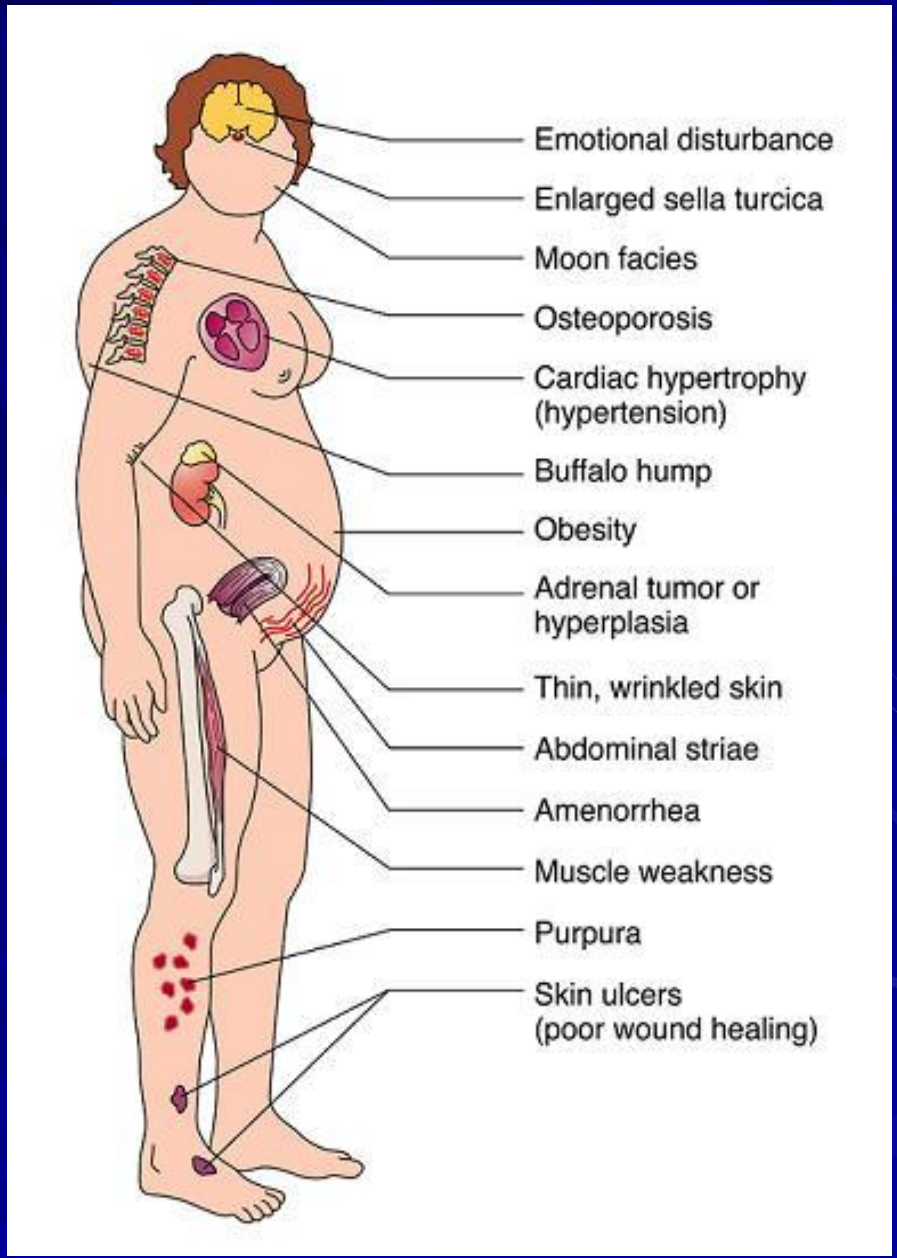
  Eczema, Allergic Conjunctivitis or Rhinitis – topically
- Hypersensitivity States: Severe Allergic Reactions – IV

3. In neoplastic diseases:

- In combination with Cytotoxic Drugs as a component of Antiemetic Treatment in the treatment of Specific Malignancies

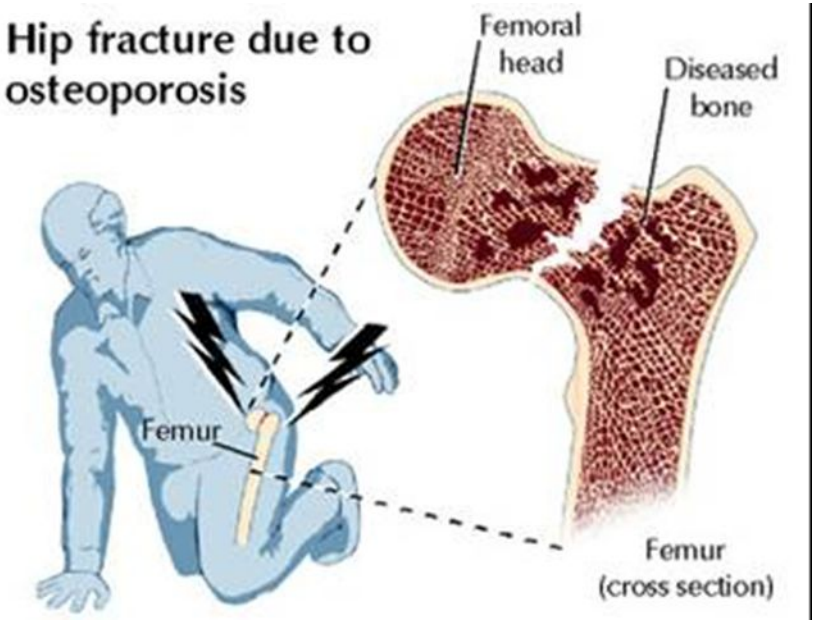
Adverse effects: *Cushing's* syndrome:

- Moon face, with red cheeks
- Thin arms and legs: muscle wasting
- BP, Itracranial Hypertension
- Osteoporosis
- Cataracts
- Thinning of skin
- Increased abdominal fat
- Buffalo hump
- Euphoria
- Depression or emotional lability
- Avascular necrosis of femoral head
- Appetite, Obesity, Hyperglycemia



Mineralocorticoids' drugs

- Mineralocorticoids' drugs - Desoxycorticosterone acetate, Desoxycorticosterone trimethylacetate, Fluorhydrocortisone acetate.
- Antagonists of mineralocorticoids:
  - Inhibitors of synthesis - Metyrapone.
  - Tissue receptors blockers - Spironolactone.



OESTROGENS

- Natural:

  Estradiol - amp 0.1%-1 ml

  Estriol - Tab 1 mg
- Synthetic:

  Ethinylestradiol - Tab 0,01 mg

  Synoestrol Tab 1 mg, amp 0.1% - 1 ml

  Mestranol

CLINICAL USEs of OESTROGENS:

- Replacement therapy:
  - Primary Ovarian Failure
    (e.g., *Turner's* syndrome)
  - Secondary Ovarian Failure
    (Menopausal)
- Contraception
- Prostate and Breast Cancer

ANTIOESTROGENS

- *Clomiphene* - Tab. 50 mg
- *Tamoxifen* - Tab. 20 mg

Clomiphene:

Interfering with the Negative Feedback of oestrogens on the hypothalamus and pituitary

=> ↓Secretion of Gn-RH

↓Secretion of Gonadotropins

=> a Stimulation of Ovulation

Clinical use:

- Infertility with Anovulatory Cycles
- Breast Tumors

PROGESTOGENS

1. The naturally occurring hormone and its derivatives:
   - Progesteron amp. 1% - 1 ml of oil solution
   - Oxyprogesterone Caproate amp. 25% - 1 ml
   - Pregnin Tab. 0.01
2. Testosterone derivatives:
   - Norethisterone Tab. 5 mg
   - Norgestrel
   - Desogestrel
   - Gestodene

CLINICAL USE of PROGESTOGENS

- 1. CONTRACEPTION:
  - combined oral contraceptive pill
  - as progesterone-only contraceptive pill
  - as injectable or implantable progesterone-only contraception
- 2. Replacement therapy
- 3. Dysfunctional uterine bleeding, dysmenorrhea, suppression of postpartum lactation, endometriosis
- 4. Endometrial carcinomas

Hormonal contraceptives

- **Oral contraceptives:**
  - **Combinations of estrogens and progestins:**
    - **Monophasic combination tablets** - Rigevidon, Minisiston, Marvelon
    - **Biphasic combination tablets** - Anteovin
    - **Triphasic combination tablets** - Triquilar, Trisiston, Tri-regol
  - **Agents containing microdoses of progestins** - Levonorgestrel *[Microlut]*, Lynestrenol *[Exluton]*, Norethisterone *[Norcolut]*.
  - **Postcoital contraceptives** - Levonorgestrel *[Postinor]*.
- **Parenteral contraceptives** - Medroxyprogesterone acetate *[Depo-Provera]*.
- **Implantable contraceptives** - Levonorgestrel *[Norplant system]*.

Masculine gonadal hormones

→ **Drugs with androgen activity:**

- Natural hormones - Testosterone (propionate, enanthate, cypionate).
- Synthetic analogues - Methyltestosterone, Drostanolone, Mesterolone.

→ **Antiandrogens:**

► **Androgen receptors inhibitors:**

- Steroid compounds - Cyprosterone acetate.
- Non-steroid compounds (carboxyanilide derivatives) - Flutamide, Bicalutamide,

► **Inhibitors of synthesis:**

- 5α-reductase inhibitors - Finasteride, Anastrozole, Letrozole.

→ **Anabolic steroides:**

- Phenobolin *[Nadrolone phenpropionate]*, Retabolil *[Nadrolone decanoate]*, Methandrostenolone


Thank you for attention!