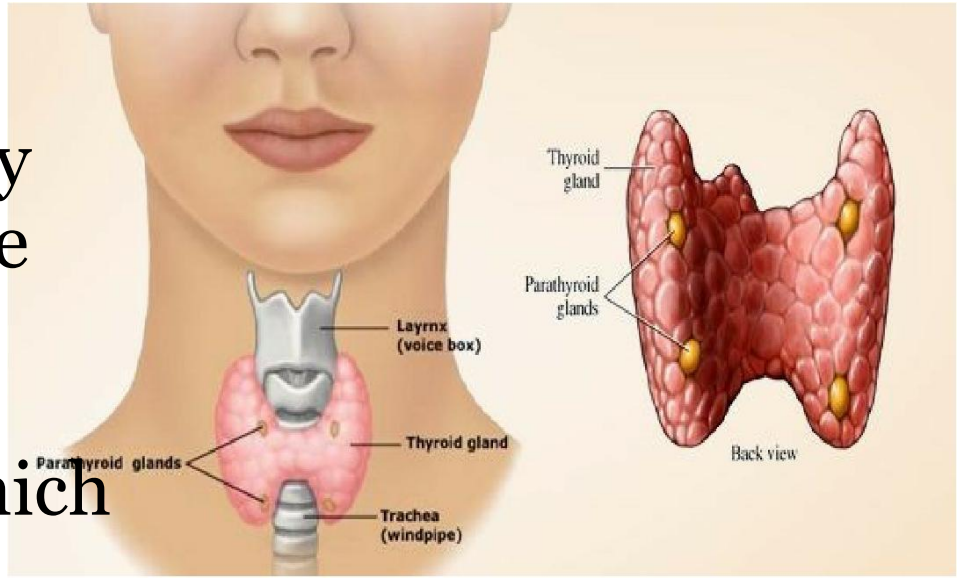
Endocrine Pharmacology

Drugs Acting on Thyroid Gland

Dr. Zena Sattam

Thyroid gland

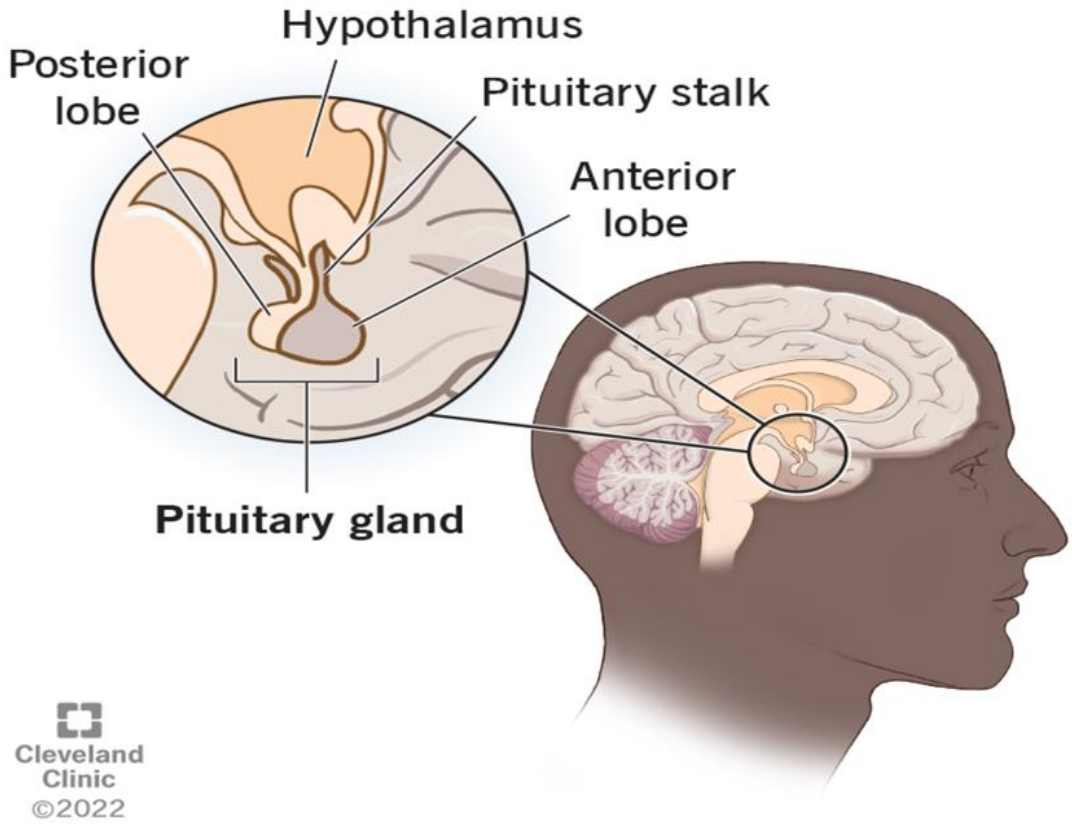
- Iodine being picked up by thyroid and used to make the thyroid hormones, thyroxin (T4) and triiodothyronine (T3) which stored in thyroid gland.



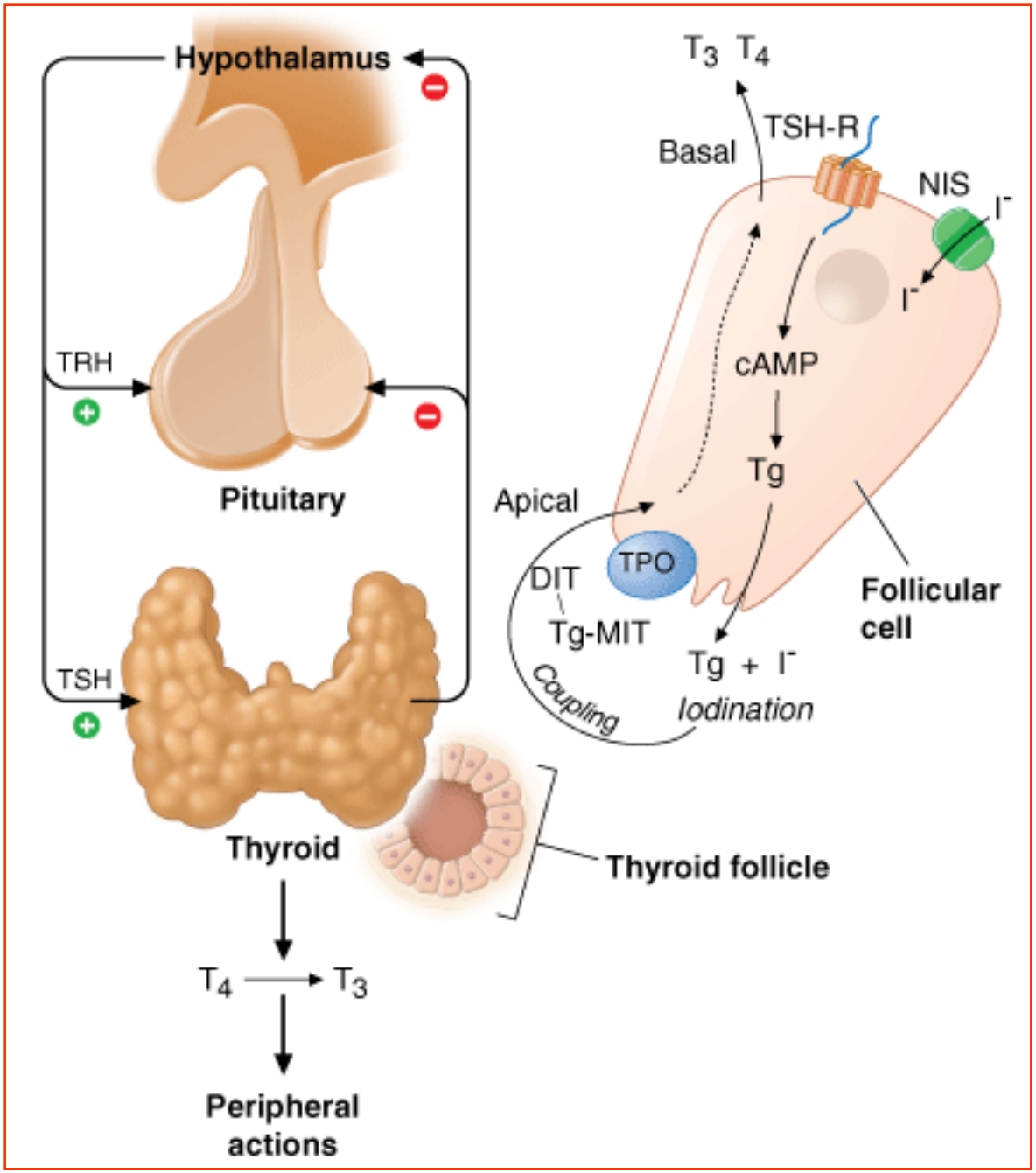
Thyroid gland

- T4 when reaches the site of action it converted to T3 which binds to the receptor on the cell surface and increase glucose metabolism in cells.
- Inside the cell, T3 binds to other receptors to generate energy and new proteins.

Pituitary Gland



Regulation of thyroid Hormone synthesis



Regulation of thyroid hormone synthesis. TG -thyroglobulin; TSH-R -thyroid-stimulating hormone receptor; TPO -thyroid peroxidase; MIT -monoiodotyrosine; DIT -diiodotyrosine; I -iodide; TRH -thyrotropin-releasing hormone; TSH -thyroid-stimulating hormone

Hypothyroidism (thyroid deficiency).

Can be treated by either increasing iodine in the diet or with T3 or T4 administration.

Levothyroxine (T4)

- To treat hypothyroidism.
- Oral tablets but full affect not seen for about 10 days.
- Large doses may produce symptoms of thyrotoxciosis including: weight loss, tachycardia, nervousness and tremors.

Liothyronine (T3)

- Same action to thyroxine but faster onset of action.
- The maximum effect after 3 days.

Nursing Implementation

- Administer a single daily dose before breakfast each day to ensure consistent therapeutic levels.
- Administer with a full glass of water to prevent difficulty of swallowing and esophageal atresia.
- Because thyroid hormones serve to increase heart rate, T4, the inactive form, is typically administered to older patients who have an increased risk for heart attack on account of their age. Synthetic T3 is reserved for younger patients, who do not have a history of heart problems.

Drugs for Hyperthyroidism

1- Radio-iodine (I-131):

- Orally, rapidly absorbed.
- Used for diagnostic purposes.
- Used to destroy malignant cells in carcinoma of thyroid glands.

2- Carbimazole , Methimazole, propylthiouracil (PTU)

- These drugs inhibit thyroid hormone production by preventing the conversion of T4 to T3 in tissues.
- Side effects: rashes, joint pain, fever, enlargement of lymph nodes.

3- beta-blockers: (e.g. Propranolol)

- Relive symptoms of thyrotoxciosis resulting from over activity of thyroid gland.
- Reduce conversion of T4 to T3 in tissues.

Nursing Implementation

-Administer **PTU** three times a day to ensure consistent therapeutic levels.

-Give **iodine** solution through a straw to decrease staining of teeth.

-**Carbimazole** cross the placental barrier & are concentrated by the fetal thyroid (caution in pregnancy)

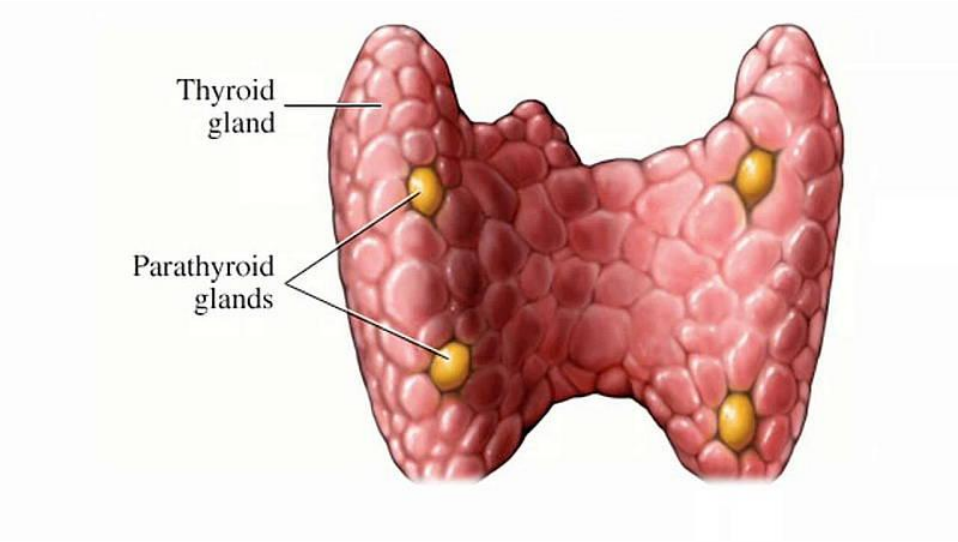
-**Methimazole** associated with congenital malformations

-Propylthiouracil is **preferable in pregnancy**

Endocrine Pharmacology

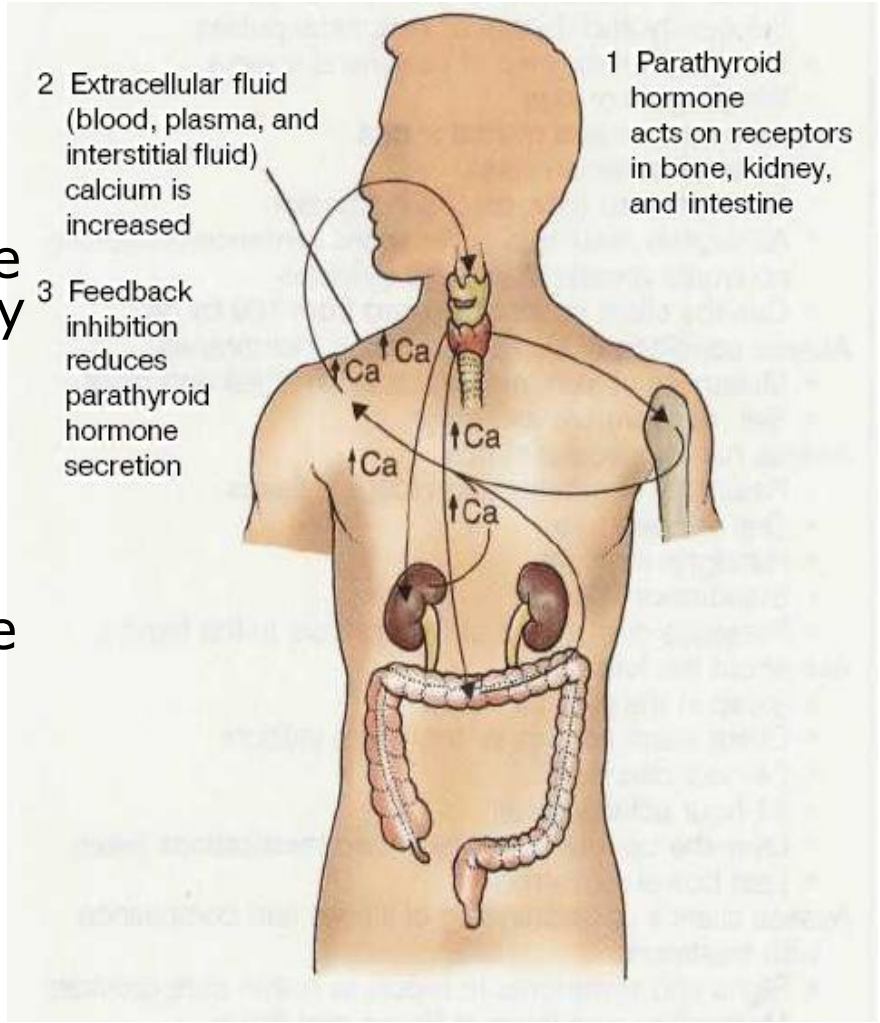
Drugs Acting on ParaThyroid Gland

Dr. Zena Sattam



Hyperparathyroidism

- The parathyroid glands maintain calcium and phosphate balance.
- Increased levels of parathyroid hormone (PTH) act directly on the kidney, causing **increased** kidney reabsorption of calcium and increased phosphate excretion.
- These processes cause **hypercalcemia** (excessive calcium) and **hypophosphatemia** (inadequate phosphate) in the patient with hyperparathyroidism.
- High levels of PTH cause renal calculi (kidney stones) and nephrocalcinosis (deposits of calcium in the soft tissue of the kidney).



Hypoparathyroidism is an uncommon endocrine disorder in which parathyroid function is decreased. Problems are directly related to a lack of parathyroid hormone (PTH) secretion or to decreased effectiveness of PTH on target tissue, the result is **hypocalcemia**.

Treatment of Hyperparathyroidism

Nonsurgical management

Diuretic and fluid therapy.

- The most common therapy for reducing serum calcium levels in patients who are not candidates for surgery is **hydration and furosemide**, a diuretic that increases kidney excretion of calcium.
- **IV saline** in large volumes also promotes renal calcium excretion.

Drug therapy.

- ***Phosphates***. Oral phosphates inhibit calcium absorption.
- ***Calcitonin***. Calcitonin decreases skeletal calcium release and increases the kidney excretion of calcium. Calcitonin is not effective when used alone because of its short duration of action. Its therapeutic effects are greatly enhanced if given in conjunction **with glucocorticoids**

Nursing implementation

- ✓ The nurse monitors cardiac function and intake and output every 2 to 4 hours during hydration therapy. Continuous cardiac monitoring may be required.
- ✓ The nurse closely monitors serum calcium levels and immediately reports any precipitous drop to the physician. Sudden drops in calcium levels may cause tingling and numbness in the muscle

Treatment of Hypoparathyroidism

- The patient is instructed to eat foods high in calcium but low in phosphorus.
- Milk, yogurt, and processed cheeses are avoided because of their high phosphorus content.

Nursing implementation

- ✓ The nurse stresses that therapy for hypocalcemia is lifelong. With adherence to the prescribed drug and diet regimen, the calcium level usually remains high enough to prevent a hypocalcemic crisis.

Endocrine Pharmacology

Drugs Acting on Pancreas

Dr. Zena Sattam

Introduction:

The disease is characterized by an absolute deficiency of insulin due to:

- Destruction of β cells.
- Loss of β-cell function. Results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins.

Classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss).

Type 1 diabetics require exogenous insulin to avoid severe hyperglycemia and the life-threatening catabolic state of ketoacidosis.

Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance.

Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin. The pancreas retains some β-cell function, but insulin secretion is insufficient to maintain glucose homeostasis.

- When blood glucose rises this will lead to release insulin from the **β-cells** in the pancreas which causes glucose to be taken up into the tissues, where it converted into energy stored as liver glycogen and fat or used to generate metabolic energy.
- **Insulin** is the **only** endocrine hormone which is hypoglycemic, the others like (glucagon, glucocorticoids and thyroid hormones are all hyperglycemic.

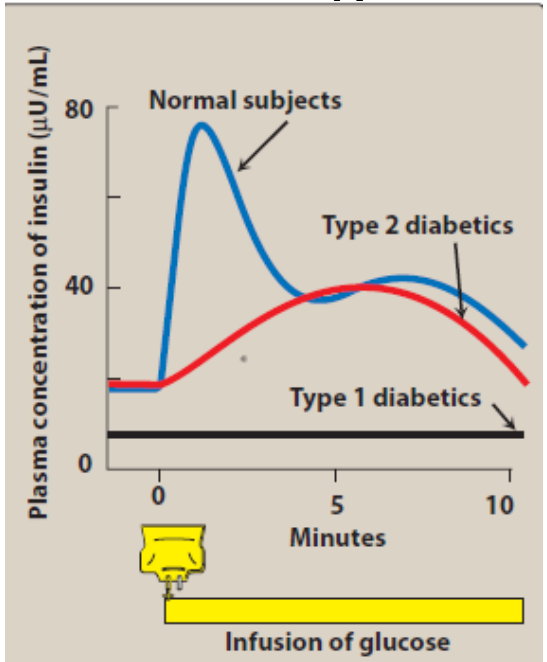
What insulin do to the body?

- Stimulate the uptake of glucose by the tissues.
- Convert glucose to glycogen in the liver.
- Increase the production of fat and protein.

Insulin: is a polypeptide hormone undergoes proteolytic cleavage to form *insulin* and C-peptide. *Insulin* secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators.

Human *insulin* is produced by recombinant DNA technology using strains of Escherichia coli.

Insulin* preparations** vary primarily in their onset and duration of activity. For example, ***insulin lispro, aspart, and ***glulisine*** have a faster onset and shorter duration of action than ***regular insulin.***



Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various *insulin* preparations.

Side effects:

Hypoglycemia
weight gain,
lipodystrophy

What the mechanism of action of insulin?

- **Insulin binds to a specific receptor on cell membranes** and this triggers the cell's response:
- An important response is the transport of glucose and other sugars away from the blood into the cell. Glucose transported to cells by glucose transporters where the **insulin increase the activity of these transporters.**

Diabetes Mellitus:

- Is a disorder in which blood level of glucose is abnormally high because: **the body doesn't release or use insulin properly.**

<u>Types of DM:</u>

1- Insulin-dependent DM (type1) (The only treatment is the insulin).

2- Non-insulin-dependent DM (type2)

Treatment of type1:

1-Short-acting insulin (soluble insulin) (Actrapid®), (Humulin-R®):

- This insulin available as suitable for **I.V** injection.
- Use to treat diabetic coma or in severe illness in diabetic patients.
- Can be given **S.C** and it started after 30 min and up to 8 hours
- But as I.V it's action start rapid but lasts up to 30 min.

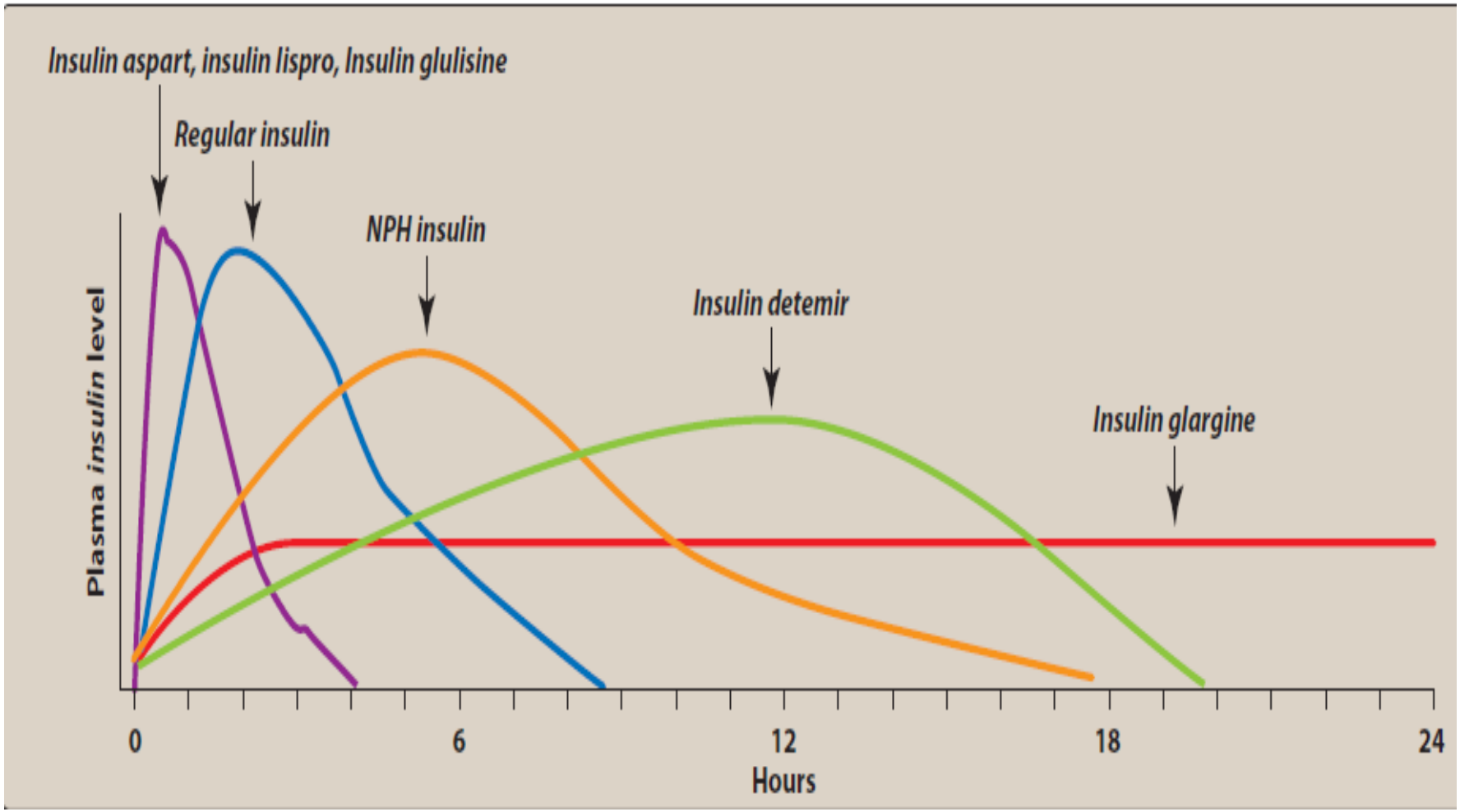
2- Intermediate-acting insulin: Biphasic isophane-insulin:

- Consist of insulin mixed with isophane.
- Example: Human Mixtard.

3- Long-acting insulin:

- Protamine-Zinc insulin
- Produced by adding zinc and protamine to insulin and it action starts after 6 hours and lasts for 24-30 hour.
- Once daily dose.

Types of Insulin preparations



NPH= neutral protamine Hagedorn

1. **Rapid- or short-acting insulins** are administered to mimic the prandial (mealtime) release of *insulin* and to control postprandial glucose.

Regular insulin should be injected subcutaneously 30 minutes before a meal, and it is **a short-acting**, soluble, crystalline zinc insulin.

Whereas **rapid-acting insulins** are administered in the 15 minutes proceeding a meal or within 15 to 20 minutes after starting a meal. Like: **insulin lispro, aspart, and glulisine.**

2. Intermediate-acting insulin :

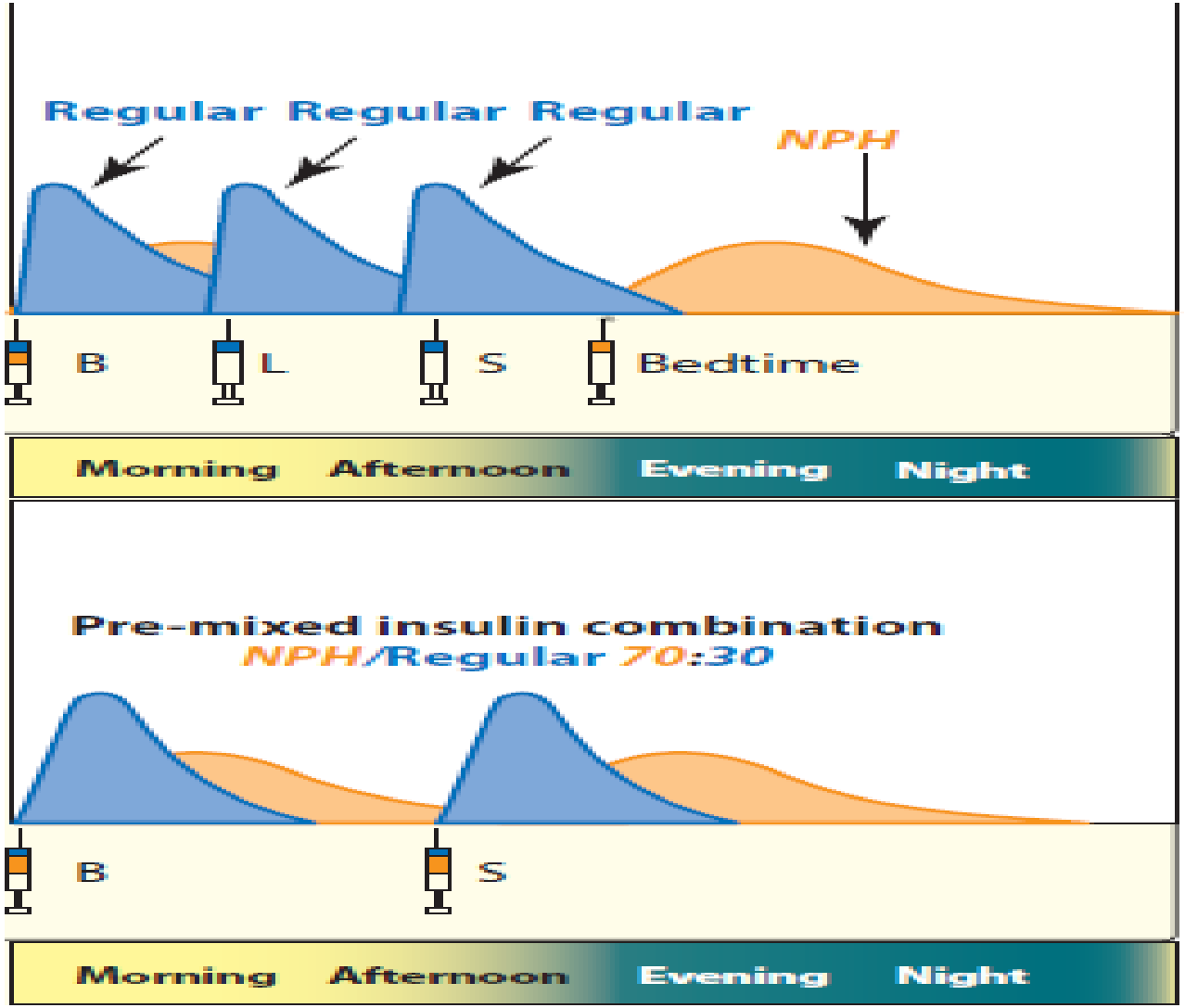
Neutral protamine Hagedorn –NPH-
insulin is used for: **#-** basal (fasting) control in type 1 or 2 diabetes and **#-** is usually given along with rapid- or short-acting *insulin* for mealtime control. *NPH insulin* should be given only subcutaneously (**never IV**), not be used in emergency e.g. diabetic ketoacidosis

3. Long-acting insulin preparations

insulin glargine form a precipitate at the injection site, releases *insulin* over an extended period. It has a slower onset than *NPH insulin* and a flat, prolonged hypoglycemic effect with no peak

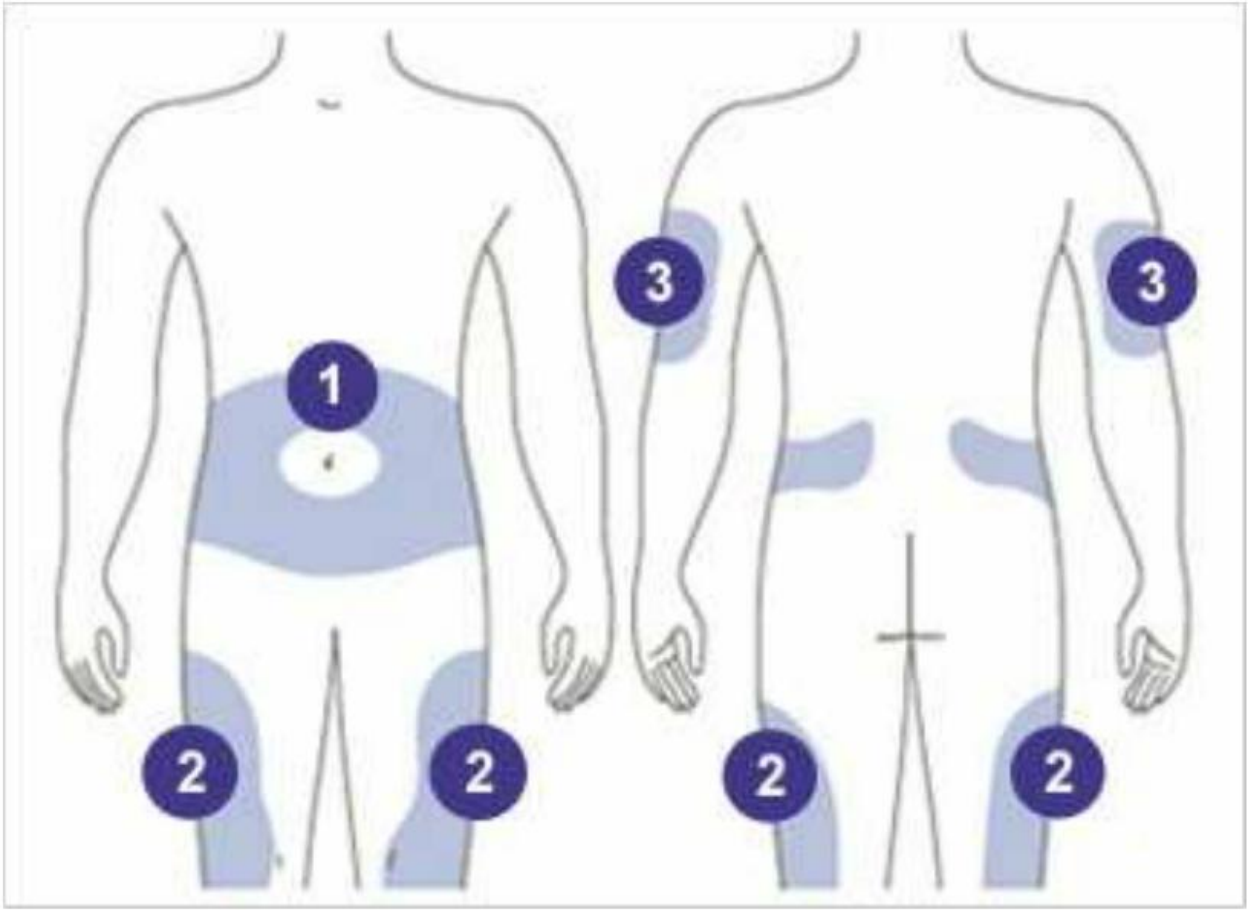
Insulin detemir

used for basal control and should only be administered subcutaneously. Neither long-acting *insulin* should be mixed in the same syringe with other insulins



Examples of regimens that provide both prandial and basal *insulin* replacement.

Sites of injection



Signs and symptoms of hypoglycemia

- Faintness
- Dizziness
- Tremor
- Sweating
- Convulsions
- If not treated → coma occur

SYNTHETIC AMYLIN ANALOG:

Amylin is a hormone that is co-secreted with insulin from β cells following food intake. It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety.
(Pramlintide) is a synthetic amylin analog By subcutaneous injection immediately prior to meals

INCRETIN MIMETICS:

The incretin effect occurs because the gut releases **incretin hormones**, they are responsible for 60% to 70% of postprandial insulin secretion.
(Exenatide) injectable incretin mimetics used for the treatment of type 2 diabetes. Administered subcutaneously.
Side effects include: consist of nausea, vomiting, diarrhea, and constipation.

Treatment of type 2 oral hypoglycemic agents

A. **Sulphonylureas:** Glibenclamid (Daonil®), Gliclazide (Diamicron®), Glipizide.

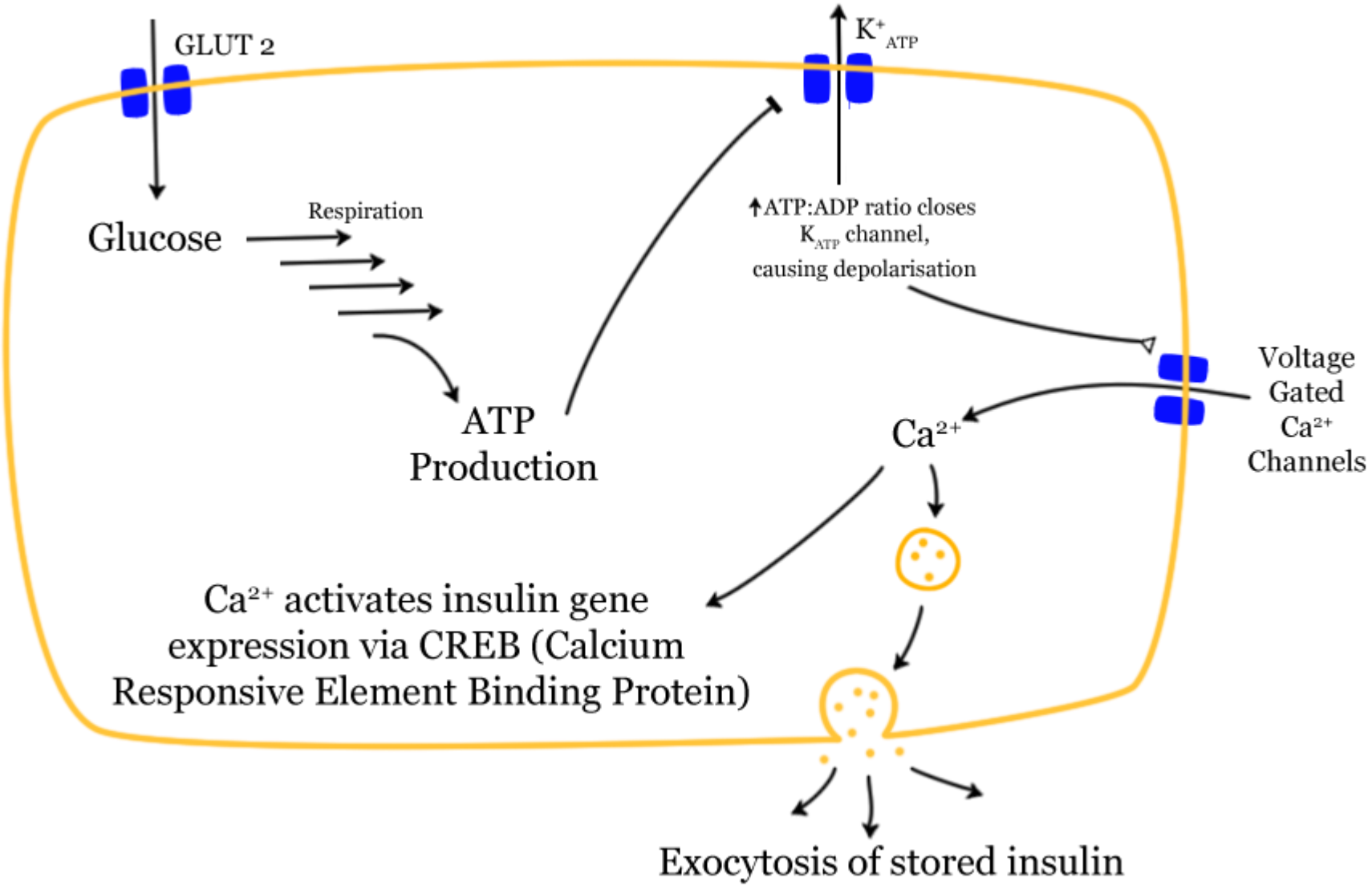
Actions:

- Lowers blood glucose by increasing insulin production by the pancreas and by increasing the sensitivity of cells to insulin.
- All drugs of this class given orally. Mostly used once or twice daily. It effect last for about 24 hours.

Side effects:

- hypoglycemic episodes
- Increase weight gain

Regulation of insulin release



B. biguanides: Metformin (Glucophage®):

Actions of metformin:

- It reduces glucose absorptions from gut.
- Inhibit gluconeogenesis. Reduce glucose release from liver
- Stimulate glucose uptake by the muscle.
- Don't cause weight gain.
- **Side effects:**

  GIT upset

C- Glinides stimulate *insulin* secretion. They bind to a distinct site on the β cell, closing ATP-sensitive K_+ channels example : *repaglinide.*

D- Thiazolidinediones are also *insulin* sensitizers. The two members of this class are *pioglitazone* and *rosiglitazone* do not promote its release from the β cells, so hyperinsulinemia is not a risk. Acting as agonists for (PPARγ) receptors.

E- α-Glucosidase inhibitors *Acarbose* [AY-car-bose] and *miglitol* [MIG-li-tol] are oral agents used for the treatment of type 2 diabetes.

α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed.

Side effects: flatulence, diarrhea, and abdominal cramping

F- Dipeptidyl peptidase-4 inhibitors *saxagliptin, sitagliptin* are orally active dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.
These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones

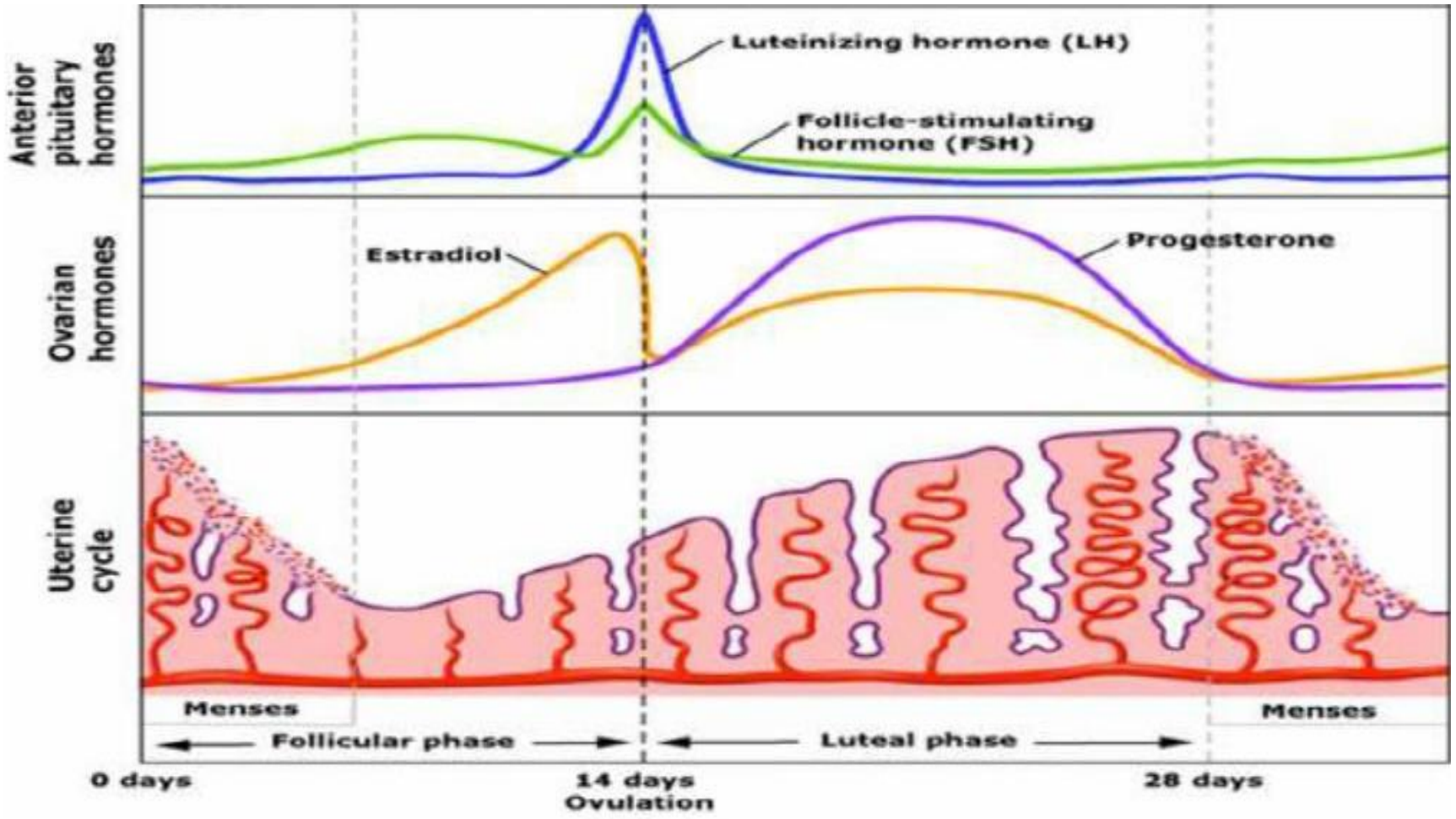
G- Sodium–glucose cotransporter-2 inhibitors *Canagliflozin* these agents decrease reabsorption of glucose, increase urinary glucose excretion,
and lower blood glucose:
causes osmotic diuresis therefore, may reduce systolic blood pressure, urinary tract infections, and urinary frequency.

Nursing Implementation:

- Insulin should not be allowed to freeze or be heated above 37°C, therefore its stored in refrigerator.
- Once opened, bottle is discarded in 30 days. After 30 days contents may not be sterile, microbes may grow in bottle.
- Having cold insulin injected is uncomfortable, therefore the patient may keep insulin at room temperature (20°-25°C). Insulin loses potency if kept above room temperature.

The menstrual cycle with plasma levels of pituitary and ovarian hormones

Dr. Zena Sattam



Pharmacological action of Estrogens:

- Required for normal sexual maturation & growth of female.
- ↓ rate of resorption of bone by antagonizing effects of parathyroid hormone, Epiphysial closure of long bones at puberty
- Distribution of body fat alteration to produce typical female body shape.
- Stimulate adipose tissue production, ↑Plasma triglyceride levels.
- ↑ in high density lipoproteins (HDL) ↓ in low-density lipoproteins (LDL), ↓ in total plasma cholesterol levels.
- ↓ Platelet adhesiveness.

Estrogen

- The potent estrogen produced by the ovary is ***Estradiol*.**
- Synthetic estrogens is ***ethinyl estradiol***
- ***tamoxifen*** and ***raloxifene:*** selective estrogen receptor modulators (SERMs). bind to estrogen receptors and exert either estrogenic or antiestrogenic effects.

Estrogen therapy

- The primary indication for menopausal symptoms such as hot flashes.
- **Contraception:** The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.
- Stimulate development of secondary sex characteristics.

Side Effects of estrogen

- Nausea and breast tenderness are among the most common adverse effect.
- The risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is Increased with use of estrogen therapy.
- Note: The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.

Tamoxifen

- ***Tamoxifen*** is currently used in the treatment of metastatic breast cancer, or as adjuvant therapy following mastectomy or radiation for breast cancer.
- It Compete with estrogen for binding to the estrogen receptor in breast tissue.
- Note: Normal breast growth is stimulated by estrogens. Therefore, some breast tumors regress following treatment with these agents.

Raloxifene

- ***Raloxifene*** acts as an estrogen agonist in bone, leading to decreased bone resorption. It is also approved for the prevention and treatment of osteoporosis in postmenopausal women
- It does not have estrogen receptor agonist activity in the endometrium and, therefore, does not predispose to endometrial cancer.
- It also lowers serum total cholesterol and low-density lipoprotein (LDL)

Clomiphene

- ***Clomiphene*** acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus.
- This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.
- *Clomiphene* is useful for the treatment of infertility associated with anovulatory cycles.

Anti-estrogens

Selective estrogen receptor modulators (SERMs)

- **Raloxifene:** Used in post-menopausal osteoporosis
- **Clomiphene:** Used in treatment of infertility due to ovulation failure
- **Tamoxifen:** Act as an antagonist on breast cells and so can be used in treatment of advanced breast cancer in postmenopausal patients.

Aromatase Inhibitors e.g Anastrozole

- Selective inhibitor of aromatase enzyme
- Decrease estrogen synthesis, used in treatment of breast cancer in post menopausal patients resistant to tamoxifen.

PROGESTOGENS

- ***Progesterone*** promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo.
- The high levels of *progesterone* that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation.
- *E.g. norethindrone*, *norethindrone acetate*, *norgestrel*, *levonorgestrel*)

Uses of Progesterone

- Hormone replacement therapy &hormonal contraception.
- Dysmenorrhea, endometriosis & bleeding disorders

Anti-progestin (Mifepristone)

- Binds strongly to progesterone receptor & inhibits activity of progesterone.
- Major use terminate early pregnancies due to interference with the progesterone needed to maintain pregnancy.
- used in treatment of endometriosis, breast cancer & other neoplasms that contain glucocorticoid or progesterone receptors.

Contraceptives

Hormonal Contraceptives

- Hormonal preparations used for reversible suppression of fertility & inhibits activity of estrogen and progesterone
- They can be used in improvement of menstrual cycle regularity, decrease risk of endometriosis and management of perimenopause.

Oral contraceptive pills (Combined pills)

- Combined pills are taken for 21 consecutive days followed by 7 pill free days causing a withdrawal bleed

Progestin-only pills:

- used for patients who are breast-feeding

Adverse effects of Oral contraceptive:

1. Weight gain (due to fluid retention or anabolic effect)
2. Nausea, depression, dizziness and irritability
3. Acne or increased pigmentation.
4. Thromboembolism and hypertension

Injectable contraceptives: Given i.m as oily solution

- Depot medroxyprogesterone acetate (DMPA) 150 mg at 3-month intervals
- Norethindrone (Norethisterone) enanthate (NEE) 200 mg at 2-month intervals.

Major limitations:

- Menstrual irregularities, excessive bleeding or amenorrhea are very common
- Return of fertility may take 6–30 months after discontinuation, May cause permanent sterility.

Androgens: Testosterone

It is the male sex hormone which is Produced by testes, adrenal gland and ovary

Uses

- Hypogonadism.
- Anemia
- Osteoporosis

Danazol

- used in the treatment of endometriosis and some benign breast disorders.
- side effects: Voice changes, hirsutism and acne.

Types of anti-androgens

1. **Androgen receptor antagonist:** e.g. Cyproterone acetate, flutamide
2. **Androgen synthesis inhibitor**:

- Finasteride

Used for hirsutism, male pattern baldness and benign prostatic hyperplasia inhibit 5α-reductase enzyme.

- Dutasteride

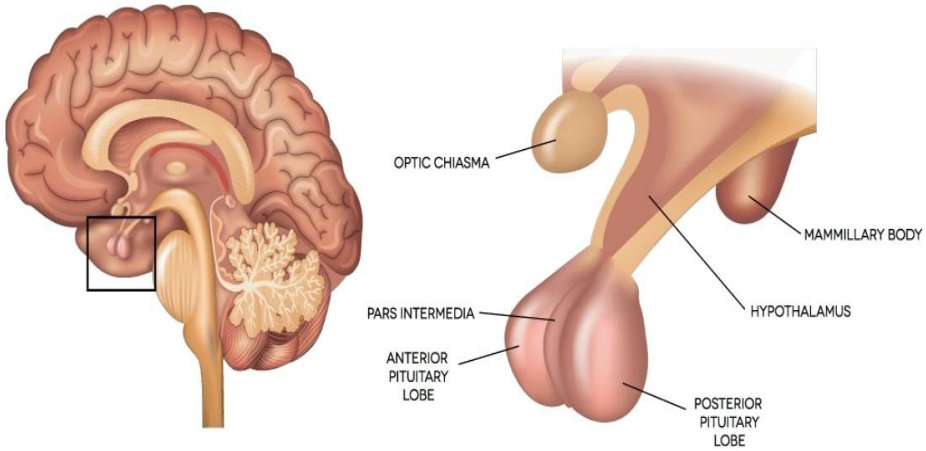
it can be used as treatment for advanced prostate cancer and in the treatment of Cushing's syndrome

Endocrine system:

- **Ductless glands** located in special areas of the body, their secretions entre the circulatory system **directly** as blood flows through the glands.
- It produce hormones and chemical compounds for regulation of the body processes.

Major glands:

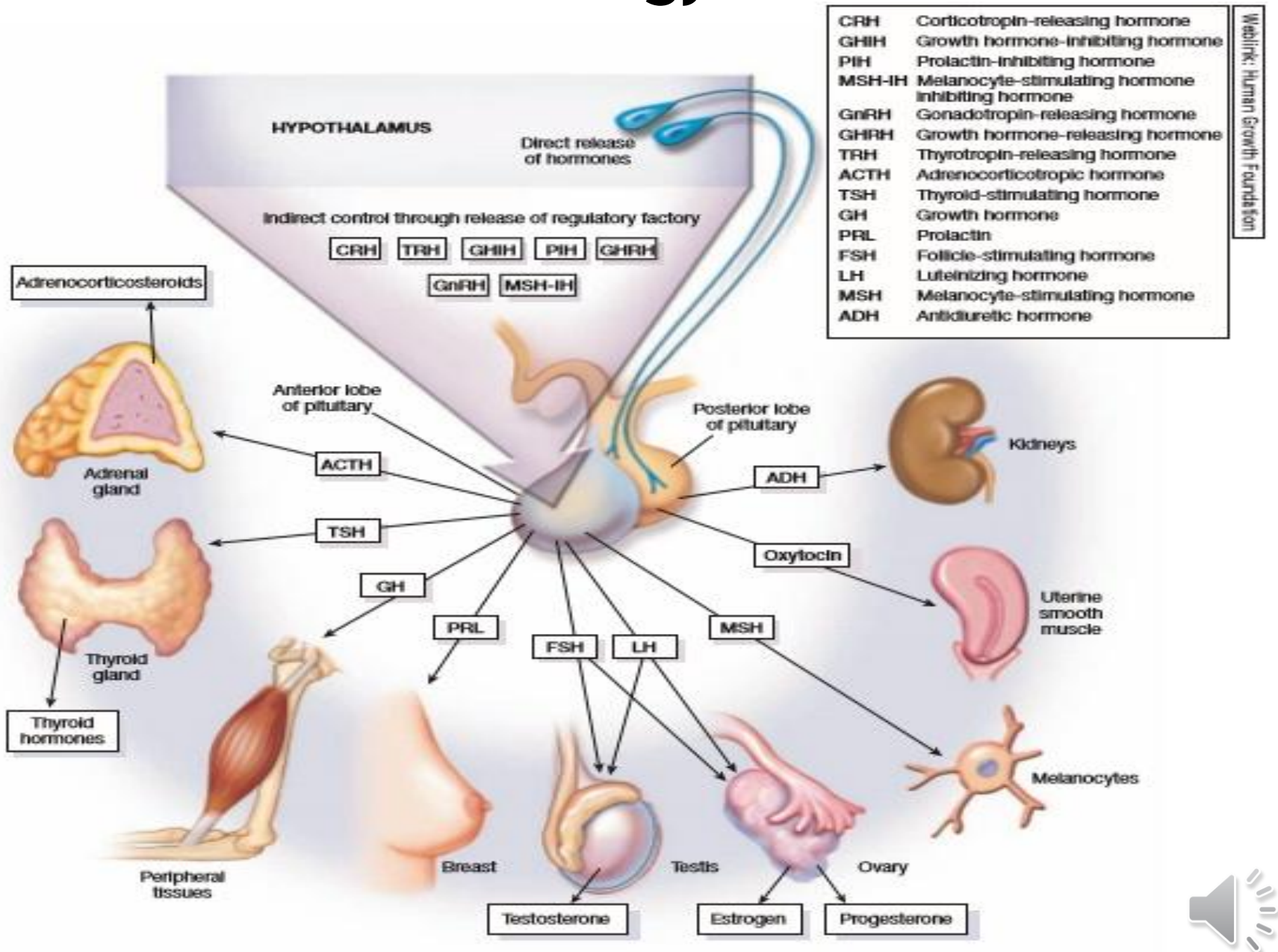
- Pituitary.
- Thyroid.
- Parathyroid
- Adrenal
- Pancreatic
- Gonads (sex glands)



Hormones :

Substances released into the blood stream from a gland or organ that affect activity of cells in another site, most of them are proteins and other steroids and fatty acids.

Endocrine Pharmacology



▲ *Figure 43.2* Hormones associated with the hypothalamus and the pituitary gland

Anterior lope Pituitary gland Hormones:

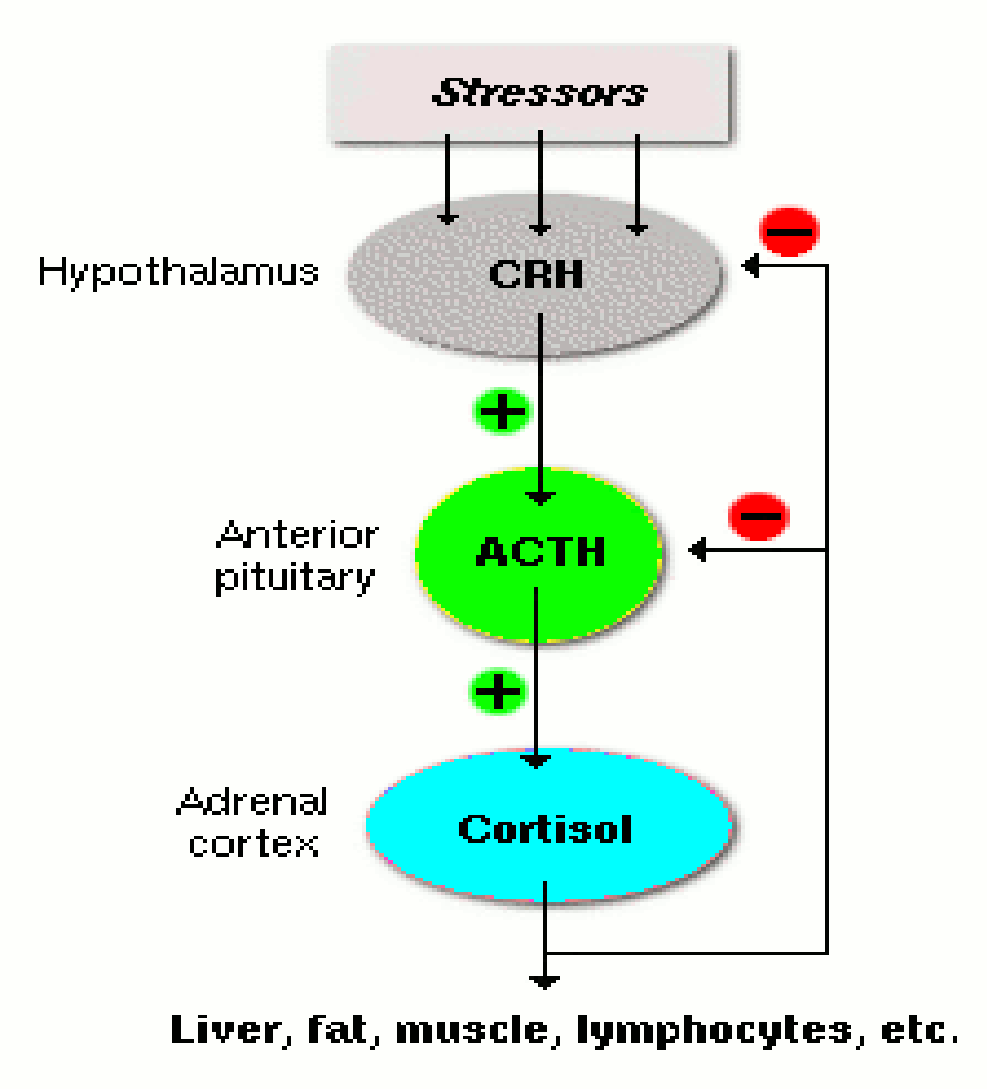
1- Adrenocorticotropic hormone (ACTH):

- Released from the Anterior lope of puitotary under the control of corticotropic releasing hormone (CRH) which is produced by hypothalamus.
- ACTH stimulate the production of cortisol from the adrenal cortex.
- When cortisol levels are high this suppress the production of ACTH and they suppress CRH.

2- luteinizing hormone (LH) and follicle stimulating hormone (FSH):

- Also known as gonadotropin hormones which mean sex hormones because they control the growth and appearance on gonads in both males and females.
- FSH extracted from the urine in postmenopausal women, it cause mature of ovarian follicle and production of estrogen.
- LH : extracted from the urine of pregnant women, produce corpus luteum and in males stimulate the release of androgens.
- FSH and LH given I.M.

Negative feedback control of cortisol



3- Thyroid-stimulating hormone (TSH)

- Released under the control by TRH from the hypothalamus and inhibited by the availability of thyroid hormone.
- TSH control the production of and release of thyroid hormones.
- Thyroid hormone regulate body metabolism.

4- Growth hormone (somatotropin (GH)):

- Stimulate growth of soft tissues and in bone.
- GH deficiency cause short stature or dwarfism, treatment must be started before epiphyseal fusion (closure of the ends of long bones) has occur and continued until complete growth.
- SC once or twice weekly.

5- Prolactin:

- It is lactogenic hormone, produce it maximum effect on the breast.
- Prolactin has powerful inhibitory effect on the ovaries and it is responsible for delaying the menstruation during lactation.
- Increase in both male and female during stress and that reduce fertility.
- **Bromocriptine** inhibit the production of prolactin.

Posterior lope of pituitary

1. **Oxytocin:**

- it causes contraction of the uterus in labour and causes milk ejection in the breast.

2. **Vasopressin:**

- In large doses it cause vasoconstriction also it's an antidiuretic hormone.
- When water intake is limited blood become more concentrated which activated the release of vasopressin to increase re-absorption of water from kidneys so increase blood volume .

Desmopressin (Minirin®) synthetic compound of vasopressin.

- In diabetes insipidus where there is no or little vasopressin release, a high output of urine produced, Desmopressin is the preferred drug.
- Oral, I.M, nasal.
- Can also treat bleeding because of the vasoconstrictive activity.

Nursing Implementation –Oxytocin For induction of labour

Principle:

- Start with LOW DOSE, escalate to achieve <u>optimal response.</u>

(3 contraction in 10min each lasting 45sec)

- OBJECTIVE - *Maintain normal pattern of uterine activity till delivery and 30-60min beyond that.*

Indications for stopping the oxytocin infusion

- Nature of uterine contractions:
  - abnormal uterine contractions occurring frequently (every 2 min or less)
  - lasting more than 60sec (hyper-stimulation)
  - ↑tonus in between contractions
- Fetal distress
- Maternal complications
- Hyper stimulation is treated with 0.25 mg **terbutaline**

Endocrine Pharmacology

Corticosteroids

Dr. Zena Sattam

Examples of Synthetic corticosteroid:

bethamethasone
prednisone
prednisolone
triamcinolone
methylprednisolone
Dexamethasone

Corticosteroids are hormones secreted by the adrenal cortex of the adrenal glands.

1. **Mineralo-corticoids:** maintain fluid and electrolyte balance, used to treat adrenal insufficiency caused by hypo-function of the pituitary or adrenal glands (Addison's Disease)
2. **Gluco-corticoids:** regulate carbohydrate, protein, and fat metabolism, have anti-inflammatory, anti-allergic, and immuno-suppressant activity

Nursing Implementation:

persons taking these for at least 1 week must not abruptly stop therapy, otherwise, the following may occur:

-fever	-malaise/fatigue	-weakness
-anorexia	-hypotension	-dizziness
-nausea	-fainting	-hypoglycemia
-dyspnea	-muscle and joint pain	-return of disease process

GlucoCorticoids:

- Given for anti-inflammatory, anti-allergenic, immunosuppressant effects
- Relieve symptoms of inflammation, but do not cure disease
- Drugs used in treatment of:
  - cancers
  - organ transplants
  - auto-immune diseases
  - rheumatoid arthritis
  - allergy signs/symptoms
  - shock
  - nausea and vomiting from chemotherapy
- Goals of treatment:
  - reduce pain and inflammation
  - minimize shock and hasten recovery
  - reduce nausea and vomiting from chemotherapy

Corticosteroids side effects:

Cause sodium (salt) and fluid retention, weight gain or swelling of the legs (edema). Loss of potassium and high blood pressure
Headache
Muscle weakness
Puffiness of the face (moon face)
Facial hair growth
Thinning and easy bruising of the skin
Slow wound healing
Glaucoma and Cataracts
Ulcers in the stomach and duodenum
Loss of diabetes control
The prolonged use of corticosteroids can cause growth retardation in children, psychiatric disturbances include depression, euphoria, , they suppress the immune system, increase rate of infections.
The long term use of corticosteroids may cause osteoporosis.
Shrinking (atrophy) of the adrenal glands.

PRINCIPLES OF ANTIMICROBIAL CHEMOTHERAPY

- Bactericidal
- Bacteriostatic

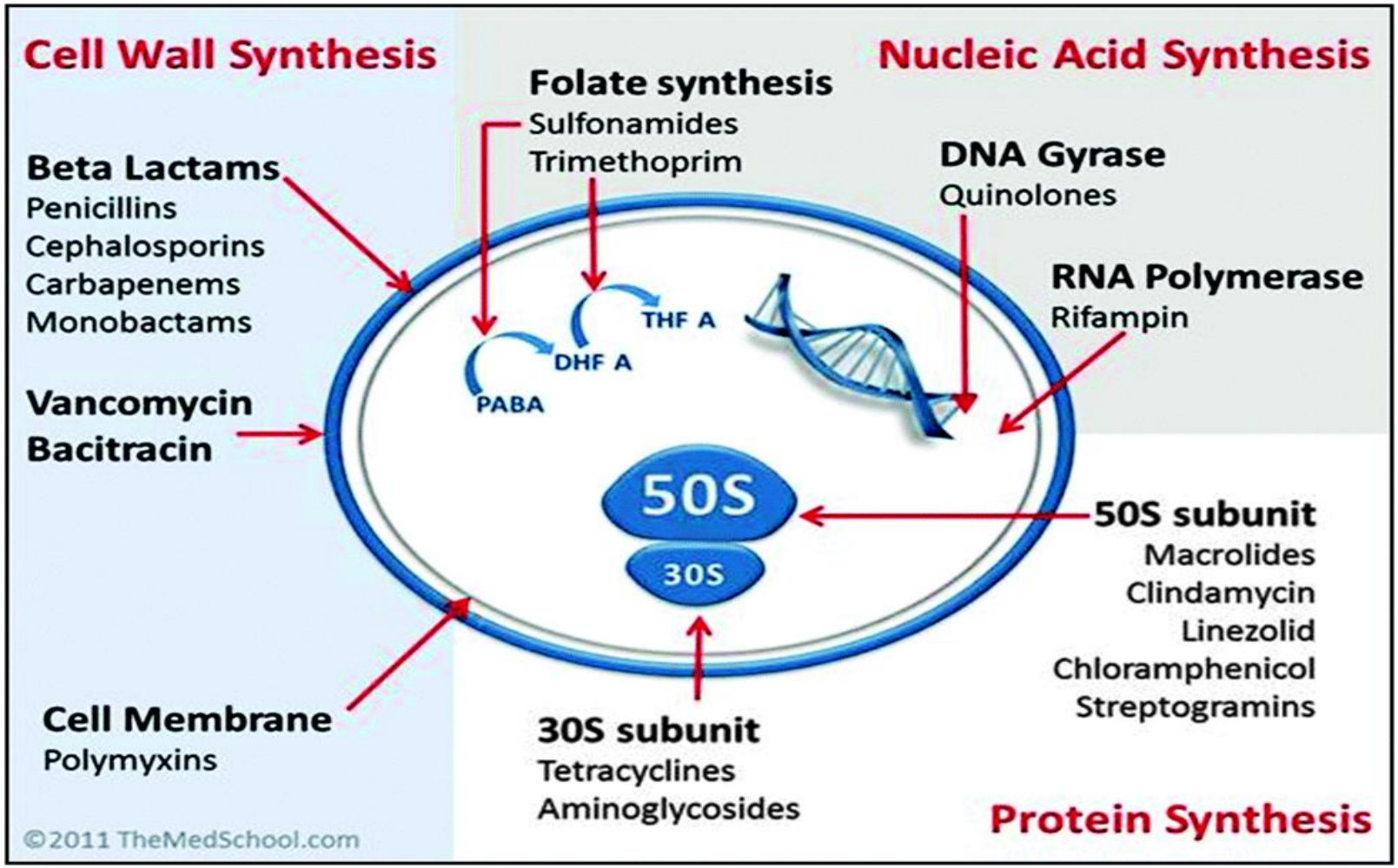
Combinations:
– Additive
– Synergistic (penicillins plus aminoglycosides)
– Antagonistic (penicillin plus tetracyclines)

Dr. Zena Sattam

Mechanism of Action of Antimicrobial Agents

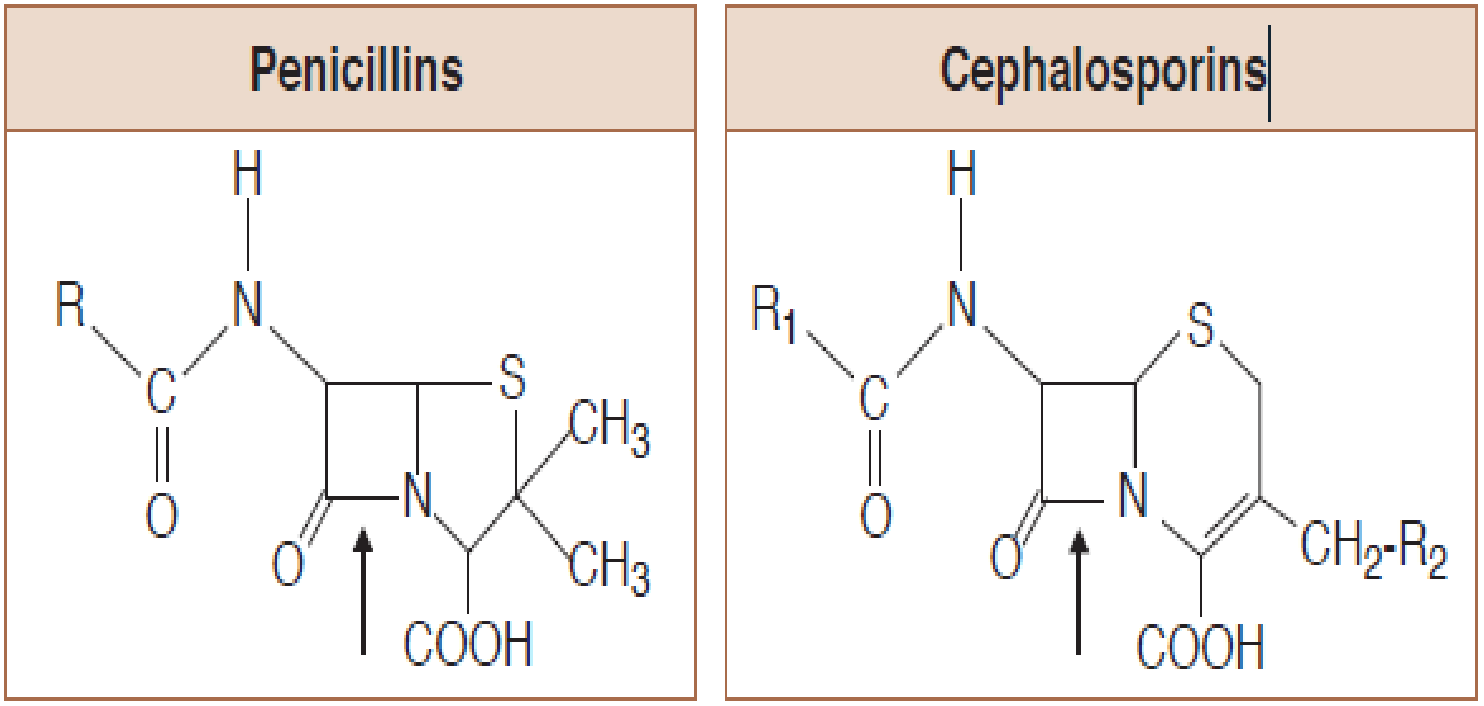
- **Inhibition of bacterial cell-wall synthesis**: Penicillins, cephalosporins, meropenem, vancomycin.
- **Inhibition of bacterial protein synthesis**: Aminoglycosides, chloramphenicol, macrolides, tetracyclines.
- **Inhibition of nucleic synthesis:** Fluoroquinolones, rifampin.
- **Inhibition of folic acid synthesis:** Sulfonamides, trimethoprim, pyrimethamine.

Mechanism of Action of Antimicrobial Agents



INHIBITORS OF CELL-WALL SYNTHESIS

Mechanism of action: All cell-wall synthesis inhibitors are bactericidal.



Beta-Lactam Antibiotics

Penicillins

- Mechanisms of action: inhibit cell-wall synthesis
- **Subgroups and antimicrobial activity:**
- **– Very narrow spectrum, beta-lactamase resistant:** nafcillin, methicillin: staphylococci.
- – **Narrow spectrum, beta-lactamase sensitive:** penicillin G and penicillin V: streptococci, pneumococci, meningococci.
- – **Broad spectrum:** ampicillin and amoxicillin: gram-positive cocci (not staph), *E. coli, H. influenzae, H. pylori* .
- **– Extended spectrum**, antipseudomonal: ticarcillin, piperacillin.

General considerations:

– Activity enhanced if used in combination with beta-lactamase inhibitors (clavulanic acid).

– Synergy with aminoglycosides against pseudomonal and enterococcal species.

Pharmacokinetics:

- – Most are eliminated via kidney, dose reduction needed only in major renal dysfunction (Nafcillin and oxacillin eliminated largely in bile).
- – Benzathine penicillin (half-life of 2 weeks)

Side effects:

- Hypersensitivity: Urticarial skin rash common. Severe reactions, including anaphylaxis.
- GI distress: especially ampicillin.

Cephalosporins

Mechanism (like penicillin): inhibit cell wall synthesis

Subgroups and antimicrobial activity:

– First generation: cefazolin, cephalexin.

- Spectrum: gram-positive cocci, *E. coli, Klebsiella pneumoniae*, and some *Proteus* species.
- Common use in surgical prophylaxis.
- kinetics: none enter CNS.

– Second generation: cefuroxime, cefaclor

- Spectrum: gram-negative coverage, including some anaerobes
- kinetics: no drugs enter the CNS, except cefuroxime

– Third generation: ceftriaxone (IM) and cefotaxime (parenteral), cefixime (oral)

- Spectrum: gram-positive and gram-negative cocci (*Neisseria gonorrhea*), plus many gram-negative rods.
- important in management of meningitis and sepsis.
- kinetics: most enter CNS.

– Fourth generation: cefepime (IV)

- Even wider spectrum. Resistant to most beta-lactamases.
- Kinetics: enters CNS.

Meropenem

- **Mechanism of action:**
- Same as penicillins and cephalosporins
- Resistant to beta-lactamases.
- **Spectrum:** Wide, Gram-positive cocci, gram-negative rods (e.g., *Enterobacter, Pseudomonas* spp.), and anaerobes.
- Important in-hospital severe life-threatening Infections.
- **Side effects:** GI distress, Drug fever, CNS effects (seizures).

Vancomycin

Mechanism of action: cell wall inhibition.

Spectrum: MRSA, Enterococci.

Pharmacokinetics: Used IV Enters most tissues (e.g., bone), but not CNS. Eliminated by renal filtration (important to decrease dose in renal dysfunction)

Side effects:

- "Red man syndrome" (histamine release).
- Ototoxicity (usually permanent).
- Nephrotoxicity (additive with other drugs).

INHIBITORS OF BACTERIAL PROTEIN SYNTHESIS

- Aminoglycosides: gentamicin
- Tetracyclines: Doxycycline
- Chloramphenicol
- Macrolides: erythromycin, azithromycin.
- Clindamycin

Aminoglycosides

- Bactericidal for aerobic bacteria.
- gentamicin, tobramycin, and amikacin.
- Streptomycin used in tuberculosis
- Used in combinations (with ampicillin or cephalosporin). not absorbed orally,
- Renal elimination, dose reduction in elderly.
- **Side effects:**
  - Nephrotoxicity
  - Ototoxicity

Tetracyclines

- **Mechanism of action:** Bacteriostatic drugs
- Broad-spectrum antibiotics on *H. pylori* (GI ulcers), *Vibrio cholera.*
- Doxycycline against prostatitis because it reaches high levels in prostatic fluid.
- Excreted by Kidney and liver. (ions like Fe2+ , Ca2+) decrease absorption.
- **Side effects:**
  - Tooth enamel possible
  - Phototoxicity, GI distress.
  - liver dysfunction during pregnancy at very high doses.

Chloramphenicol

- Bacteriostatic with a wide spectrum of activity
- Backup drug for infections due to Salmonella typhi
- Orally effective, with good tissue distribution, including CSF.
- **Side effects:**
  - Dose-dependent bone marrow suppression common;
  - aplastic anemia rare (1 in 35,000).
  - “Gray baby” syndrome in neonates

Macrolides

- Bacteriostatic.
- Erythromycin, azithromycin, clarithromycin
- Macrolides are wide-spectrum antibiotics e.g *H.* pylori.
- They inhibit liver enzyme cytochrome P450s
- **Side effects:**
  - gastrointestinal distress
  - reversible deafness at high doses
  - Increased QT interval

Clindamycin

Narrow spectrum: gram-positive cocci (MRSA) and anaerobes.

Concentration in bone has clinical value in osteomyelitis due to gram positive cocci.

Side effect: pseudomembranous colitis (most likely cause).

INHIBITORS OF BACTERIAL NUCLEIC ACID SYNTHESIS

- Quinolone
- Sulphonamide

Sulphonamides

- **1- Trimethoprim :**
- Used for urinary infections and bronchitis.
- shouldn't be used in the first 3 monthes of pregnancy.
- **Side effects:** nausea, rashes.

- **2- Co-trimoxazole:**
- Is a mixture between trimethorphin and sulfamethoxazole.

Used for the treatment of chronic bronchitis , UTI, and the treatment of severe salmonella and other intestinal tract infections.

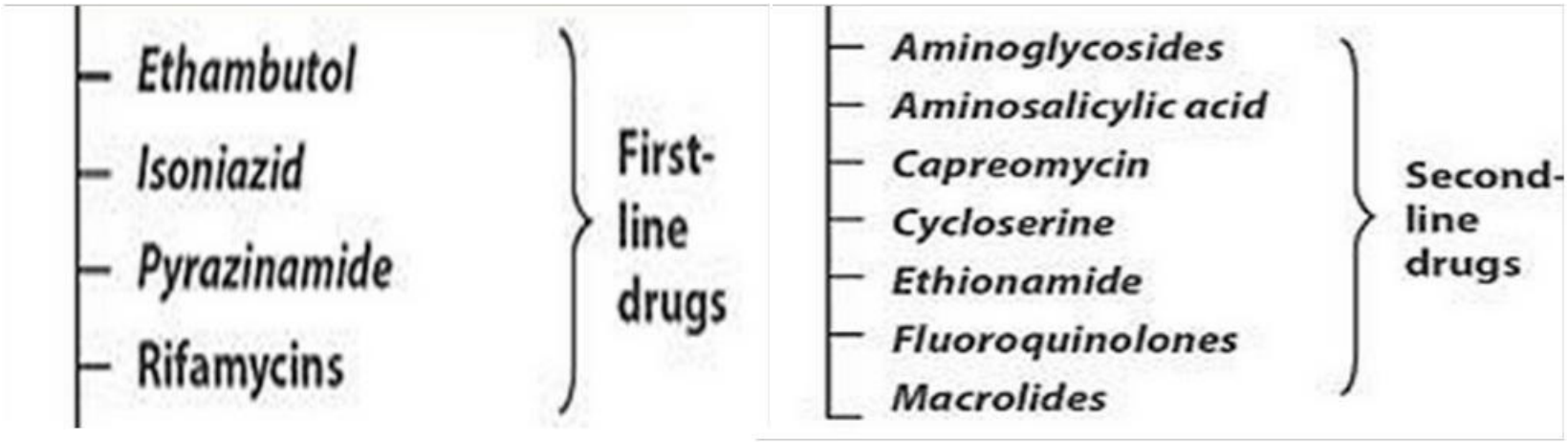
Quinolones

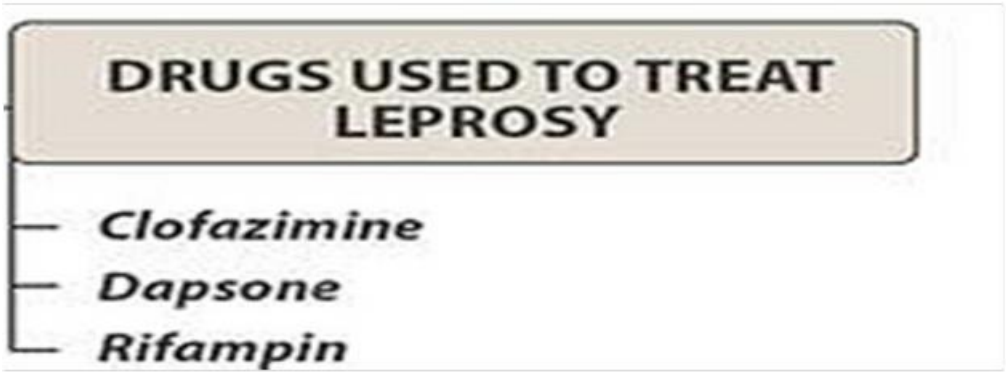
- Interfere with enzyme which is important for cell division in bacteria.
- **1- Ciprofloxacin**
- Used in typhoid, UTI, and gonorrhea.
- Preferable in adults as a prophylactic for close contact with meningococcal meningitis.
- Given *orally* or *infusion*
- Avoided in children and with epileptic patients.

- **2- Norfloxacin (Noracin®) and Nalidixic acid (Negram®)**
- For uncomplicated UTI.
- 3-4 days course.
- Other examples:

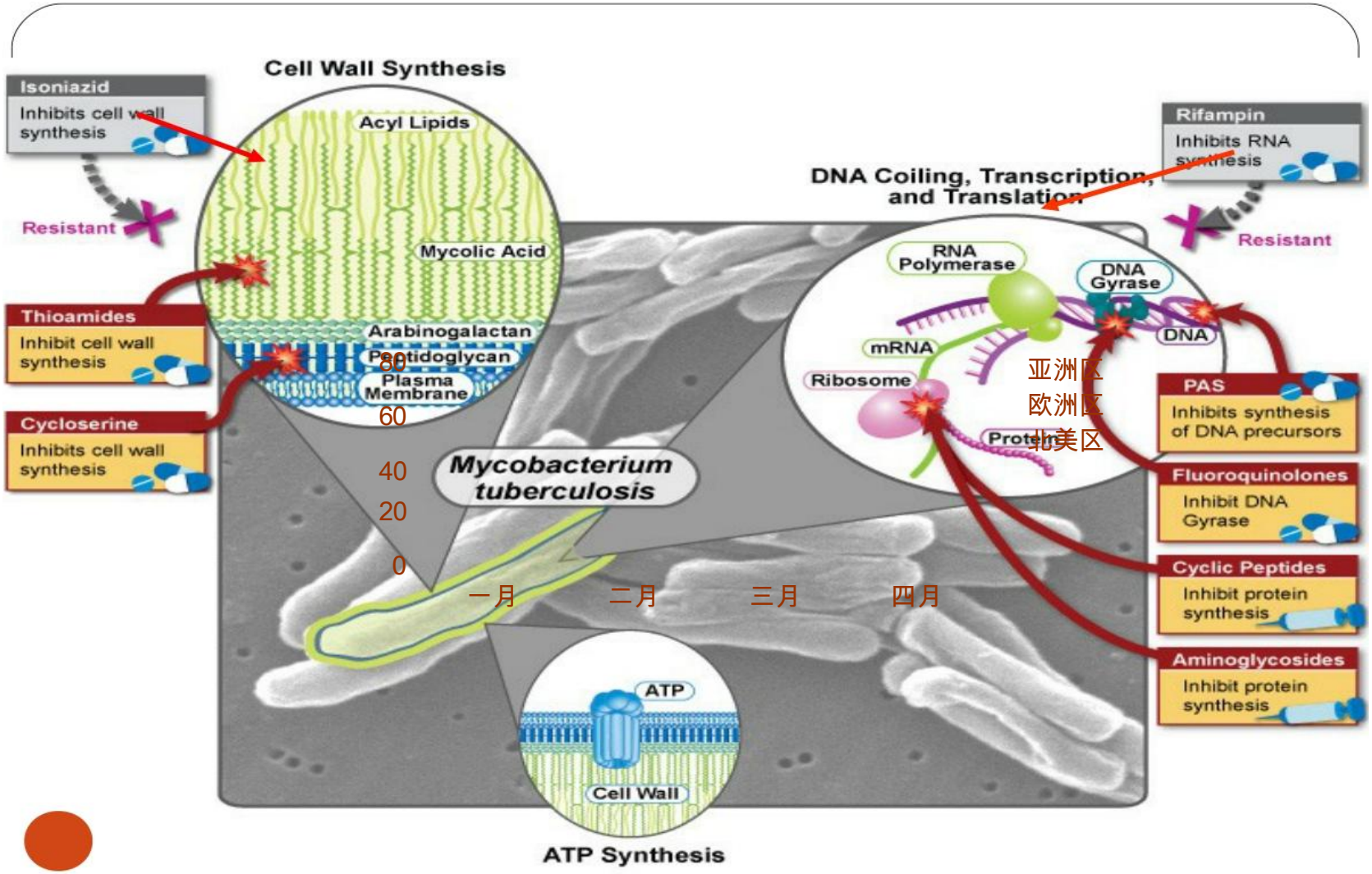
Levofloxacin , ofloxacin

CLASSIFICATION OF ANTIMYCOBACTERIALS





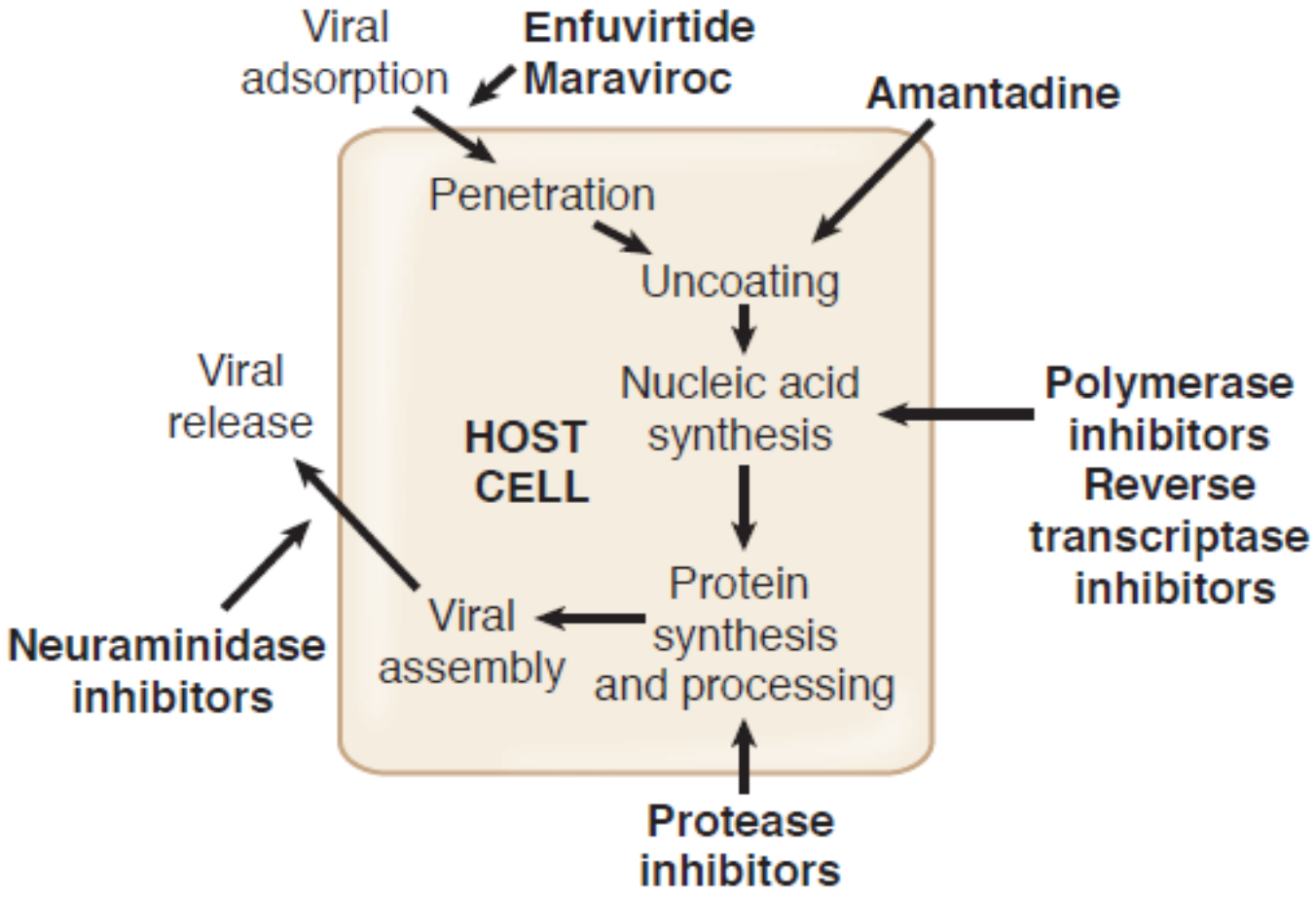
MECHANISM OF ANTIMYCOBACTERIALS



UNCLASSIFIED ANTIBIOTIC: METRONIDAZOLE

- Metronidazole: In anaerobes, converted to free radicals, binds to DNA and bactericidal.
- Antiprotozoal: *Giardia*, *Trichomonas*, *Entamoeba*
- *Bacteroides* species *Clostridium* species (drug of choice in pseudomembranous colitis) and *H. Pylori.*
- Side effects: Metallic taste, Disulfiram-like effect in alcoholics.

Site of Antiviral drug actions



Antiviral drug

- Acyclovir: Inhibit viral DNA polymerases
- Amantadine: Block viral penetration
- Oseltamivir: Inhibit viral neuraminidase inhibit influenza viruses A and B.
- Zidovudine: Inhibit viral reverse transcriptase treat HIV infections.

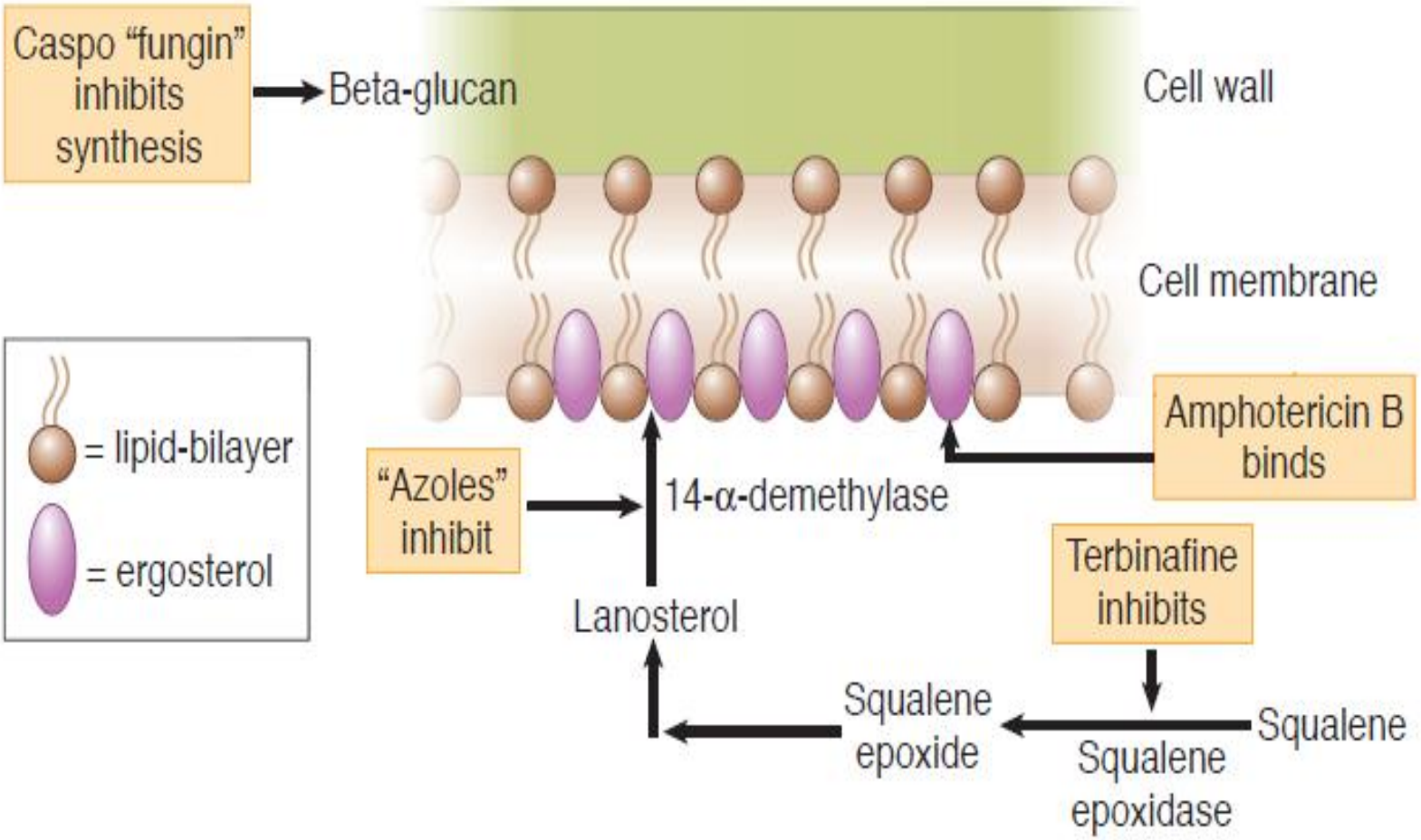
Antiprotozoal Agents

- Metronidazole: used for Amebiasis, Giardiasis and Trichomoniasis.
- Pyrimethamine + Sulfadiazine used for Toxoplasmosis
- Stibogluconate used for Leishmaniasis
- ANTIMALARIAL DRUGS
- Chloroquine for treatment.
- Prophylaxis: chloroquine +/– primaquine

DRUGS FOR HELMINTHIC INFECTIONS

- Most intestinal nematodes (worms):
- Albendazole (↓ glucose uptake and ↓ microtubular structure).
- Pyrantel pamoate (NM agonist → spastic paralysis).
- Most cestodes (tapeworms) and trematodes: Praziquantel (↑ Ca2+ influx, ↑ vacuolization).

Mechanism of Action of Antifungal Drugs



Antifungal Drugs

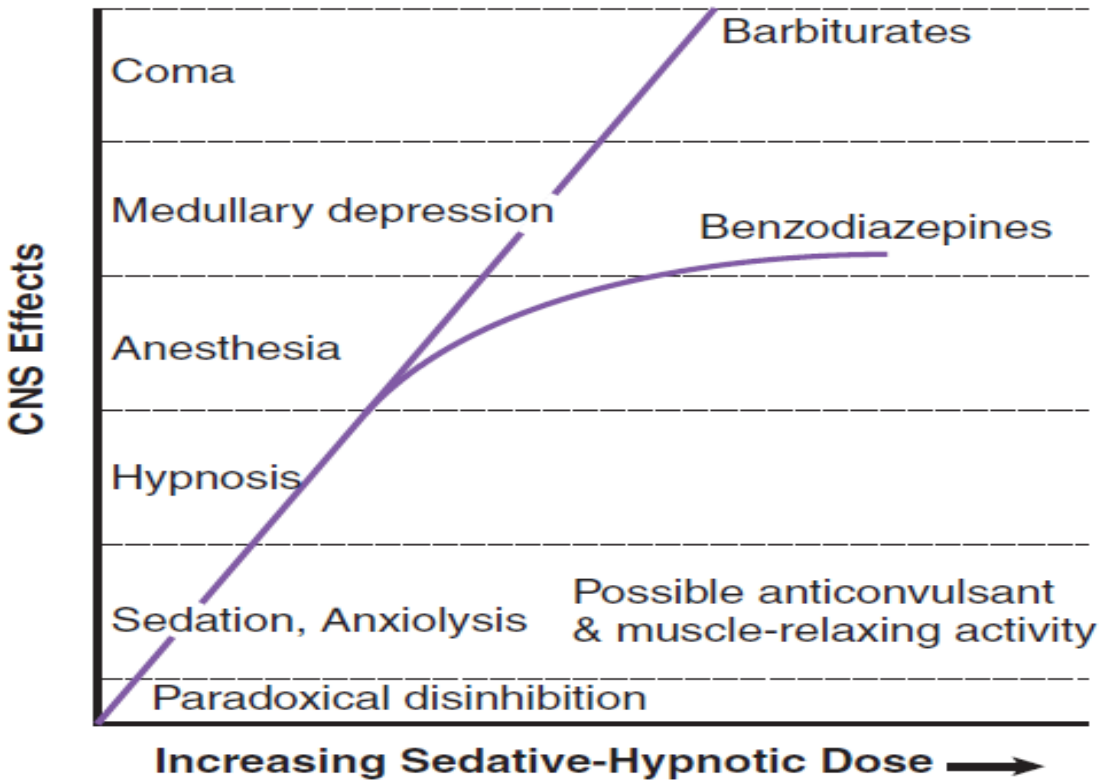
- POLYENES (Amphotericin B, Nystatin): interact with ergosterol in fungal membranes to form artificial "pores," which disrupt membrane permeability, wide fungicidal spectrum, slow IV infusion, Nephrotoxic.
- Nystatin (too toxic for systemic use)—used topically for localized infections (e.g., candidiasis).
- AZOLES (Ketoconazole, Fluconazole, itraconazole, Clotrimazole and Miconazole) are fungicidal and interfere with the synthesis of ergosterol, used in esophageal and invasive candidiasis.
  - Effective orally
  - Absorption of ketoconazole ↓ by antacids
  - Absorption of itraconazole ↑ by food
  - Inhibition of hepatic enzymes
  - ↓ synthesis of steroids, including cortisol and testosterone →↓ libido, gynecomastia, menstrual irregularities.
- Griseofulvin, Terbinafine effective orally.

Sedative-Hypnotic-Anxiolytic Drugs

Dr. Zena Sattam

- Sedative-hypnotic-anxiolytic drugs include the benzodiazepines, barbiturates, and alcohols.
- S-H drugs ideally should reduce anxiety without affecting mental or motor function. However, most do affect mental or motor function.
- Benzodiazepines: example are **Diazepam, Lorazepam** are used for anxiety, **Mechanism**: Potentiate GABA.
- **Uses of** Barbiturates e.g. **Phenobarbital** is used for seizures
- Chronic use leads to tolerance, Cross-tolerance occurs between BZs, barbiturates, and ethanol.
- **Withdrawal signs** of BZs: Rebound insomnia and Anxiety.
- **Additive effects** occur with other CNS depressants (possible life-threatening respiratory depression), such as anesthetics, antihistamines, opiates.
- **Buspirone** has no effect on GABA, is used for generalized anxiety. Non sedative

CNS effects associated with increasing doses of Sedative-Hypnotic Drugs



Cause dose-dependent CNS depression that extends from sedation to anesthesia to respiratory depression and death.

DRUGS USED IN DEPRESSION

- Depression symptoms are caused by deficiency of CNS norepinephrine (NE) and/or serotonin (5HT).
- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
- **E.g. fluoxetine, sertraline, citalopram**
- **Mechanism**: selective blockade of 5HT reuptake.
- **Uses**: Major depression and Anxiety disorders.
- **Side effects**: agitation, sexual dysfunction, weight loss
- **Tricyclic Antidepressants (TCAs)**
- E.g. **amitriptyline, imipramine,** and **clomipramine**
- **Mechanism**: blockade of 5HT and NE reuptake.
- **Uses**: Major depression.
- **MAO Inhibitors: phenelzine** for depression.

Drugs Used in Parkinson Disease

- In Parkinson disease, **loss of dopamine DA neurons with excessive ACh activity** → extrapyramidal dysfunction. Muscle rigidity, Resting and tremor.
- Note/ **DA → ↓ prolactin**. Thus DA agonists are used in hyperprolactinemic states. DA antagonists may cause endocrine dysfunction, including gynecomastia and galactorrhea.
- Note/ Activation of DA receptors → ↑ emesis. DA agonists (e.g., apomorphine) are emetic, and DA antagonists are antiemetic.
- **Levodopa** Prodrug converted to dopamine.
- **Side effects** include: Psychosis, Hypotension and Vomiting
- Dopamine-receptor agonists:
- **Bromocriptine**
- **Use**: hyperprolactinemia and acromegaly
- **Side effects**: dyskinesias and psychosis

Other Drugs in Parkinson for decreasing ACh function :

- **Benztropine** and **Trihexyphenidyl**, which are muscarinic blockers.
- **Actions**: ↓ tremor and rigidity but have little effects on bradykinesia.
- **Side effects**: atropine-like side effects e.g dry mouth, tachycardia and urine retention.
- **Amantadine:** Antiviral, which block muscarinic receptors and ↑ dopamine release.

ANTIPSYCHOTIC DRUGS in **Schizophrenia**

- Symptoms arise because of excessive dopaminergic activity in mesolimbic system.
- Dopamine agonists cause psychosis.
- Dopamine antagonists have antipsychotic actions.
- **Side effects**:
- Dyskinesias
- ↑ prolactin (galactorrhea)
- ↑ eating disorders (weight gain)
- e.g. **Chlorpromazine, Haloperidol, Olanzapine, Risperidone**

Anticonvulsants

- Seizures result from episodic electrical discharges in cerebral neurons associated with prolonged depolarization.
- Note/ ↓ axonal conduction by :

1- Preventing Na+ influx **Phenytoin, Carbamazepine**

- **Side effects**: CNS depression, Osteomalacia (↓ vitamin D), Teratogenicity, induce liver enzymes.

2- ↑ inhibitory effect by facilitation of GABA

3- ↓ excitatory effects of glutamic acid

4- block Ca2+ influx

- **Valproic acid** inhibit Na+ influx, enhance GABA and Blockade Ca2+ channels.
- **Side effects**: inhibits liver enzymes, Teratogenicity
- Other examples: **Ethosuximide, Lamotrigine, Gabapentin.**

Enhanced Na^+ Channel Inactivation