جامعة الفرات الاوسط التقنية
كلية التقنيات الصحية والطبية، كوفة
قسم تقنيات صحة المجتمع
المرحلة الثانية
مادة الدوائيات
الفصل الدراسي الثاني

المفردات الدراسية

اسم المادة	باللغة العربية / باللغة الانكليزية	السنة الدراسية	عدد الساعات الأسبوعية			
			نظرية	عملي	مجموع	عدد الوحدات
لغة التدريس للمادة	اللغة الانكليزية	الثانية	2	2	4	6
	دوائيات / Pharmacology					

أهداف المادة:

الهدف العام: ان يكون الطالب ملما بفهم تأثير الأدوية واستخداماتها المتعددة.

الهدف الخا ص: فهم طريقه عمل الأدوية باختلاف شعبها وتعارض الأدوية وحركية الدواء والآثار الجانبية لكل دواء

المفردات النظرية-الدوائيات-المرحلة الثانية- الفصل الاول	
الأسبوع	**تفاصيل المفردات**
الاول	Drugs Affecting the Endocrine System I
الثاني	Drugs Affecting the Endocrine System II
الثالث	Anti-inflammatory, Antipyretic, and Analgesic Agents
الرابع	Gastrointestinal and Antiemetic Drugs
الخامس	Drugs for Disorders of the Respiratory System
السادس	Principles of Antimicrobial Therapy
السابع	Chemotherapeutic Drugs – I
الثامن	Chemotherapeutic Drugs – II
التاسع	Drugs Affecting the Cardiovascular & Renal System I
العاشر	Drugs Affecting the Cardiovascular & Renal System II
الحادي عشر	Drugs Affecting the Cardiovascular & Renal System III

Review & Exam	الثاني عشر
Histamine and Serotonin	الثالث عشر
Anti-inflammatory, Antipyretic, and Analgesic Agents	الرابع عشر
Drugs of Abuse	الخامس عشر

ENDOCRINE PHARMACOLOGY

Learning objective

At the end of this chapter the student is expected to learn the following:

1. The mechanism of action, uses and side effects of oral hypoglycemic agents
2. Drugs used as oxytocic agents
3. Types of hormonal contraception with their uses and adverse effects including preparations
4. Actions, therapeutic uses and adverse effects of glucocorticoids

II .OXYTOCICS

These are group of drugs that cause contraction of the uterus.

Oxytocin

Actions:

1. Oxytocin stimulates the uterus and cause physiologic type of contraction

2. It also causes ejection of milk through contraction of the myo-epithelial cells around the alveoli of the mammary gland.

Pharmacokinetics: It is inactivated orally and absorbed rapidly after intramuscular administration. It can also be absorbed from nasal and buccal membrane.

***Use*:** Induction of labor in women with uterine inertia, Relief of breast engorgement during lactation (few minutes before breast feeding) as nasal spray, Postpartum hemorrhage.

***Side effect*:** Oxytocin may cause over stimulation and leads to rupture of the uterus in the presence of cephalo-pelvic disproportion. Therefore it's contraindicated in woman with uterine scar. When given intravenously may cause water retention leading to water intoxication.

Prostaglandins

They induce labor at anytime during pregnancy but most effective at the third trimester. In female reproductive system prostaglandin E & F are found in ovaries, endometrium and menstrual fluid which is responsible for initiating and maintaining normal birth process. PGF, PGF2ά, PGE stimulate both the tone and amplitude of the uterine contraction.

Adverse reaction: nausa, vomiting, headache, diarrhea, fever, etc.

PGs should be used cautiously in the presence of hypertension, angina, and diabetes. They are contraindicated in the presence of cardiac, renal, pulmonary or hepatic disease

Ergometrine

It is one of the ergot alkaloids with the ability to cause contraction of the uterine smooth muscle. It causes sustained uterine contraction. It is completely absorbed after subcutaneous and intravenous administration. It is metabolized in the liver and eliminated in the urine .Liver damage enhances the toxicity of ergot alkaloid.

Use: after delivery of placenta if bleeding is severe (Prevent postpartum bleeding)

Adverse effect: Nausa, vomiting but serious toxic effects are rare.

III. Female Sex Hormones and Hormonal Contraception

Oestrogens

These drugs can be classified into three groups.

1. Natural – estradiol, esterone, estriol
2. Semisynthetic – Ethnylestradiol
3. Synthetic: Diethylstibosterol

Natural

Estradiol: Estradiol is most potent, major secretory product of ovary.It is oxidized into esterone by liver; estrone is hydrated to estriol and synthesized by ovarian follicle, adrenal cortex,

fetoplacental unit, and testis. Androgen and testestrone are precursor for estrogen. Certain tissue can make estrone from androgen.

Semisynthetic

Ethylestadiol: Highly potent, effective orally

*Absorption and Fate**:*** It is absorbed from GI and skin and rapidly metabolized in the liver

Physiologic actions:

Genital system

Ovary: estrogen affects the ovary through indirectly influencing the secretion of gonadotrophin

Uterus: it affects the 'proliferative phase' of the endometrium and also increases the growth and sensitivity of myometrium for oxytocin.

Cervix: it makes cervical mucus thin and alkaline

Vagina: Stratification, cornification and glycogen deposit is affected by estrogen.

Breast

Estrogen causes the growth of gland and duct system

Anterior pitutary

Estrogen inhibit release of gonadotrophins (FSH, LH)

***Metabolic action*:**

a) Retention of salt and water

b) Plasma lipid level: it increases the level of high density lipoprotein and triglycerides while decreases the level of low density lipoprotein and cholesterol.

c) Increases Catt bone deposition

d) It has a mild anabolic action

Blood coagulation

Enhance level of factor II, VII, IX, X so, increase the coagulability of blood and may predispose to thromboembolic condition

Therapeutic use: contraceptive in combination with progestogens, Functional uterine bleeding, Dysmenorrhea, Alleviation of menopausal disorder, Osteoporosis, Replacement therapy in ovarian failure, Prevents senile and atrophic vaginitis

Side effects: Thromboembolism, Sodium and water retention, Withdrawal bleeding, nausea, endometrial carcinoma

Contraindication: History of thromboembolism condition, Undiagnosed uterine bleeding, endometrial Carcinoma, liver disease

PROGESTOGENS

Progestrone is natural occuring progestational hormone.it is synthesized by corpus luteum, placenta, adrenal cortex, testis. It is less effective orally due to complete metabolism by liver so it's given through intramuscular route.

***Actions on g*enital organs:**

Ovary - Inhibition of ovulation

Uterus - converts the endometrum for secretory phase and makes the myometrium less sensitive to oxytocin. It also causes relaxation of the uterus in late pregnancy.

Metabolic actions:

(a) Thermogenic action

(b) Competes with aldosterone at renal tubule so inhibits sodium reabsorption.

Synthetic /Senisynthetic progestogens:

Derivative of progestrone: Hydroxyprogesterone capriot/medroxyprogestrone

Derivative of testestrone: Dimethisterone

Nortestrone: Norethisterone

Therapeutic use: Hormonal contraception**,** functional uterine bleeding**,** dymennorrhea ,Ammenorrhea**,** Endometrial Carcinoma**,** Premenustral tension

ORAL CONTRACEPTIVEs

These are drugs taken orally to prevent conception. They are available in the following forms:

1. Combined regimen type

2. sequential regimen type

3. triphasic pill regimen

Combined regimen: involves the administration of pills containing combination of Estrogen and Progestogen. They are administered starting 5th day of menustral cycle for 21 days.

They can also be classified as fixed dose combination (monophasic), biphasic and triphasic pills. Fixed dose combination: the commonest procedure is to administer one pill containing both an estrogen and progestin daily at bed time for 21 days. In biphasic and triphasic **pills:** these are

combined oral contraceptive pills containing varying proportion of an estrogen and a progesterone designed to stimulate the normal pattern of menustral cycle.

Formulation:

a) low estrogen, low progesterone(0.03mg ethinylestradiol+0.15 mg norgestril

b) Low esterogen, high progestogen

(0.03 mg ethinylestradiol + 1.5 mg norethindrone)

c) High estrogen, high progestrone

(0.05 mg ethinylestradiol + 0.5 mg norgestril)

Mechanism: includes inhibition of release of FSH and LH, increase viscosity of cervical mucus endometrial changes, interfere with contraction of cervix, uterus and fallopian tube

Single Entity preparation

A. Continuous progestrone

i) Oral progestrone

Norethindone (Norgestril)

ii) Depot

IM injection of long acting progestogen.

e.g. Medroxyprogestrone acetate (Depoprovera®)

iii) Subcutanous implant

L – norgestril (Norplant®)

Mechanism: It makes cervical mucus thick, though & hostile and also alter endometrial wall

B. Post coital "morning after" pill

Oestrogen like Diethyl stilbosterol used within 72 hrs

Combined oral contraceptive pills can also be used.

Side effects of oral contraceptive: Thromboembolic complication, Weight gain & fluid retention,

Menstrual disorder, Breast tenderness & fullness, Skin changes, Nausea & vomiting, Depressed mood, Reduced lactation

Beneficial effects of estrogen /progesterone oral contraceptive

1) Reduced risk of endometrial Carcinoma, ovarian cyst

2) regular Menses, No excessive blood loss

3) Less premenustrual tension and dysmennorrhea

4) Relief of endometriosis

Contraindication: In patients withcardiovascular diseases (hypertension, coronary heart disease) Thromboemolic disease, breast Cancer, diabetes mellitus, liver disease, women > 35 years

(esp. smokers and hypertensives)

Drug interaction:

1. Effect reduced when taken with enzyme inducers like Rifampicin, Phenytoin, Phenobarbitone etc. It may result in unexpected pregnancy and spotting.

2. Oral contraceptive antagonize the effect of Coumarin anticoagulant and some antihypertensives

Ovulation inducing drug

These are drugs used in the treatment of infertility due to ovulatory failure.

Clomiphen

It is antiestrogenic drug. It interferes with estrogen feedback inhibition at hypothalamus and anterior pitutary so enhance secretion of FSH, LH causing ovarian stimulation which finally leads to ovulation.

ADRENCORTCCAL HORMONES

Adenocortical hormones control the metabolism of carbohydrate (CHO), protein, fat and water /electrolytes

Adencortical hormones are classified into:

a) Glucocorticoid - Cortisone

- Hydrocortisone (Cortisol)

b) Mineralocorticoid - Aldosterone

- Desoxycorticosterone

c) Sex Hormone - Estrogen

- Androgen

Glucocorticoids

The important glucorticoid secreted in man is *hydrocortisone.* It posseses some mineralocorticoid activity as well. Cortisone is less potent and is converted to hydrocortisone by liver. They are classified as

1. Short acting e.g cortisone, hydrocortisone
2. Intermediate acting e.g predinsolone, triamcinolone
3. Long acting e.g dexamethasone, betamethasone)

Dexamethasone and betamethasone have got a high glucorticoid activity while cortisone and hydrocortisone have high mineralocorticoid action. Therapeutic activity in inflammatory disorder

is proportional to the glucocorticoid activity.

Actions on CHO metabolism*:*

- antinsulinic effect
- decreases Peripheral utilization of glucose,
- increases gluconeogenesis
- promote glycogen storage

Protein metabolism:

- Inhibit protein synthesis,
- Increases catabolism

Fat metabolism:

- Interferes with fat storage causing deposits with characteristic distribution (neck, supraclavicular area, and face

Electrolyte and H2O metabolism

- Sodium and water retention
- Hypokalmia

Suppression of pitutary adenocortical system

CNS: Euphoria and stimulation

CVS: Restore vascular reactivity

GIT: Increase gastric acid secretion

Blood: Increase number of RBC, Hypercoagulability

Uric acid: Increased excretion

Calcium metabolism: increased Ca++excretion, interfere with Ca++ absorption

Antinflammatory: Inhibit exudation, capillary dilatation, migration of phagocyte, fibroblast, inhibit fibrous tissue formation

Antiallergic: through inhibition of antibody production suppress tissue inflammatory response.

Absorption and fate: It has fair absorption, bound to α -globuin (transcortin).And in the liver, cortisone is converted into hydrocortisone.

Therapeutic use

1) Replacement therapy: In Addisons disease and Addisonian crisis

2) Antinflammatory: in conditions like Collagen disease (rheumatoid carditis, arthritis),

3) Hypersensitivity reactions: (Bronchial Asthma, status asthmatic), Blood disease due to circulating antibodies (autoimmune disease), Skin disease (eczema), Eye disease (allergic inflammation of the eye), Nephrotic syndrome, Acute gout.

4) Immunosuppression: In tissue / organ transplantation.

Precautions

- Check weight for fluid retention

- Test urine for sugar
- Follow blood pressure through measurement and check bones by X-ray for osteoporosis
- Doses should be tapered slowly (Don’t stop abruptly)
- Increase dose in surgery, infection
- Encourage diet rich in K+, protein and adequate calcium, low Nacl
- Rule- out infection before initiation of treatment

Side effects:

- Due to prolonged use: Weight gain and edema hypokalmia, hyperglycemia, osteoporosis, psychiatric disturbance, susceptibility to infection (like TB), peptic ulceration, cushing syndrome, retarded growth
- Complication with rapid withdrawal results in adrenacortical insufficiency due to depression of adrenocortical activity

Contraindication:

They are contraindicated in patients with peptic ulcer disease, acute infection like active tuberculosis, diabetes mellitus, psychosis, pregnancy

Mineralocorticoid

Aldosterone

It is the main mineralocorticoid of adrenal cortex. It increases absorption of Na at distal tubule and increases K+ excretion. They are not widely used in therapeutics rather its antagonists are of value in cases of edema.

Thyroid and Antithyroid Drugs

They inhibit the function of the thyroid gland and used in hyperthyroidism.

Antithyroid drugs include:

1. Thiourea compounds, e.g. , propylthiouracil, methimazole, carbimazole
2. Ionic inhibitors, e.g. , potassium percholate, potassium thiocyanate
3. Iodide, e.g. , Lugol’s iodine, potassium iodide
4. Radioactive iodine (131I)

Thiourea Compounds

Inhibit the formation of throid hormone through inhibiting the oxidation of iodide to iodine by peroxidase enzyme and blocking the coupling of iodothryosines to form
iodothyronines.

They are contraindicated in pregnant and lactating women.

Toxicities include drug fever, skin rashes, increased size and vascularity of the thyroid gland, and agranulocytosis.

Ionic Inhibitors

Potassium percholate prevents the synthesis of thyroid hormones through inhibition of uptake and concentration of iodide by the gland. It has the risk of aplastic anemia, therefore no longer used in the treatment of hyperthyroidism.

Iodides:

Improve manifestations of hyperthyroidism by decreasing the size and vascularity of the gland so they are required for preoperative preparation of the patient for partial
thyroidectomy. Iodides act through inhibition of the “protease” enzyme which releases T3 and T4 from
thyroglobulin, and organification.

Radioactive Iodine:

It is used in hyperthyroidism as sodium 131I orally. It is trapped and concentrated as ordinary iodine, which emits beta rays that act on parenchymal cells of the gland. It is contraindicated in pregnancy and lactation as it affects thyroid gland in the fetus and the infant. Its important toxicity is hypothyroidism.

Propranolol

This is an important drug which controls the peripheral manifestations of hyperthyroidism (tachycardia, tremor). In addition, it decreases the peripheral conversion of T4 to T3.

Thryoid Storm (Crisis)

This is a sudden acute exacerbation of all the symptoms of thyrotoxic which rarely occur after thyroidectomy. Manifestations include hyperpyrexia, gastrointestinal symptoms, dehydration, tachycardia, arrhythmia, restlessness, etc. which may progress to shock and death.

Management: It consists of infusion of intravenous fluids, supportive management, and also administration of propylthiouracil, sodium iodide, hydrocortisone, and propranolol.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

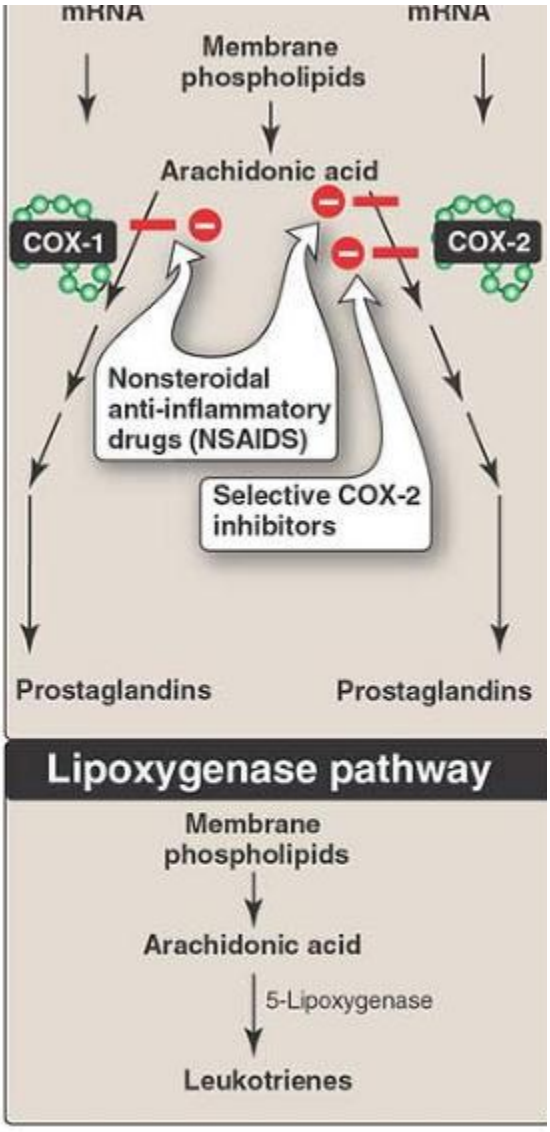
Learning objective

At the end of this chapter the student is expected to learn the following:

1. Identification the different nonsteroidal antiinflammatory drugs
2. The mechanism of action, therapeutic uses, and adverse effect of NSAIDs.

Aspirin

Mechanism of Action: Aspirin irreversibly blocks the enzyme cyclooxygenase; the drug decreases the formation of both the prostaglandins and thromboxane A2 but not the leukotrienes.



Anti-inflammatory Effects: aspirin also interferes with the chemical mediators of the kallikrein system. Thus, aspirin inhibits granulocyte adherence to damaged

vasculature, stabilizes lysosomes, and inhibits the migration of polymorphonuclear leukocytes and macrophages into the site of inflammation.

Analgesic Effects: Aspirin is most effective in reducing pain of mild to moderate intensity.

Antipyretic Effects: Aspirin blocks the pyrogen-induced production of prostaglandins and the central nervous system response to interleukin-1.

Platelet Effects: Aspirin inhibits platelet aggregation by inhibition of thromboxane synthesis.

Inhibition of platelet aggregation: It reduces the incidence of thrombosis in coronary artery bypass grafts. It may also reduce the incidence of myocardial infarction.

Clinical Uses

*Analgesic, antipyretics, and anti-inflammatory effects***:** acute abdomen, renal colic, pericarditis, myocardial infarction, cancer pain, rheumatoid arthritis, rheumatic fever, and other inflammatory joint conditions.

Adverse Effects

Gastrointestinal Effects: The gastritis .

Central Nervous System Effects: "salicylism" tinnitus, decreased hearing, and vertigo reversible by reducing the dosage.

Newer Nonsteroidal Anti-Inflammatory Drugs

These drugs are reversible inhibitors of cyclooxygenase.

Ibuprofen

Ibuprofen is extensively metabolized in the liver, and little is excreted unchanged.

Gastrointestinal irritation and bleeding occur, though less frequently than with aspirin. In addition to the gastrointestinal symptoms, rash, pruritus, tinnitus, dizziness, headache, and fluid retention have been reported. Rare hematologic effects include agranulocytosis and aplastic anemia. Effects on the kidney include acute renal failure, interstitial nephritis, and nephritic syndrome, occurring very rarely.

Diclofenac

Diclofenac is a potent cyclooxygenase inhibitor with anti-inflammatory, analgesic, and antipyretic properties. The drug is rapidly absorbed following oral administration and has a half-life of 1-2 hours. It accumulates in the synovial fluid. The potency of diclofenac as a cyclooxygenase inhibitor is greater than that of naproxen. The drug is

recommended for chronic inflammatory conditions such as rheumatoid arthritis and osteoarthritis and for the treatment of acute musculoskeletal pain. Adverse effects include gastrointestinal distress, occult gastrointestinal bleeding, and gastric ulceration.

Mefenamic Acid

Mefenamic acid, another fenamate, possesses analgesic properties but is probably less effective than aspirin as an anti-inflammatory agent and is clearly more toxic.

NSAIDS FOR SPECIAL INDICATIONS

Indomethacin

Indomethacin is slightly more toxic but in certain circumstances more effective than aspirin. Indomethacin is well absorbed after oral administration and highly bound to plasma proteins. Metabolism occurs in the liver and unchanged drug and inactive metabolites are excreted in bile and urine.

Clinical Uses: treatment of patent ductus arteriosus, acute gouty arthritis and ankylosing spondylitis, pericarditis and pleurisy.

Adverse Effects: The gastrointestinal effects may include abdominal pain, diarrhea, gastrointestinal hemorrhage, and pancreatitis. CNS effects include be associated with dizziness, confusion, and depression. Serious hematologic reactions' including thrombocytopenia and aplastic anemia has been reported.

Acetaminophen

Acetaminophen is the active metabolite of phenacetin responsible for its analgesic effect. It is a weak prostaglandin inhibitor in peripheral tissues and possesses no significant anti-inflammatory effects.

Adverse Effects: It is hepatotoxic (contraindicated in patients with known liver diseases), and also causes hemolytic anemia and methemoglobinemia

DRUGS USED IN GOUT

Gout is a familial metabolic disease characterized by recurrent episodes of acute arthritis due to deposits of monosodium urate in joints and cartilage. Formation of uric acid calculi in the kidneys may also occur.

NSAIDS in Gout

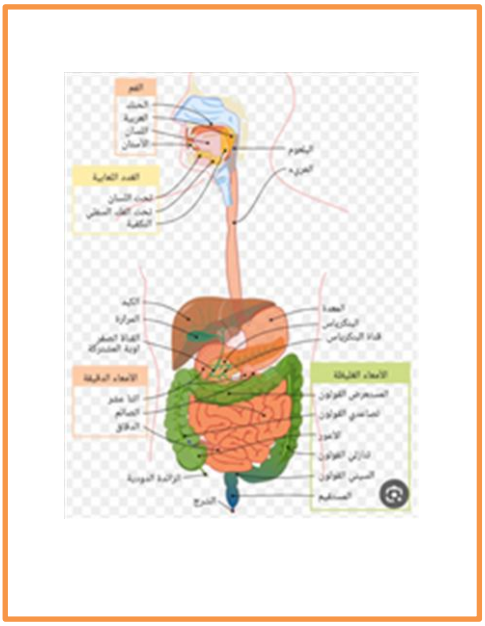
Indomethacin and other NSAIDs inhibit urate crystal phagocytosis. Indomethacin is the agent most often used today to treat acute gout. All other NSAIDs except aspirin can be used to treat acute gouty episodes.

DRUGS USED IN GASTROINTESTINAL DISEASES

Learning objectives

After completing this chapter the student will be able to:

1. Descibe different drugs used for treatment of gastrointestinal diseases,
2. Understand the basic pharmacological principles of these drugs,
3. Know the adverse effects of these drugs,



I. **Drugs used in Acid-peptic disease**

II. **II. Laxatives and cathartics (purgatives)**

III. **Antidiarrhoeals**

IV. **IV. Antiemetics**

I. Drugs used in Acid-peptic disease:

A: Gastric acid neutralizers (antacids)

Antacids are divided into :

- **Systemic,** e.g. sodium bicarbonate are absorbed into body fluids and may alter acid – base balance. It can be used in the treatment of metabolic acidosis.
- **Non systemic,** do not alter acid – base balance significantly. They are used as gastric antacids; and include aluminum, magnesium and calcium compounds e.g. (Al(OH)3, MgS2O3 , Mg(OH)2, CaCO3)

B. Gastric acid secretion inhibitors (antisecretory drugs):

Antagonists of ***acetylcholine***, ***histamine*** and ***gastrin*** inhibit acid secretion.

Antisecretory drugs include:

- H2-receptors blocking agents such as cimetidine, ranitidine, famotidine . Cimetidine *is the proto type of the group.*

adverse effects : muscular pain, headache, dizziness,

- **Proton pump inhibitors** such as**,** ***omeprazole***, ***lansoprazole, etc.*** inhibit H+ - K+-ATPase (proton pump) which is the common terminal step in the three secretagogues to release hydrogen ion into the gastric lumen.
- **Anticholinergic agents** such as pirenzepine, dicyclomine

C. Cytoprotective (mucosal protective) agents.

Locally active agents help to heal gastric and duodenal ulcers by forming a protective barrier between the ***ulcers*** and ***gastric acid, pepsin,*** and ***bile salts***.

• They do not alter the secretion of gastric acid. These drugs include ***sucralfate*** and ***colloid bismuth compounds***. (e.g. tripotassium, dicitratobismuthate) .

Other drugs that can to eradicate H.pylori such as amoxicillin, metronidazole, clarithromycin and tetracycline are included in the anti-ulcer treatment regimens.

• Protaglandins have both antisecretory and mucosal protective effects.

Example: **Misoprostol**- used for prevention of NSAID – induced ulcer.

II. Laxatives and cathartics (purgatives) :

Laxative and cathartics are classified depending on mode of action as:

1. Bulk forming laxatives: are substances that are largely unabsorbed from the intestine.

They include **hydrophilic colloids** such as psyllium, bran, methylcellulose, etc. **Osmotic laxatives** such as magnesium sulfate, magnesium hydroxide, sodium phosphate, etc. also belong to bulk – forming laxatives.

2. Stimulant (irritant) laxatives (cathartics): e.g. castor oil, bisacodyl, phenolphthalein, cascara sagrada, glycerine, etc.
3. Fecal softeners –e.g. ***docusate***.
4. Lubricant laxatives e.g. ***liquid paraffin*** (mineral oil). It lubricates the intestine and is thought to soften stool by retarding colonic *absorption of fecal water*.

III. Antidiarrhoeals:

• For symptomatic treatment of diarrhea, opiates and opiate derivatives are the most effective. They decrease diarrhea by slowing propulsive movements in small and large intestine. Morphine is effective but not used because of serious potential adverse effects, other synthetic drugs such as diphenoxylate and loperamide are commonly used

• Adsorbent – demulcent products such as kaolin – pectin preparation

• Anticholinergic agents e.g. atropine are occasionally used to decrease abdominal cramping and pain associated with diarrhea.

• Severe diarrhea by salmonella, shigella, campylobacter and clostridia. Species can be treated by antibiotics (ampicillin, chloramphinicol, colistin, co-trimoxazole.

IV. Antiemetics:

• Are drugs used to prevent or treat nausea and vomiting .

• Antiemetic drugs are generally more effective in prophylaxis than treatment. Antiemetic drugs include:

Phenothiazines (neuroleptics) such as chlorpromazine

• Acts on CTZ(Chemoceptor trigger zone) and vomiting center

• Block dopamine receptors

Antihistamines – such as promothazine, dimehydrinate etc.

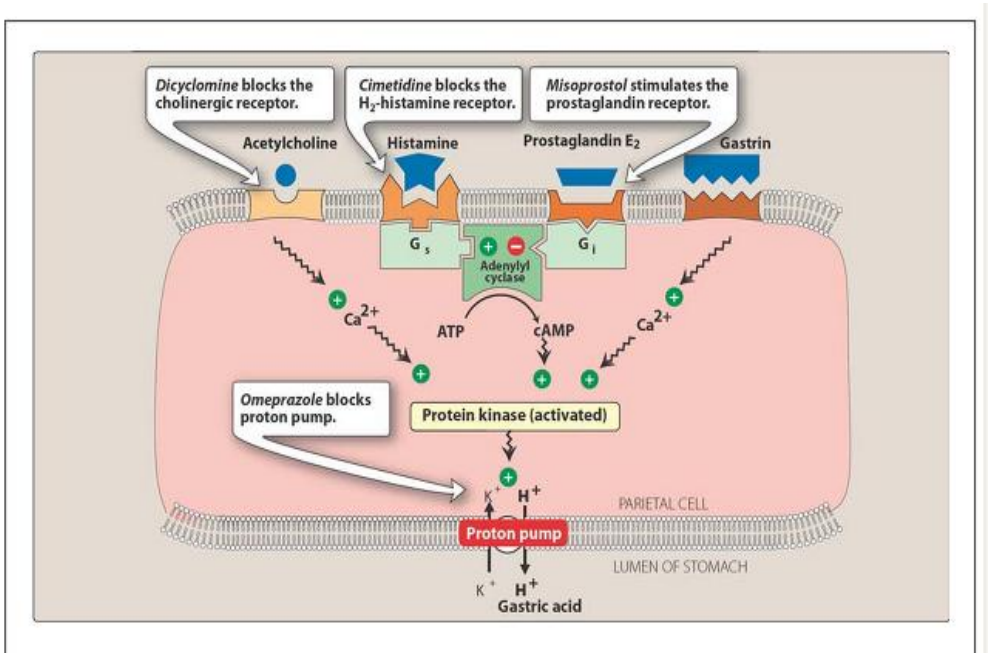
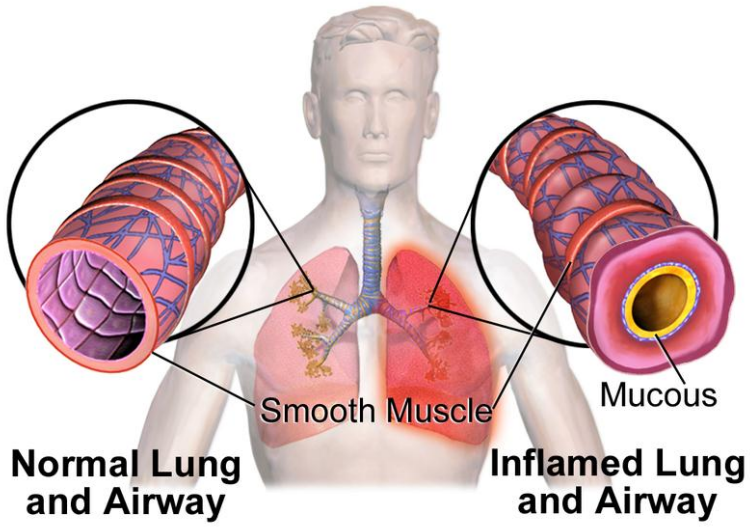


Figure. Effects of acetylcholine, histamine, prostaglandin E_2, and gastrin on gastric acid secretion by the parietal cells of stomach. G_s and G_i are membrane proteins that mediate the stimulatory or inhibitory effect of receptor coupling to adenylyl cyclase.

THEORY PHARMACOLOGY-LECT.4

DRUGS ACTING ON THE RESPIRATORY SYSTEM



Learning Objectives

At the end of the chapter the students will be able to learn:

1. Detail description of drug used to treat bronchial asthma, cough, nasal congestion as a result of some disorders and allergic condition.
2. Broad classification of drugs used to treat bronchial asthma
3. The pharmacokinetics, mechanism of action, side effects of each group of drugs used to treat bronchial asthma.

I.Bronchial asthma

II.Anti-tussives

III.Decongestants

I.Bronchial asthma

Pharmacotherapy of Bronchial asthma

Drug used in the treatment of bronchial asthma can be grouped into three main categories:

1. Bronchodilators

a. β- Adrenergic agonists which include:

- Non selective β-agonists e.g. adrenaline
- Selective β-agonists e.g. salbutamol

b. Methylxanthines; theophylline derivatives

c. Muscranic receptor antagonists e.g. Ipratropium bromide

2. Mast cell stabilizers, e.g. cromolyn sodium.

3. Antiinflammatory agents: corticosteroids

1. β- Adrenergic agonists (Sympathmimetic agents)

a) Non- selective- β-agonists

- Epinephrine, ephedrine.

b). Selective β-agonists

- Salbutamol, terbutaline .

Mechanism of Action

β-Agonists stimulate adenyl cyclase and increase formation of cAMP in the airway tissues.

- Relax smooth muscles

- Inhibit release of inflammatory mediator or broncho constricting substances from mast cells.

Side effects

Tremors, anxiety, insomnia, tachycardia, headache, hypertension and etc.

2. METHYLXANTHINES

theophylline, theobromine, and caffeine.

The theophylline preparations most commonly used for therapeutic purposes is aminophylline (theophylline plus diethylamine).

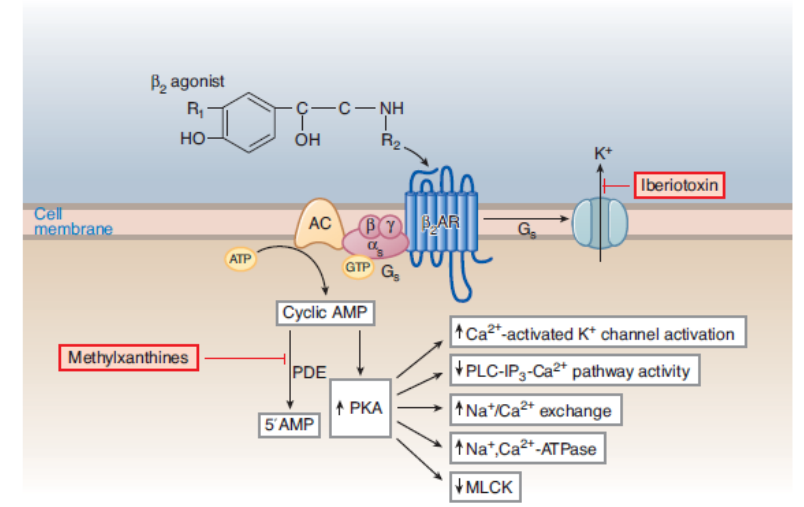
Mechanism of Action

1. Competitively inhibit phosphodiesterase (PDE) enzyme leading to increased cAMP level.
2. They competitively inhibit the action of adenosine on adenosine (A1 and A2) receptors

(adenosine has been shown to cause contraction of isolated airway smooth muscle and to provoke histamine release from airway mast cells.

3. Inhibit the release of histamines and leukotriens from the mast cells

of the three natural xanthines, agents **theophylline** is most selective in its smooth muscle effect, while caffeine has the most marked central effect.



Adverse Effects:

Anorexia, nausea vomiting, abdominal discomfort, headache, anxiety, insomnia, seizures, arrhythmias

3. Muscaranic receptor Antagonists

e.g Ipratropium bromide

Mechanism of Action

Muscarinic antagonist competitively inhibit effect of acetylcholine at muscarinic receptors – hence block the contraction of air way smooth muscle and the increase in secretion of mucus that occurs in response to vagal activity e.g atropine sulfate.

Systemic adverse effects : include urinary retention, tachycardia, loss of accommodation and agitation and local effects like excessive dryness of mouth

4. Anti-Inflammatory agents: Corticosteroids(hydrocortisone, predinisolone, tiamcinolne), **Bronchodilator.** Aerosol .

Used both for treatment and prophylactic purposes

Mechanism of action

They are presumed to act by their broad anti- inflammatory efficacy mediated in part by inhibition of production of inflammatory mediators. They also potentiate the effects of β- receptor agonists and inhibit the lymphocytic-eosinophilic airway mucosal inflammation

Effects on airway

• decreases bronchial reactivity

• increases airway caliber

• decreases frequency of asthma exacerbation and severity of symptoms

Side effects:

- Suppression of the hypothalamic-pituitary-adrenal axis

- Osteoporosis

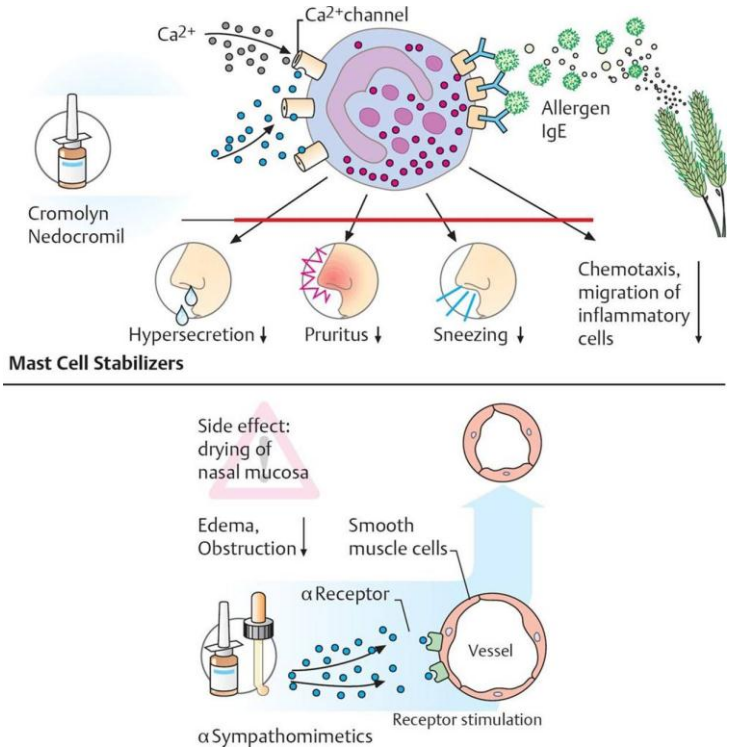
- Sodium retention and hypertension

- Impairment of growth in children

5. Mast cell stabilizers e.g cromolyn sodium

Mechanism of action

Stabilize the mast cells so that release of histamine and other mediators is inhibited through alteration in the function of delayed chloride channel in cell membrane. It has no role once mediator is released and is used for casual prophylaxis.



Side effects

Poorly absorbed so minimal side effect; Throat irritation, cough, dryness of mouth, chest tightness and wheezing

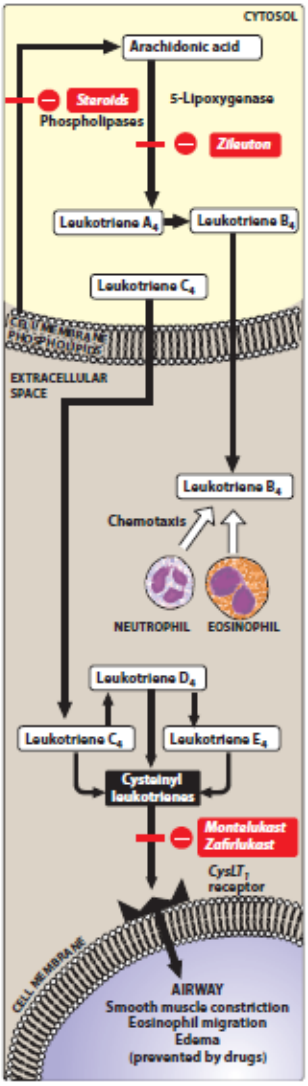
6. Leukotriene modifiers(montelukast)

Mechanism of action

selective antagonists of the cysteinyl leukotriene- 1 receptor, they block the effects of cysteinyl leukotrienes.

Adverse effects

Elevations in serum hepatic enzymes, headache and dyspepsia.



II.Anti- Tussive

Cough is a protective reflex, which serves the purpose of expelling sputum and other irritant materials from the respiratory airway.

Types:

- Useful productive cough

- Effectively expels secretions and exudates

- Useless cough

- Non-productive chronic cough
- Due to smoking and local irritants

Anti-tussives are drugs used to suppress the intensity and frequency of coughing.

Two Types of Anti-tussives:

1. Central anti- tussives

- Suppress the medullay cough center and may be divided into two groups:

- Opioid antitussive e.g. codeine, hydrocodeine, etc
- Non opioid antitussives e.g. dextromethorphan

2. Peripheral antitussives

- Decrease the input of stimuli from the cough receptor in the respiratory passage.

e.g: Demulcents e.g. liquorices lozenges, honey

Local anesthetics e.g. lidocaine aerosol

Demulcents coat the irritated pharyngeal mucosa and exert a mild analgesic effect locally.

Codeine

Codeine is a narcotic relatively less addicting drug and central antitussive agent and its main

Side effects : dryness of mouth, constipation and dependence.

Dextrometrophan

Dextromethorphan is an opioid synthetic antitussive, essentially free of analgesic and addictive properties and the main side effects are respiratory depression

Expectorant is a drug that aid in removing thick tenacious mucus from respiratory passages, e.g. Ipecac alkaloid, sodium citrate, saline expectorant, potassium salts

Mucolytics are agents that liquefy mucus and facilitate expectoration, e.g.acetylcysteine.

III.Decongestants

Classification:

- Xylometazoline
- oxymetazoline

Mechanism of Action

Mucus membrane decongestants are α1 agonists, which produce localized vasoconstriction on the small blood vessels of the nasal membrane. Reduce congestion in nasal passages.

CHEMOTHERAPEUTIC DRUGS

Learning Objectives

At the end this section the student will able to:

1. Describe the general mechanisms of action of antimirobial drugs.
2. Illustrate the mechanims of antimicrobial drug resistance.
3. Explain the indications, and adverse effects of frequently used antibiotics.
4. Describe the major adverse effects and clinical uses of aminoglycosides.
5. Describe the mechanims of action and the adverse effects of antituberculois drugs.
6. Classify antifungal drugs.
7. Classify antiretroviral drugs.
8. Explain the common adverse effects of anti cancer drugs.
9. Describe the clinical uses, and the major adverse effects of antimalarial drugs.
10. Discuss drugs used in the treatment of different forms of amoebiasis.
11. Describe drugs used for gardiasis and trichomonisis.
12. Discuss drugs used in the treatment of toxoplasmosis, and pneumocystiois.
13. Explain drugs used in the treatment of leshmaniasis and trypanosomiasis.
14. Discuss the use, mechanism of action and problems associated with anthelminthic drugs.

INTODUCTION

Chemotherapy*:* is the use of chemical agents (either synthetic or natural) to destroy infective agents (microorganisms' i.e bacteria, fungus and viruses, protozoa, and helminthes) and to inhibit the growth of malignant or cancerous cells.

Antimicrobials*:* are chemical agents (synthetic/natural) used to treat bacterial, fungal and viral infections.

Antibiotics*:* are substances produced by various species of microorganisms (bacteria, fungi, actinomycetes) that suppress the growth of other microorganisms. Antimicrobial drug exhibits *selective toxicity*. I.e. the drug is harmful to the parasite without being harmful to the host.

bactericidal : antimicrobial agents lead to the death of the susceptible microbe (e.g. bacteria).

Bacteriostatic *:* antimicrobial agents inhibits the growth of the susceptible microbe (e.g. bacteria).

Anticancer agents*:* Drugs or chemicals used to manage neoplastic diseases.

Antiprotozoals*:* are drugs used to treat malaria, amoebiasis, gardiasis, trichomoniasis,

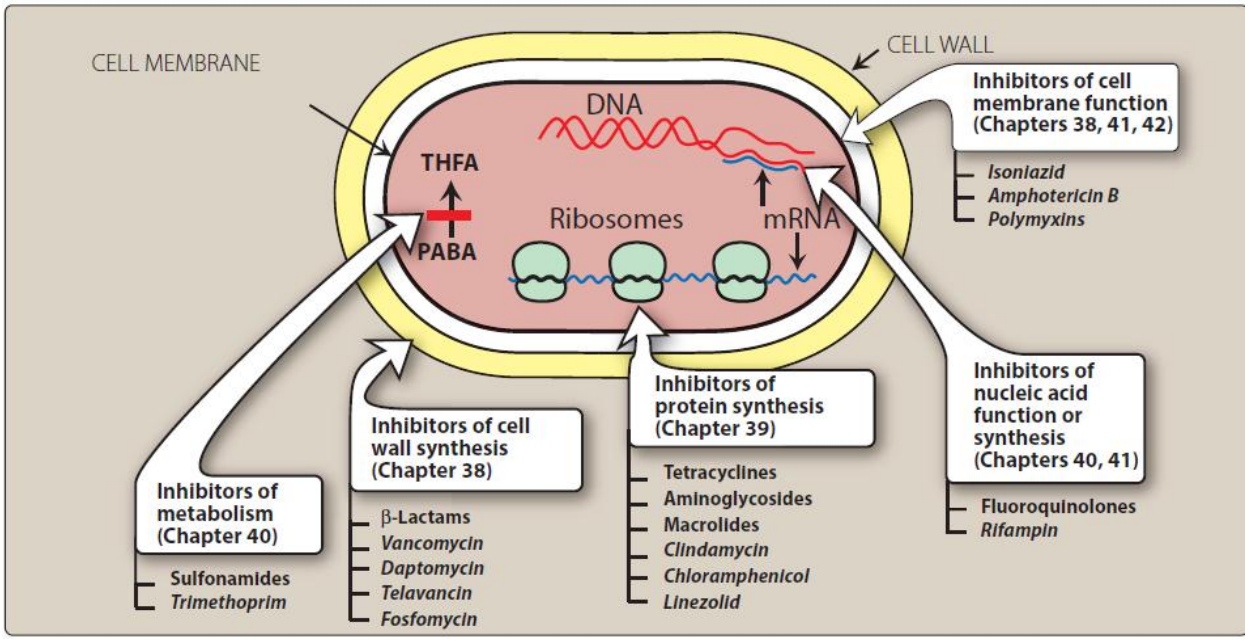
toxoplasmosis, pneumocystis carinii pneumonia, trypanosomiasis and leshmaniasis.

Anthelminthics*:* are drugs used in the treatment of intestinal and tissue worms.

ANTIMICROBIAL DRUGS

Mechanisms of antimicrobial drug action:

1. Inhibition of cell wall synthesis
2. Cell membrane function inhibitors
3. Inhibition of protein synthesis
4. Inhibition of nucleic acid synthesis
5. Antimetabolites



Mechanisms of resistance to antibiotics

1. Production of enzymes that inactivate the drug (eg. β -lactamase, which inactivates beta lactam antibiotics; acetyl transferases, which inactivate chloramphenicol; kinases and other enzymes, which inactivate aminoglycosides.
2. Alteration of the drug-binding site: this occurs with penicillins, aminoglycosides and erythromycin.
3. Reduction of drug uptake by the bacterium: eg. Tetracyclines
4. Alteration of enzymes: eg. Dihydrofolate reductase becomes insensitive to trimethoprim.

Anibacterial agents

Cell wall synthesis inhibitors

Members the group: Beta-lactam antibiotics, vancomycin, bacitracine, and cycloserine

Beta-lactam antibiotics: Penicillins, cephalosporins, carbapenems, and monobactams.

Penicillins

The prototype of penicillins is penicillin G and is naturally derived from a genus of moulds called penicillium.

Classification: Penicillins can be classified into three groups:

Natural Penicillins, Antistaphylococcal penicillins, and *Extended-spectrum penicillins.*

Mechanism of Action: Penicillins inhibit bacterial growth by interfering with a specific step in bacterial cell wall synthesis. Sensitive pencillins are inactivatived by betalactamase enzymes.

Antistaphylococcal Penicillins: [Methicillin, Nafcillin ,Oxacillin, cloxacillin, and dicloxacillin)]. The only indication is infections caused by beta-lactamase-producing staphylococci.

Extended Spectrum Penicillins: Aminopenicillins (ampicillin, amoxicillin), Carboxypenicillins .

Adverse Reactions: Grouped into three: *Allergy*: Skin rashes, fever, bronchospasm, Oral lesions, interstitial nephritis and **anaphylactic shock**.

*Biological**:*** **antibiotic assoicated enterocolitis (ampicillin)**, *Toxic:* **diarrhea (ampicillin), nephritis**, especially methicillin, and platelet dysfunction (antipseudomonal penicillins).

Cephalosporins

Cephalosporins can be classified into four generations depending mainly on the spectrum of antimicrobial activity :

First-generation cephalosporins : Cefadroxil, cefazolin, and **cephalexin.**

*Second-generation cephalosporins :*Cefaclor, cefamandole, and **cefuroxime.**

*Third-generation cephalosporins :*cefotaxime, ceftazidime, and **ceftriaxone.**

Fourth-generation cephalosporins ***(e.g.cefepime)*** It is similar to third-generation agents; however, it is more resistant to hydrolysis by betalactamases.

It has good activity against P aeruginosa.

Adverse Effects: hypersensitivity reactions that are identical to those of penicillins. Overgrowth of resistant organisms and fungi may induce **superinfection.**

Carbapenems include imipenem and meropenem

Beta-lactamase inhibitors: (clavulanic acid, sulbactam, and tazobactam)**.**

Cell Membrane Function Inhibitors **:** ploymyxin B and colistin.

Protien Synthesis Inhibitors

Protien synthesis inhibitors are divided into two groups: bacteriostatic and bactericidal. Chloramphenicol, macrolides, clindamycin , and tetracyclines are bacteriostatic ,whereas aminoglycosides are bactericidal**.**

Tetracyclines

Tetracyclines are classified as short acting (chlortetracycline, **tetracycline**, oxytetracycline), intermediate acting (demeclocycline and **methacycline**), or long-acting (**doxycycline** and minocycline) based on serum half-lives.

Mechanisms of action:

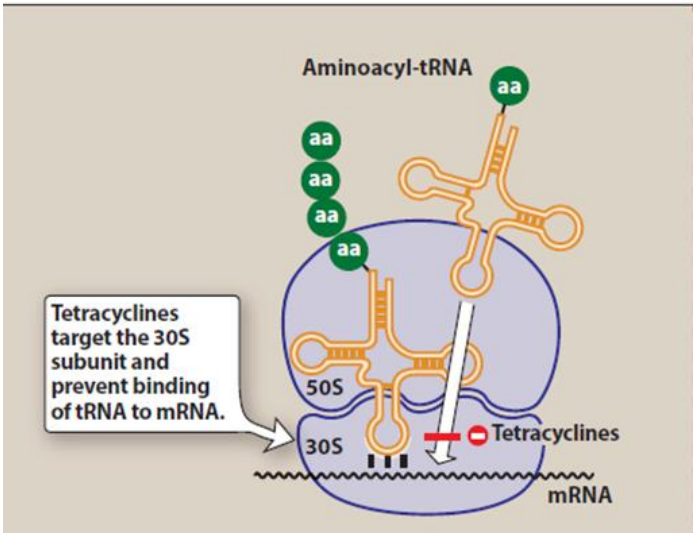
Tetracyclines bind to 30S ribosomal subunit at a site that blocks binding of charged tRNA to the 50S site of the ribosome.

Antimicrobial activity: **Tetracyclines are broad-spectrum antibiotics.** They are active against for many gram-positive and gram-negative bacteria, including anaerobes, rickettsiae, chlamydiae, mycoplasmas.

Adverse reactions

Gastrointestinal adverse effects: Nausea, vomiting, and diarrhea intestinal functional disturbances, anal pruritus.

Bony structures and teeth*:* Tetracyclines are readily bound to calcium deposited in newly formed bone or teeth in young children. **It causes discoloration, and enamel dysplasia.**



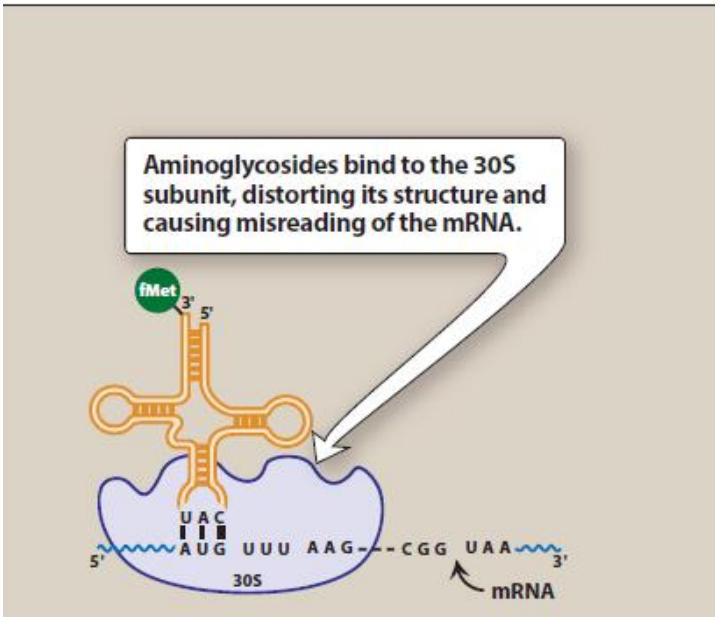
Aminoglycosides:

Streptomycin, neomycin, kanamycin, amikacin, gentamicin.

Mechanisms of action:

(1)They interfere with the "initiation complex" of peptide formation; **(2) they induce misreading of mRNA, which causes incorporation of incorrect amino acids into the peptide, resulting in a nonfunctional or toxic protein**; and (3) they cause a breakup of polysomes into nonfunctional monosomes. These activities occur more or less simultaneously, and the overall effect is irreversible and lethal for the cell.

Adverse effects: **Ototoxicity , Nephrotoxicity**



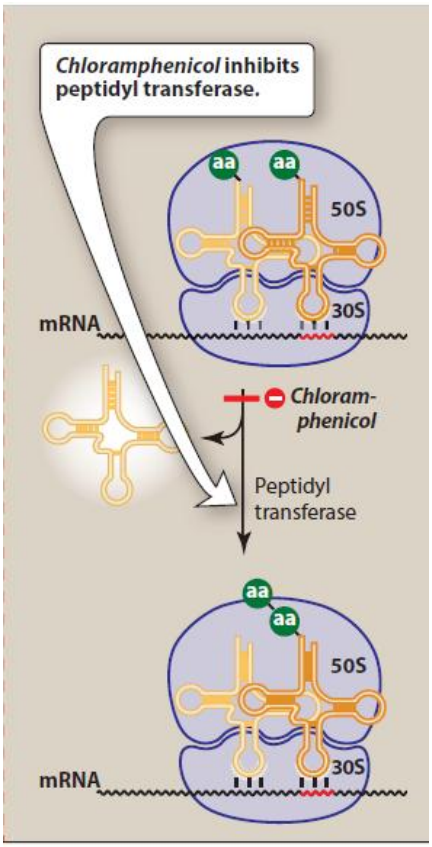
Chloramphenicol

Chloramphenicol is a **bacteriostatic broad-spectrum antibiotic** that is active against both aerobic and anaerobic gram-positive and gram-negative organisms. It is active also against rickettsiae. *Haemophilus influenzae*, *N. meningitidis*, and some strains of *Bacteroides* are highly susceptible, and for them chloramphenicol **may be bactericidal.**

Adverse Reactions

Gastrointestinal disturbances: nausea, vomiting, and diarrhea.

Bone marrow disturbances: **Aplastic anemia** .



Macrolides: *include erythromycin, clarithromycin and azithromycin.*

Mechanisms of action:

Macrolides, clindamycin, prevent transfer of the growing polypeptide chain within the 50S site so a new charged tRNA cannot bind to the ribosome so, stops protein synthesis.

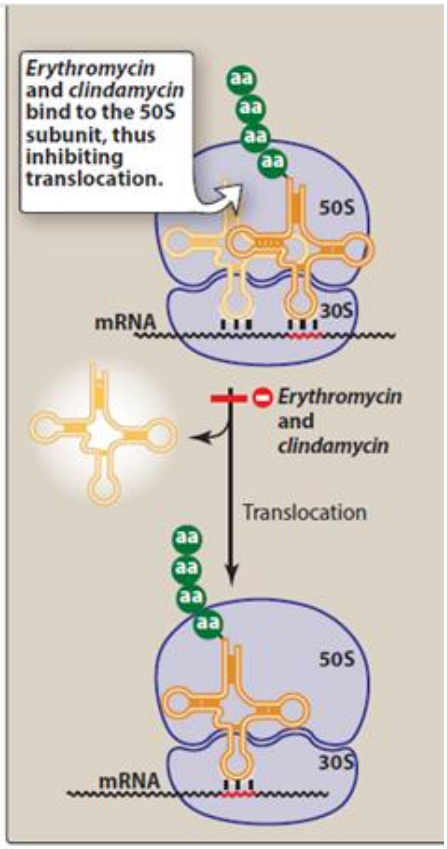
Erythromycin

Antimicrobial Activity: Erythromycin is effective **against gram-positive organisms**, especially pneumococci, streptococci, staphylococci, and corynebacteria. **Gram-negative organisms** such as Neisseria species, Bordetella pertussis, Treponema pallidum, and Campylobacter species are susceptible.

Adverse Reactions

Gastrointestinal Effects: Anorexia, nausea, vomiting, and diarrhea.

Liver Toxicity: Erythromycins, particularly the estolate, can produce acute **cholestatic hepatitis** (reversibile).



Nucleic Acid Synthesis Inhibitors

Nalidixic acid

Nalidixic acid is the first antibacterial quinolone. They inhibit normal transcription and replication of bacterial DNA. Because of their relatively weak antibacterial activity, these agents were useful only for the treatment of urinary tract infections and shigellosis.

Fluoroquinolones

Quinolones are synthetic fluorinated analogs of nalidixic acid, that nucleic acid synthesis.

Ofloxacin and ciprofloxacin inhibit gram-negative cocci and bacilli, including *Enterobacteriaceae, Pseudomonas, Neisseria, Haemophilus, and Campylobacter.*

Clinical Uses: Fluoroquinolones are effective in **urinary tract infections** even when caused by multidrug-resistant bacteria, eg, Pseudomonas. These agents are also effective for bacterial diarrhea caused by Shigella, Salmonella, E coli, or Campylobacter.

Adverse Effects: nausea, vomiting, and diarrhea.

Rifampin

Rifampin binds strongly to the bacterial DNA-dependent RNA polymerase and thereby inhibits RNA synthesis. It is well absorbed after oral administration and excreted mainly through the liver into bile.

Adverse effects : thrombocytopenia, nephritis, **cholestatic jaundice and hepatitis**.

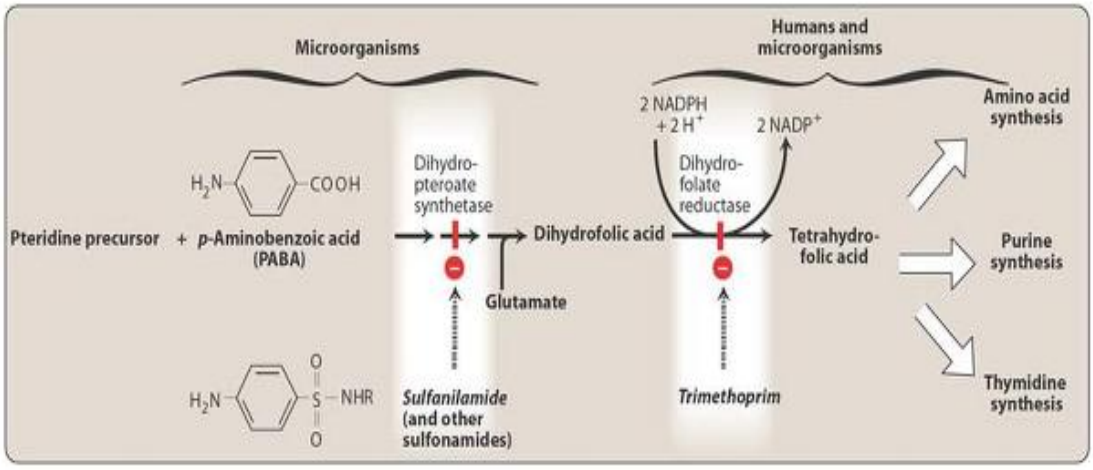
Antimetabolites

Sulfonamides

Sulfonamides can be divided into three major groups: (1) oral, absorbable; (2) oral,

nonabsorbable; and (3) topical. The oral, absorbable sulfonamides can be classified as short-, medium-, or long acting on the basis of their half-lives.

Mechanisms of action:



Sulfonamides inhibit both gram-positive and gram-negative bacteria, *Nocardia, Chlamydia trachomatis,* and some protozoa. Some enteric bacteria, such *as E coli, Klebsiella, Salmonella, Shigella, and Enterobacter*, are inhibited.

Pharmacokinetics: They are absorbed from the stomach and small intestine and distributed widely to tissues and body fluids, placenta, and fetus. Sulfonamides and inactivated metabolites are then excreted into the urine, mainly by glomerular filtration.

Clinical Uses

Oral Absorbable Agents: Sulfisoxazole and **sulfamethoxazole** are short- to medium-acting agents that are used to **treat urinary tract infections**, respiratory tract infections, bronchitis, pneumonia, otitis media, and dysentery.

Topical Agents bacterial conjunctivitis and as adjunctive therapy for trachoma. Silver sulfadiazine is preferred for prevention of infection of burn wounds.

Adverse Reactions: fever, skin rashes, photosensitivity, urticaria, nausea, vomiting, , diarrhea and **crystalluria.**

Trimethoprim

Trimethoprim inhibits bacterial dihydrofolic acid reductase. Dihydrofolic acid reductases convert dihydrofolic acid to tetrahydrofolic acid, a stage leading to the synthesis of purines and ultimately to DNA.

Trimethoprim can be given alone in **acute urinary tract infections.**

Trimethoprim-Sulfamethoxazole(Cotrimoxazole)

The half-life of trimethoprim and sulfamethoxazole is similar.

Trimethoprim, + sulfamethoxazole = bactericidal,

Sulfonamide = bacteriostatic.

Clinical uses*:* Trimethoprim-sulfamethoxazole is effective treatment for pneumonia, shigellosis, systemic Salmonella infections, **urinary tract infections**, and prostatitis.

ANTIFUNGAL AGENTS

The antifungal drugs fall into two groups: antifungal antibiotics and synthetic antifungals.

Antifungal antibiotics

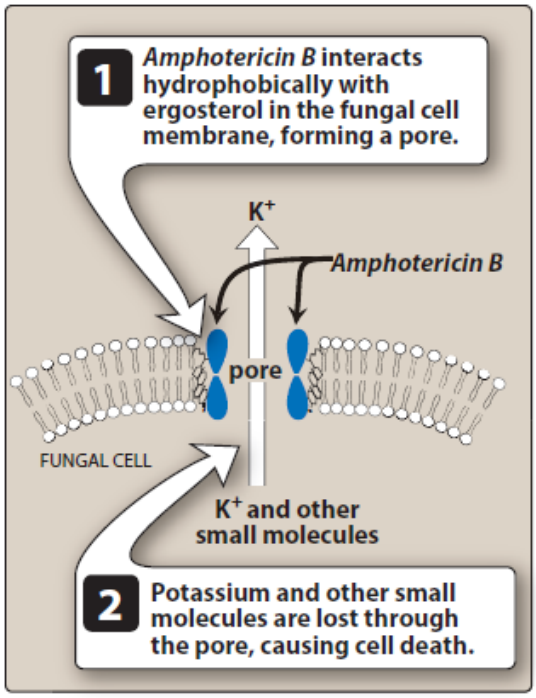
Amphotericin B

Mechanism of Action: Amphotericin B binds to ergosterol (a cell membrane sterol) and alters the permeability of the cell by forming amphotericin B-associated pores in the cell membrane. The pore allows the leakage of intracellular ions and macromolecules, eventually leading to cell death.

***Adverse Effects**:* fever, muscle spasms, vomiting, headache, hypotension ,liver damage, **anemia.**

***Antifungal Activity:* Amphotericin B is a broad-spectrum antifungal agent.** It has activity against yeasts including; Candida albicans and Cryptococcus neoformans; molds, Aspergillus fumigatus.

Clinical Use: serious fungal infections (immunosuppressed patients, severe fungal pneumonia, and cryptococcal meningitis with altered mental status).



Nystatin

Nystatin has similar structure with amphotericin B and has the same pore-forming mechanism of action. Nystatin is active against most **Candida species** and is most commonly used for suppression of local candidal infections.

Griseofulvin

Griseofulvin is a fungistatic and used is in the treatment of dermatophytosis.

Adverse effects include an allergic syndrome much like serum sickness, hepatitis.

Synthetic Antifungal Agents : Flucytosine

Imidazoles** : **Ketoconazole** ,Clotrimazole and **miconazole

Triazoles** : Itraconazole ,**Fluconazole

ANTIVIRAL AGENTS

Antiherpes Agents: Acyclovir,Ganciclovir ,Foscarnet ,Idoxuridine ,Vidarabine

Acyclovir

Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competitive inhibition of the viral DNA polymerase and by binding to the DNA template as an irreversible complex.

Clinical Uses: Intravenous acyclovir is the treatment of choice for herpes simplex encephalitis, neonatal HSV infection and for severe primary, recurrent **HSV** genital and labial infections and for those who cannot ingest oral pills

Adverse Reactions*:* Nausea, diarrhea, and headache .IV infusion may be associated with **renal insufficiency or neurologic toxicity.**

Other Antiviral Agents *: Amantadine, Rimantadine*

TREATMENT OF PROTOZOAL INFECTIONS

1. Treatment of Malaria

Four species of Plasmodium are responsible for human malaria: P. vivax, P. malariae, P. ovale, and P. falciparum, P falciparum. The effectiveness of antimalarial agents varies between parasite species and between stages in their life cycles.

1.1. Parasite Life Cycle

1.2. Drug Classification

The antimalarial drugs are classified by their selective actions on the parasite's life cycle.

1) Tissue schizonticides: drugs that eliminate tissue schizonts or hypnozoites in the liver (eg, **primaquine**).

2) Blood schizonticides: drugs that act on blood schizonts (eg, **chloroquine**, amodiaquine, proguanil, pyrimethamine, mefloquine, quinine) .

3) Gametocides are drugs that prevent infection in mosquitoes by destroying gametocytes in the blood (eg, **primaquine** for P falciparum and chloroquine for P vivax, P malariae, and P ovale.).

4) Sporonticidal agents are drugs that render gametocytes noninfective in the mosquito (eg, **pyrimethamine**, proguanil).

1.3. Individual antimalarial drugs

Chloroquine, Primaquine, Quinine, Proguanil and _Pyrimethamine, Sulfones_ and Sulfonamides, Pyrimethamine-Sulfadoxine (Fansidar) , Mefloquine, Doxycycline, Halofantrine, Qinghaosu (Artemisinin) .

2. Drugs used in amebiasis

The choice of drug depends on the clinical presentation and on the desired site of drug action, ie, in the intestinal lumen or in the tissues.

2.1. Tissue amebicides eliminate organisms primarily in the bowel wall, liver, and other extraintestinal tissues and are not effective against organisms in the bowel lumen.

2.1.1. **Metronidazole**, and tinidazole are highly effective against amebas in the bowel wall and other tissues.

2.1.2. **Emetine** and dehydroemetine act on organisms in the bowel wall and other tissues but not on amebas in the bowel lumen.

2.1.3. **Chloroquine** -Active principally against amebas in the liver.

2.2. Luminal Amebicides act primarily in the bowel lumen.

2.2.1. Diloxanide furoate

2.2.2. Iodo-quinol

2.2.3. **Tetracyclines, paromomycin and erythromycin**

2.4. Antiamoebic drugs

Metronidazole

Mechanism of Action: The nitro group of metronidazole is chemically reduced by ferredoxin within sensitive organisms. The reduction products appear to be responsible for killing the organisms by reacting with various intracellular macromolecules.

Clinical Uses: amebiasis, urogenital trichomoniasis, giardiasis, anaerobic infections, acute ulcerative gingivitis, and bacterial vaginitis and Helicobacter pylori infection.

Adverse effects: Nausea, headache, dry mouth, or metallic tastes occur commonly. Rare adverse effects include vomiting, diarrhea, insomnia, and paresthesias. It has a disulfiram-like effect.

Other Nitroimidazoles

Other nitroimidazole derivatives include **tinidazole**, and ornidazole.

Chloroquine,Dehydroemetine_ Emetine ,Diloxanide Furoate, Iodoquinol, Paromomycin Sulfate Other Antibiotics .

The tetracyclines (oxytetracycline) Erythromycin .

3. Drugs used in Giardiasis_ and Trichomoniasis

Metronidazole is a drug of choice for gardiasis and trichomoniasis, and the alternate drug is **tinidazole.**

4. Treatment of Leishmaniasis

The drug of choice is sodium antimony gluconate (sodium stibogluconate). Alternative drugs are **amphotericin B** and pentamidine.

5. Treatment of Pneumocystis Carinii Pneumonia, Trypanosomiasis_

5.1. Pentamidine

TREATMENT OF HELMINTHIC INFECTIONS

Anthelmintic drugs are used to eradicate or reduce the numbers of helminthic parasites in the intestinal tract or tissues of the body. Most anthelmintics are active against specific parasites; thus, parasites must be identified before treatment is started.

Individual Drugs

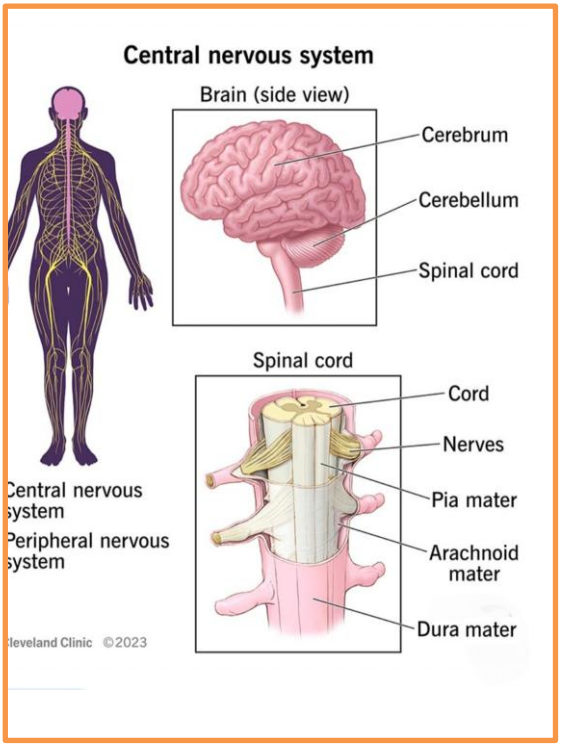
Albendazole Diethylcarbamazine Citrate, **Ivermectin**, Levamisole, Mebendazole, Metrifonate, Niclosamide, Oxamniquine, Piperazine, Praziquantel, Pyrantel Pamoate, Suramin**,** Thiabendazole

DRUGS ACTING ON THE CENTRAL NERVOUS SYSTEM

Learning Objectives

At the end this section the student will be able to:
1. Describe the major adverse effects of sedative hypnotic drugs.
2. Describe the drugs used in epilepsy.
3. Illustrate the approaches in the management of parkinsonism.
4. Explain the site of action, uses and adverse effects of antipsychotic drugs.
5. Describe the major adverse effects opioid analgesics.

Introduction



Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors.

NEUROTRANSMISSION IN THE CNS

In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system (ANS). For example, transmission of information in both the CNS and in the periphery involves the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral

ANS and those in the CNS. The circuitry of the CNS is much more complex than that of the ANS, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral ANS, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of multiple neurotransmitters, whereas the ANS uses only two primary neurotransmitters, acetylcholine and norepinephrine.

SYNAPTIC POTENTIALS

In the CNS, receptors at most synapses are coupled to ion channels. Binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions and the direction of their

movement.

A. Excitatory pathways

Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following:

1) Stimulation of an excitatory neuron causes the release of neurotransmitter molecules، such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na+) ions.

2) The influx of Na+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold. 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential.

Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.]

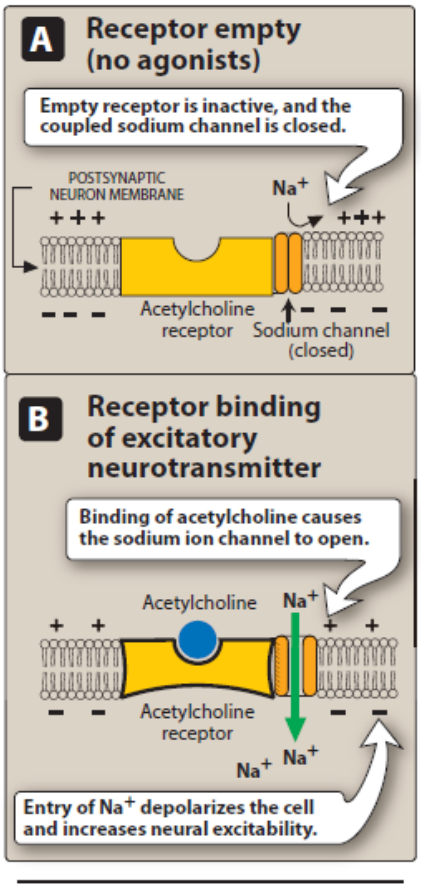


Figure. Shows an example of an excitatory pathway.

B. Inhibitory pathways

Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following:

(1Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K+) and chloride (Cl−).

2) The influx of Cl− and efflux of K+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials.

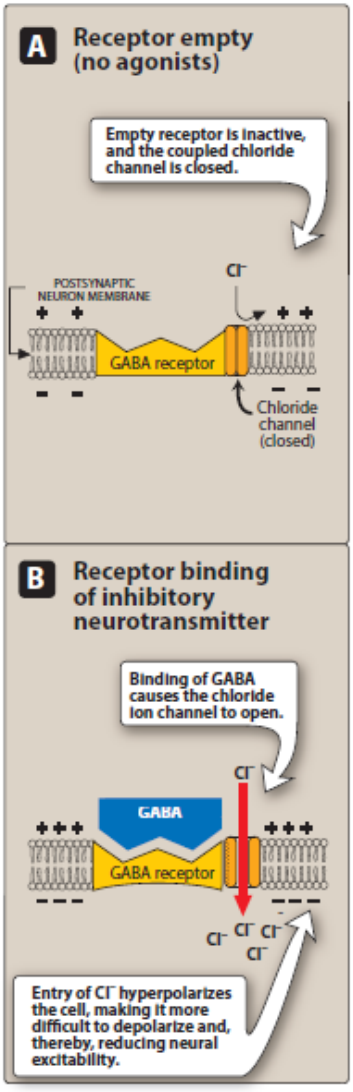


Figure . Shows an example of an inhibitory pathway.

C. Combined effects of the EPSP and IPSP

Most neurons in the CNS receive both EPSP and IPSP input. Thus، several different types of neurotransmitters may act on the same neuron, but each binds

to its own specific receptor. The overall action is the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons‹ the axons of which may synapse with specific regions of the brain. Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective modulation of certain neuronal pathways.

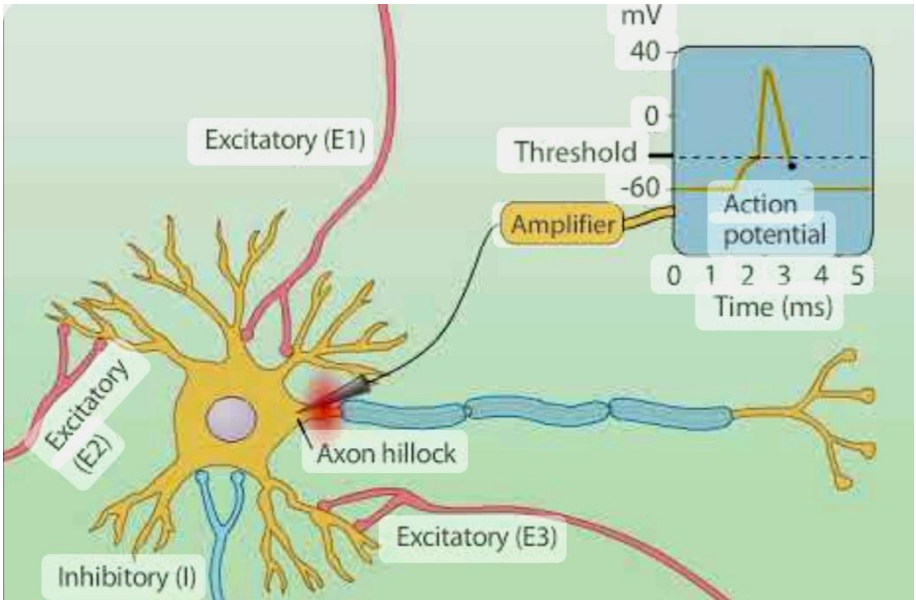


Figure. The neurons receive both EPSP and IPSP

GENERAL ANESTHETICS

Inhalation anesthetics

The main agents are: Halothane, nitrous oxide, enflurane and ether.

1. Halothane: Is the most widely used agent, highly lipid soluble, potent. It causes arrhythmia, hangover and the risk of liver damage is high if used repeatedly.

2. Nitrous oxide: Odorless and colorless gas. It is rapid in action and also an effective analgesic agent. Its potency is low, hence must be combined with other agents.

3. Ether: Has analgesic and muscle relaxant properties. It is highly explosive, causes respiratory tract irritation, postoperative nausea and vomiting.

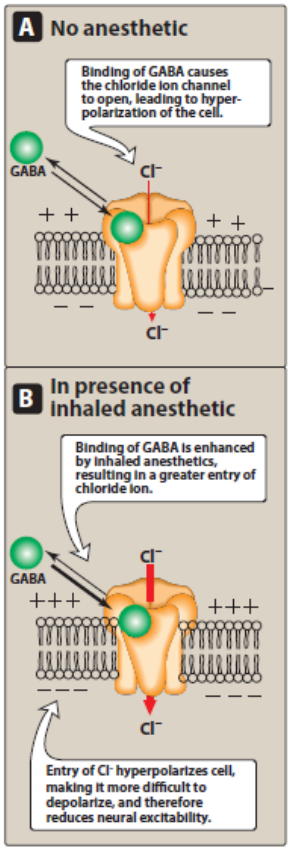


Figure :An example of modulation of a ligand-gated membrane channel modulated by inhaled anesthetics. GABA = γ-aminobutyric acid؛ Cl− = chloride ion.

INTRAVENOUS ANESTHETICS

1. **Thiopentone:** Thiopentone is a barbiturate with very high lipid solubility. After intravenous administration the drug enters to tissues with a large blood flow (liver, kidneys, brain, etc) and more slowly to muscle. It causes cardiovascular depression.
2. **Ketamine:** acts more slowly than thiopentone and produces a different effect, known as dissociative anaesthesia in which there is a marked sensory loss and analgesia, as well as amnesia and paralysis of movement, without actual loss of consciousness. Ketamine causes dysphoria, hallucinations during recovery.
3. Propofol: Propofol is an IV sedative/hypnotic used for induction and/or maintenance of anesthesia. It is widely used and has replaced thiopental as the first choice for induction of general anesthesia and sedation. Because propofol is poorly water soluble.

1. Onset: Induction is smooth and occurs 30 to 40 seconds after administration. Following an IV bolus, there is rapid equilibration between the plasma and the highly perfused tissue of the brain.

2. Actions: Although propofol depresses the CNS, it is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, yawning, and hiccups. Transient pain at the injection site is common. Propofol decreases blood pressure without depressing the myocardium. It also reduces intracranial pressure, mainly due to systemic vasodilation. It has less of a depressant effect than volatile anesthetics on CNS evoked potentials, making it useful for surgeries in which spinal cord function is monitored. It does not provide analgesia, so supplementation with narcotics is required. Propofol is commonly infused in lower doses to provide sedation. The incidence of postoperative nausea and vomiting is very low, as this agent has some antiemetic effects.

Benzodiazepines including diazepam, lorazepam, and midazolam are used in general anesthetic procedures. Benzodiazepines prolong the postanesthetic recovery period but also cause a high incidence of amnesia.

Opioid analgesic anesthesia: Opioid analgesics can be used for general anesthesia, in patients undergoing cardiac surgery and fentanyl and its derivates are commonly used for these purposes.

Preanesthetic medication: It is the use of drugs prior to the administration of anaesthetic agent with the important objective of making anaesthesia safer and more agreable to the patient. The drugs commonly used are, opioid analgesics, barbiturates, anticholinergics, anti emetics and glucocorticoids.

SEDATIVE AND HYPNOTIC DRUGS

Anxiolytic drugs are used to treat the symptoms of anxiety, whereas **hypnotic drugs** used to treat insomnia.

Classes of anxiolytic and hypnotic drugs:

1. *Benzodiazepines.* used as sedative and hypnotic agents.
2. *5- HT1A receptor agonist* (e.g. buspirone). It is recently introduced anxiolytic.
3. *Barbiturates* (phenobarbitone). used as sedative hypnotics.
4. β *-adrenoceptor antagonists* (e.g. propranolol). They are used to treat some forms of anxiety, where physical symptoms (sweating, tremor, and tachycardia), are troublesome. They are not used as hypnotics.
5. *Miscellaneous drugs* (chloral hydrate, paraldehyde, and diphenhydramine).

Benzodiazepines

Based on their duration of action roughly divided into short acting (flurazepam, triazolam), medium acting (lorazepam) and long acting compounds (diazepam, chlordiazepoxide, clonazepam).

Pharmacodynamics

Act by binding to a specific regulatory site on the GABA receptor, thus enhancing the inhibitory effects of GABA

Clinical Uses

Treatment insomnia, Anxiety, As anticonvulsants, Chronic muscle spasm and spasticity

Unwanted effects

• Toxic effects, prolonged sleep ,drowsiness, confusion, amnesia, and impaired motor coordination.

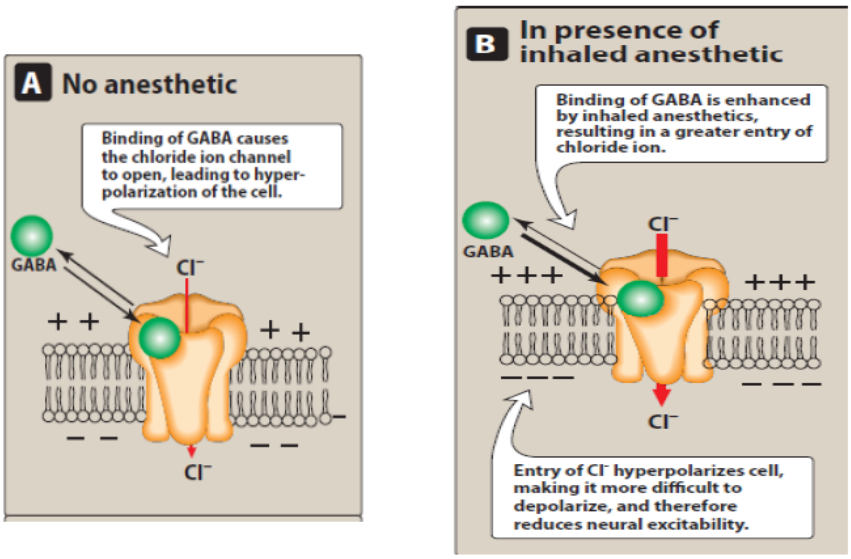


Figure: mechanism of action of benzodiazepines

5 - HT1A receptor agonist

Buspirone is a potent agonist of. *5 - HT1A* receptors. Buspirone does not cause sedation, motor incoordiation. The main side effects are nausea, dizziness, headache, and restlessness.

Barbiturates

They are non-selective CNS depressants, which produce effects ranging from sedation and reduction of anxiety, to unconsciousness and death from respiratory and cardiovascular failure. Barbiturates act by enhancing action of GABA.

ANTIEPILEPTIC DRUGS

phenytoin, carbamazepine, and phenobarbitone.

Mechanism of action

Anticonvulsant drugs act by two mechanisms: by reducing electrical excitability of cell membrane and by enhancing GABA mediated synaptic transmission.

MANAGEMENT OF PARKINSONISM

Parkinsonism: It is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability. It is due to the imbalance between the cholinergic and dopaminergic influences on the basal ganglia. Thus, the aim of the treatment is either to increase dopaminergic activity (by dopamine agonist) or to decrease cholinergic (antimuscarinic drugs) influence on the basal ganglia,**e.g. Levodopa**

Dopamine agonists e.g: Bromocryptine

Monoamine Oxidase Inhibitors: **Selegiline** (deprenyl).

Amantadine

Amantadine, an antiviral agent, was by chance found to have antiparkinsonism properties. Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine.

Acetylcholine Blocking Drugs (*Benztropine)*

Adverse Effects

drowsiness, mental slowness, inattention, restlessness, and confusion, hallucinations.

ANTIPSYCHOTIC AGENTS

Antipsychotic agents are classified into *typical neuroleptics* (chlorpromazine, thioridazine, haloperidol, flupenthixol) and *atypical neurolopitics* (clozapine, sulpiride).

Clinical uses

Schizophrenia,Mania,Vomiting

Adverse Reactions

• Extra pyramidal reactions

• Seizures

• Autonomic nervous system effects (antimuscarinic effects, orthostatic hypotension)

• Metabolic and Endocrine Effects (weight gain, hyperprolactinemia, infertility, loss of libido)

ANTIDEPRESSANT AGENTS:

Antidepressants are the drugs which are mainly used in the management of depression.Types of antidepressant drugs

1. Tricyclic antidepressants (TCAs)
2. Monoamine oxidase inhibitors (MAOI)
3. 5-HT uptake inhibitors
4. Atypical antidepressants

Mechanisms of action

Tricyclic antidepressanat TCAs (imipramine, amitriptyline) block the uptake of amines (noradrenaline and 5-HT) by nerve terminals by competition for the carrier transport system. In addition, TCAs block α1- adrenoceptors, muscarinic, histamine (H1) and 5-HT receptors.

Monoamine oxidase inhibitors (MAOI): *Tranylcypromine* selectively inhibits MAO-A. MAO-A has a substrate preference for 5 –HT. MAOI causes a rapid and sustained increase in the 5-HT, noradrenaline and dopamine. Selective 5-HT uptake inhibitors: *fluoxetine, fluvoxamine* lack antimuscarinic and cardiovascular effects.

Adverse Effects: Postural hypotension, dry mouth, blurred vision, constipation, urine retention, sedation , atropine-like effects, weight gain.

ANALGESICS

Opioid Analgesics

They are divided into two; morphine analogues and synthetic derivatives.

Morphine analogues .They may be agonist (*codeine and heroin*), partial agonists (*nalorphine*) or antagonists (*naloxone*).

Synthetic derivatives. Pethidine, methadone, pentazocine.

Pure agonists. They all have high affinity to mu receptors and varying affinity to delta and kappa receptors (codeine, methadone, dextropropoxyphene).

Partial antagonists and mixed agonist-antagonists: Nalorphine, and pentazocine.

Mechanism of Action: Opioid agonists produce analgesia by binding to specific receptors, located primarily in brain and spinal cord regions involved in the transmission and modulation of pain.

Effects of mixed agonist-antagonists: Pentazocine

Clinical use of opioid analgesics

constant pain, acute pulmonary edema (pulmonary edema associated with left ventricular failure), cough suppression, diarrhea, and preanaesthetic medication.

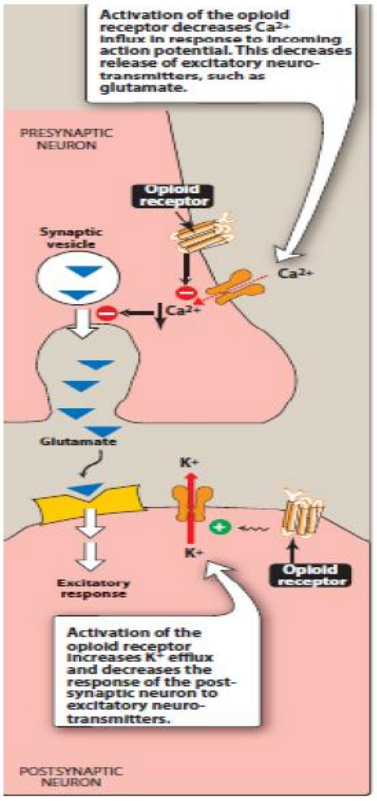


Figure : Mechanism of action of μ opioid receptor agonists in the spinal cord.

CNS stimulants: CNS stimulant can be classified into

1. *convulsants and respiratory stimulants* eg. Srychnine picrotoxin, nikethaimide

2. psychomotor stimulants ,Eg. Amphetamine, cocaine, caffeine

3. psychotomimetic drug ,Eg. Lysergic and diethylamide (LSD) psilocybin, phencyclidine.

Convlsants and respiratory stimulants: Certain short acting respiratory stimulants like doxapram, amiphenazole can be used in respiratory failure. Strychnine, picrotoxin and leptazole are used as chemical tools in experimental pharmacology in various animal models.

Psychomotor stimulants: Drugs like amphetamine cause increased motor activity, euphoria, excitement and anorexia due to release of noradrerline and dopamine.

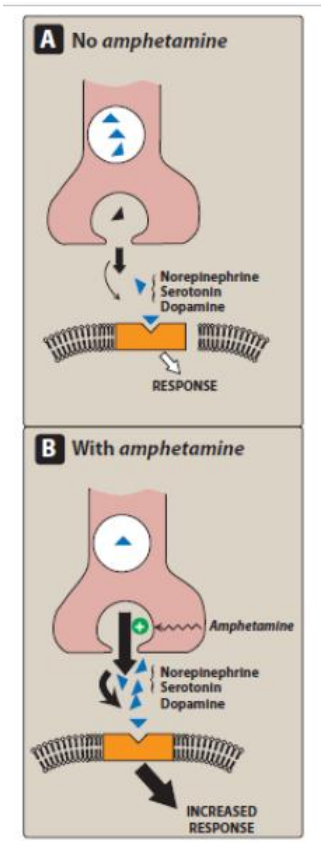


Figure : Mechanism of action of amphetamine.

***Clinical uses*:** Amphaetamine is useful in the treatment of narcolepsy and attention deficit in children. Cocaine is occasionally used as a local aneasthetic , mainly in ophthalmology and minor nose and throat surgery.

Psycho mimetic drugs: Drugs like LSD, phencyclidine and psilocybin cause sensory changes, hallucinations and delusions, resembling symptoms of acute schizophrenia. They are not used clinically but are important as drugs of abuse.

LOCAL ANESTHETICS

Local anesthetics are either esters (procaine, dibucaine, benzocaine, etc) or amides (lidocaine, prilocaine, bupivacaine, etc). The ester containing compounds are usually inactivated in the plasma and tissues by non-specific esterases. Local anesthetics block the initiation of action potentials by preventing the voltage-dependant increase in Na+ conductance. Local anesthetics are used in minor surgery, dentistry, abdominal surgery and painless childbirth. The unwanted effects are: CNS effects (agitation, confusion, respiratory depression, and convulsion), CVS effects (myocardial depression, hypotension) and occasional hypersensitivity reactions.

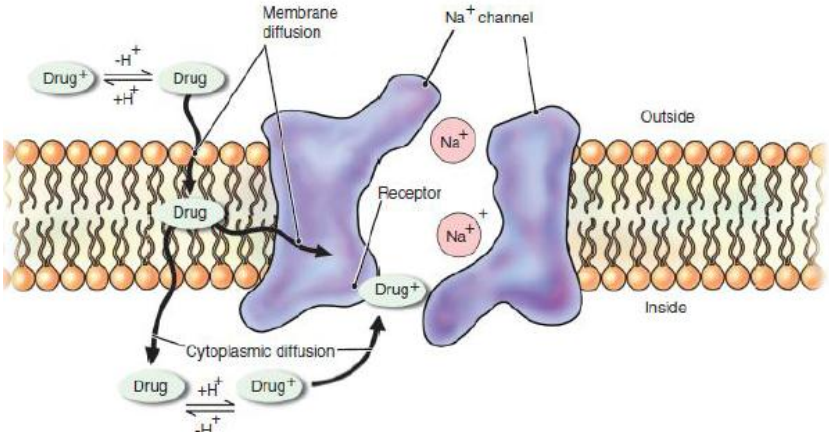


Figure : Mechanism of action of local anesthetics.

AUTACOIDS

Learning Objectives:

After going through this unit, the student will be able to:

1. Explain the role of histamine in anaphylactic reactions
2. List some of the therapeutic uses and adverse effects of H_1 antagonists
3. Describe the major pharmacological actions of prostaglandins E and F

1. Histamine

It is formed by decarboxylation of histidine and major portion is stored in mast cells and basophils.

Mechanisms of Action: It acts on 2 major types of receptors

a. Stimulation of H1 receptors results in smooth muscle contraction, increased vascular permeability, and mucus production. These effects are blocked competitively by H1 antagonists.

b. Activation of H2 receptors increases gastric acid production, and this effect is blocked by H2 blockers such as cimetidine.

Both types of receptors are involved in vascular dilatation and edema formation.

Pharmacological Actions:

1. ***Cardiovascular system***

a. dilatation of capillaries and venules

b. fall in blood pressure. blood vessels.

c. positive inotropic and chronotropic actions on the heart, impairs AV conduction, and increases coronary blood flow.

2. ***Smooth Muscles***:

Histamine directly stimulates the smooth muscles of various tissues including the bronchi and

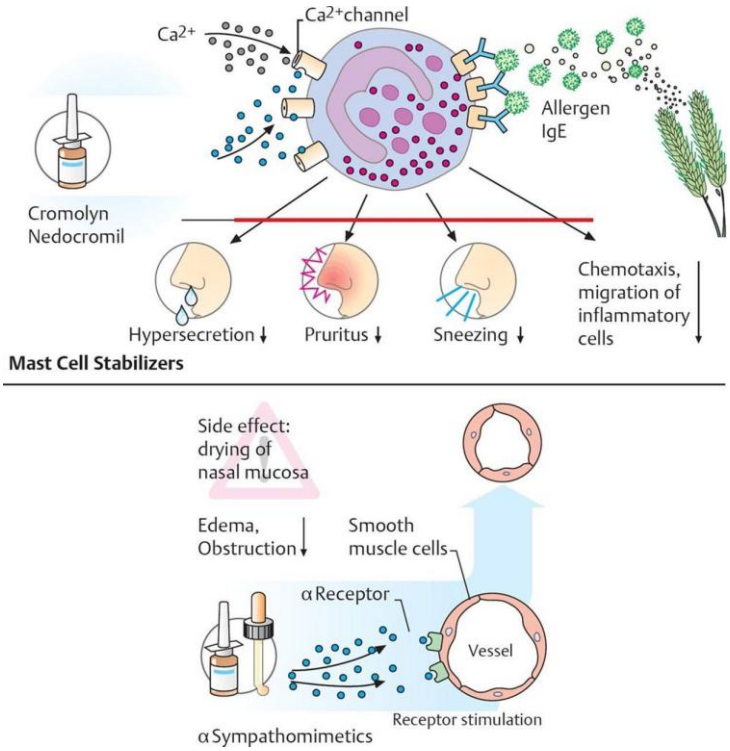
uterus. Histamine-induced bronchospasm is effectively antagonized by adrenaline.

3. ***Exocrine Glands***:

It is a powerful stimulant of HCl secretion by the gastric mucosa.

4. ***CNS***:

5. ***Miscellaneous*** actions include induction of itching and pain. Anaphylaxis and other forms of allergic reactions.



Antihistaminc Drugs

These drugs competitively block histamine receptors and are of two types:

1. H1 receptor antagonists

2. H2 receptor antagonists (used in the treatment of acid-peptic disease)

H1 Receptor Antagonists

Classification of H1 recepror antagonists:

1. Potent and sedative: such as diphenhydramine and promethazine.

2. Potent but less sedative: such as cyclizine and chlorpheniramine

3. Less potent and less sedative: such as pheniramine

4. Non-sedative: such as terfenadine, loratadine, and cetrizine.

Pharmacological Actions:

- Antihistaminic Actions:-they block histamine effects at various sites.

Most of them produce CNS depression resulting in sedation, drowsiness, inability to concentrate, and disturbances of coordination.

Therapeutic Uses:

1. ***Allergic Disorders***:-Including urticaria, seasonal hay fever, atopic and contact dermatitis.

They are not effective in bronchial asthma and common cold.

Adverse Effects:

- Sedation. dryness of the mouth, allergic reactions.

2. 5-Hydroxytreptamine (Serotonin)

Pharmacolocial Actions:

5-HT causes constriction of renal, splanchnic, meningeal, and pulmonary arteries and veins and venules, but dilatation of the blood vessels of skeletal musles, coronaries, and skin capillaries

Serotonin Agonists:

Sumatriptan is a selective agonist of 5-HT1 receptors and is highly effective in treating acute attacks of migraine, but is not useful in the prevention. It relieves the nausea and vomiting, but the headache may recur, necessitating repeated administrations. Adverse effects include flushing and heat at the injection site, neck pain, dizziness, and tingling of the hands.

The drug is contraindicated with symptomatic ischemic heart diseases, angina, and

hypertension as it may cause coronary vasoconstriction.

Buspirone, another serotonin agonist, is a useful effective anxiolytic agent.

Serotonin Antagonists:

a. ***Methysergide:*** blocks the actions of 5-HT on a variety of smooth muscles. It also has a weak direct vasoconstrictor effect. It is an effective prophylactic agent for migrainous headaches. But has no effect in treating acute attacks.

Adverse reactions : gastrointestinal irritation, drowsiness, vertigo, and psychic disturbances.

b. ***Cyproheptadine:*** is a potent antagonist of 5-HT and to a smaller extent of histamine and acetylcholine. It stimulates appetite probably by acting directly on the hypothalamus. It can block the release of hydrocortisone, and the production of aldosterone. It is mainly used to relieve the itching associated with skin disorders such as allergic dermatitis. The common adverse reaction is drowsiness.

c. ***Ondansetron***: is specific 5-HT3 receptor antagonist. Given orally or intravenously, it is useful in the management of nausea and vomiting associated with cytotoxic therapy.

Adverse reactions : headache, constipation, and allergic reactions.

d. Prochlorperazine and haloperidol have anti-5-HT activity and are sometimes used for resistant acute attacks.

3. Prostaglandins:

The prostaglandins are synthesized from polyunsaturated fatty acids at their sites of action. PG E2 and PG F2 are the two main prostaglandins.

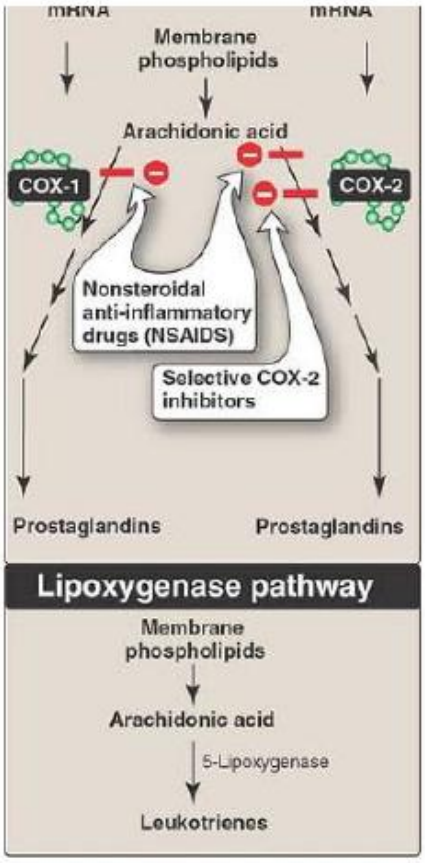
They play an important role in the development of the inflammatory response in association with other mediators.

Synthesis of important prostaglndins and leukotriens:

Essential Fatty Acids in the diet Cell membrane phospholipids Arachidonic acid

5-Lipooxygenase Cyclooxygenase

Leukotrienes Prostaglandins (PGE2, PGF2, TXA2, PGI2)



Pharmacological Actions:

a. Smooth muscle: most stimulate myometrium and are known to be important in the initiation and maintenance of labor. Prostaglandin E has bronchodilator action.

b. GIT: they increase intestinal motility. PG E inhibits gastric acid secretion and has

cytoprotective action on the gastroduodenal mucosa. Both PG E and F produce contraction of the longitudinal muscle of the gut. They also stimulate intestinal fluid secretion, resulting in diarrhea.

c. CVS: PGE is peripheral vasodilator and powerful natriuretic. PGF constricts arterioles and veins.

d. Platelets: Thromboxane causes platelet aggregation and vasoconstriction. PG I

(prostacycline) is found in the vascular endothelium and is a potent inhibitor of platelet aggregation and is a vasodilator.

e. Miscellaneous: Prostaglandins are important in pain generation and perception. PGE and PGI produce hyperalgesia associated with inflammation. In addition, PG E is a potent pyrogenic substance.

Natural prostaglandins such as carboprost, dinoprostone and misoprostol find clinical application.

Therapeutic uses include cervical ripening and labor induction, control of postpartum hemorrhage, induction of abortion, and prophylaxis of NSAID-induced peptic ulcers. etc.

Adverse Effects include fever, diarrhea, abdominal cramps, headache, nausea, and vomiting.

DRUG OF ABUSE

Drug of abuse

Learning objective

1. Identify Types of Drugs: Understand the various categories of drugs of abuse, including stimulants, depressants, opioids, hallucinogens, and cannabinoids.
2. Understand Effects and Risks: Recognize the short-term and long-term effects of drug abuse on physical and mental health, as well as social implications.
3. Explore Prevention Strategies: Learn about effective prevention methods, including education, community programs, and policy interventions.
4. Examine Treatment Options: Gain knowledge of the different treatment approaches for drug abuse, including detoxification, counseling, and medication-assisted treatment.
5. Promote Awareness: Develop the ability to discuss the impacts of drug abuse and advocate for healthy behaviors and resources within communities.

Introduction

Drug abuse is a complex issue that impacts individuals and communities. The term "drugs" encompasses a wide range of substances that can lead to addiction, including legal ones like alcohol and tobacco, and illegal ones like heroin and cocaine.

Types of Drugs

Stimulants: Such as cocaine and amphetamines, which increase the activity of the nervous system.

Depressants: Including benzodiazepines, commonly used to treat anxiety but can lead to dependence.

Opioids: Like heroin and prescription painkillers, which are used for pain relief but can result in physical and psychological addiction.

Hallucinogens: Such as LSD and PCP, which alter perception and sensory experiences.

Effects of Drugs

Physical Effects: Changes in heart rate, blood pressure, and impacts on liver and kidney functions.

Psychological Effects: Anxiety, depression, and mood disorders.

Social Effects: Deterioration of personal relationships, job loss, and legal problems.

Causes of Addiction

Biological Factors: Genetic makeup can increase susceptibility to addiction.

Psychological Factors: Exposure to stress or negative experiences in childhood.

Social Factors: Peer influence and the surrounding social environment.

Treatment Approaches

Psychotherapy: Such as cognitive-behavioral therapy to address underlying issues.

Medications: To alleviate withdrawal symptoms and reduce cravings.

Social Support: Support groups like the 12-step program for ongoing recovery.

Conclusion

Addressing drug abuse and addiction requires a collective effort from society, including education, awareness, and therapeutic support. It's crucial to approach this issue with understanding and empathy to facilitate healing and a return to a healthy life.

Review & Exam

Q1/ Choose between the brackets.

1. Antihistamine drug that is used as Antiemetics

   A. domperidone B. metochlopromide C. promethazine D. all of them E. not all of them

2. Which category of drugs increases alertness and energy?

a. Depressants b. Opioids c. Stimulants d. Hallucinogens

3. What is the primary risk associated with opioid misuse?

a. Weight gain b. Overdose and dependence c. Increased energy d. Hallucinations

4. Which of the following is considered a depressant?

a. Cocaine b. LSD c.Alcohol d. Marijuana

5. What is one common effect of hallucinogens?

a. Increased heart rate b. Euphoria c. Hallucinations d. Sedation

6. Which strategy is essential for preventing drug abuse?

a. Increased availability of drugs b. Education and awareness programs
c. Ignoring the issue d. Promoting experimental use

7. Amrinone act via inhibition phosphodiasterase which is responsible of inactivation of cyclic AMP leading to increase

A. cTMP B. cKMP C. cRMP D. cAMP E. all of them

The systemic antacid…….

A. $Al(OH)_3$ B. MgS_2O_3 C. $Mg(OH)_2$ D. all of them E. not allof them

8. one of mode of action of the antisecretory drugs include…….

A. H1-receptors blocking agents B. H2-receptors blocking agents C. H3-receptors blocking

Agents D. all of them E. not allof them

9. Proton pump inhibitor is……

A. mebeverine B. chlorodizeproxide C. cimetidine D. omeprazole E. not all of them

10. Sucralfate is an agent used in…….

A. diarrhea B. constipation C. acid peptic disease D. all of them E. not all of them

11. …… used for prevention of NSAID – induced ulcer

A. misoprostol B. amrinon C. indomethacin D. all of them E. not all of them

12. Selective β-agonists used in bronchial asthma(Salbutamol, ephedrine, atenolol, dexamethasone, all of them, not all of them).

13. The drug is prescribed as anticholinergic and used in Asthma (ipratropium, cromolyn sodium, ephedrine, all of them, not all of them).
14. Aspirin in its action decreases both of PGF, TXs, and ILs.
15. Intravenous anaesthestic drug

    A. ether B. halothan C. ketamine D. all of them E . not all of them

16. Barbiturates act by enhancing action of……

    A. AAGA B. GBAA C. GABA D. all of them E. not all of them

Q2/ Classify the serotonine drugs.

Q3/ Q2/ Mention the mechanisms of bacteria resistances against different antibiotics.