Class- *Third Year B. Pharm.* ***Subject- Pharmacology III***

Subject Incharge- *Miss. Rohini R. Pujari* ***LECTURE SYNOPSIS No.-***

NOOTROPIC DRUGS- CLASSIFICATION AND PHARMACOLOGY

These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders. They do elicit pharmacological effects, but widely different mechanisms of action are claimed and therapeutic benefits are uncertain.

The indications of cognition enhancers include:

- Senile dementia of Alzheimer type (DAT) & multi infarct dementia (MID).
- 'Common symptoms' of the elderly; dizziness and memory disturbances.
- Mental retardation in children, learning defects, attention deficit disorder.
- Transient ischaemic attacks (TIAs), cerebrovascular accidents-stroke.
- Organic psychosyndromes and sequelae of head injury, ECT, brain surgerv

The above therapeutic field is barren and commercially highly profitable. A variety of drugs have been briskly promoted by manufacturers and wishfully prescribed by physicians.

The mechanism by which they are believed to act are:

- Increasing global/regional cerebral blood flow (CBF)
- Direct support of neuronal metabolism.
- Enhancement of neurotransmission.
- Improvement of descrete cerebral functions, Eg. memory.

A11 nootropic drugs are tested for their vasodilator activity. The basic assumption has been that improvement in cerebral circulation is possible, real and therapeutically useful.

Classification:

a. Cholinergic activators: Tacrine, Rivastigmine, Donepezil, Calantamine

b. Glutamate (NMDA) antagontst: Memantine

c Miscellaneous cerebroactive drugs: Piracetam, Pyritinol (Pyrithioxine), Dihydroergotoxine (Codergocrine), Piribedil, Ginkgo biloba

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DRUG DEPENDENCE

Dependence is defined as a compulsive craving that develops as a result of repeated administration of the drug.

- Dependence occurs with a wide range of psychotropic drugs, acting by many different mechanisms.
- The common feature of dependence-producing drugs is that they have a positive reinforcing action ('reward') associated with activation of the mesolimbic dopaminergic pathway.

Dependence is often associated with

- tolerance to the drug, which can arise by various biochemical mechanisms;
- a physical abstinence syndrome, which varies in type and intensity for different classes of drug;
- psychological dependence (craving), which may be associated with the tolerance-producing biochemical changes.

Psychological dependence, which usually outlasts the physical withdrawal syndrome, is the major factor leading to relapse among treated addicts.

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INTRODUCTION TO PATIENT ADDICTION REHABILITATION CENTER

The management of drug abuse and addiction must be individualized according to the drugs involved and the associated psychosocial problems of the individual patient. An understanding of the pharmacology of the drug or combination of drugs ingested by the patient is essential to rational and effective treatment. This may be a matter of urgency for the treatment of overdose or for the detoxification of a patient who is experiencing withdrawal symptoms. It must be recognized, however, that the treatment of the underlying addictive disorder requires months or years of rehabilitation. The behavior patterns encoded in memory during thousands of prior drug ingestions do not disappear with detoxification from the drug, even after a typical 28-day inpatient rehabilitation program. Long periods of outpatient treatment are necessary. There probably will be periods of relapse and remission. While complete abstinence is the preferred goal, in reality, most patients are at risk to resume drug-seeking behavior and require a period of retreatment. Maintenance medication can be effective in some circumstances, such as methadone, buprenorphine, or naltrexone for opioid dependence and disulfiram, naltrexone, or acamprosate for alcoholism. The process can best be compared to the treatment of other chronic disorders such as diabetes, asthma, or hypertension. Long-term medication may be necessary, and cures are not likely. When viewed in the context of chronic disease, the available treatments for addiction are quite successful in that the majority of patients improve, but improvement does not necessarily persist after treatment has ceased.

Long-term treatment is accompanied by improvements in physical status as well as in mental, social, and occupational function. Unfortunately, there is general pessimism in the medical community about the benefits of treatment such that most of the therapeutic effort is directed at the complications of addiction, such as pulmonary, cardiac, and hepatic disorders. Prevention of these complications can be accomplished by addressing the underlying addictive disorder.

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PRINCIPLE OF REHABILITATION OF DRUG ADDICTS- ALCOHOL, TOBACCO, OPIOIDS.

Clinical use of drugs in substance dependence

- ***Tobacco dependence:***
  - Short-term **nicotine** is the drug of choice as adjunct to behavioural therapy in smokers committed to giving up ,
  - **bupropion** is also effective but lowers seizure threshold, so is contraindicated in people with risk factors for seizures.

- ***Alcohol dependence:***
  - Long-acting benzodiazepines (e.g. **chlordiazepoxide**) can be used to reduce withdrawal symptoms and the risk of seizures; they should be tapered over 1-2 weeks and then discontinued because of their abuse potential.
  - **Disulfiram** is used as an adjunct to behavioural therapy in suitably motivated alcoholics after detoxification; it is contraindicated for patients in whom a hypotensive acetaldehyde-induced reaction would be dangerous
  - **Acamprosate** can help maintain abstinence; it is started as soon as abstinence has been achieved and maintained if relapse occurs, it is continued for 1 year.

- ***Opioid dependence:***
  - opioid agonists or partial agonists (e.g., respectively, **methadone** and **buprenorphine**) administered orally or sublingually may be substituted for injectable narcotics, many of whose harmful effects are attributable to the route of administration
  - **naltrexone**, a long-acting opioid antagonist, is used as an adjunct to help prevent relapse in detoxified addicts (opioid-free for at least 1 week)
  - **lofexidine**, an α2 agonist is used short term to ameliorate symptoms of opioid withdrawal, and is then tapered over a further 2-4 days.

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DRUGS FOR COUGH- INTRODUCTION & CLASSIFICATION

Classification:

Pharyngeal demulcents: They sooth the throat and reduce afferent impulses from the inflamed/ irritated pharlmgeal mucosa, thus provide symptomatic relief in dry cough arising from throat. Lozenges, cough syrups, linctuses containing syrup, glycerine.

Expectorants (Mucokinetics): They increase bronchial secretion or reduce its viscosity, facilitating its removal by coughing.

- **Bronchial secretion enhancers**: Sodium or Potassium citrate, Potassium iodide, Guaiphenesin (Glyceryl guaiacolate), balsum of Tolu, Vasaka, Ammonium chloride.
- **Mucolytics:** Bromhexine, Ambroxol, Acetyl Cisteine, Carbocisteine

Antitussives (Cough centre suppressants): They act by an ill-defined effect in the brain stem, depressing an even more poorly defined 'cough centre'. New opioid analogues that suppress cough by inhibiting release of excitatory neuropeptides through an action on μ receptors on sensory nerves in the bronchi are being assessed.

- **Opioids:** Codeine, Pholcodeine.
- **Nonopioids:** Noscapine, Dextromethorphan, Chlophedianol.

Antihistamines: Chlorpheniramine, Diphenhydramine, Promethazine.

Adjuvant antitussives: Bronchodilators Salbutamol, Terbutalin.

DRUGS FOR BRONCHIAL ASTHMA- INTRODUCTION & CLASSIFICATION

Antiasthma drugs: bronchodilators

- **β_2-Adrenoceptor agonists** (e.g. **salbutamol**) are first-line drugs .
  - They act as physiological antagonists of the spasmogenic mediators but have little or no effect on the bronchial hyper-reactivity.
  - Salbutamol is given by inhalation; its effects start immediately and last 3-5 hours, and it can also be given by intravenous infusion in status asthmaticus.
  - **Salmeterol** or **formoterol** are given regularly by inhalation; their duration of action is 8-12 hours.
- **Theophylline** (often formulated as **aminophylline)** is a third-line drug for asthma. Theophylline:
  - is a methylxanthine
  - inhibits phosphodiesterase and blocks adenosine receptors
  - has a narrow therapeutic window: unwanted effects include cardiac dysrhythmia, seizures and gastrointestinal disturbances
  - is given intravenously (by *slow* infusion) for status asthmaticus, or orally (as a sustained-release preparation) as add-on therapy to inhaled corticosteroids and long-acting β_2 agonists (step 4)
  - is metabolised in the liver by P450; liver dysfunction and viral infections increase its plasma concentration and half-life (normally approximately 12 hours)
  - interacts importantly with other drugs; some (e.g. some antibiotics) increase the half-life of theophylline , others (e.g. anticonvulsants) decrease it.
- **Cysteinyl leukotriene receptor antagonists** (e.g. **montelukast**) are third-line drugs for asthma. They:
  - competitively antagonise cysteinyl leukotrienes at $CysLT_1$ receptors are used mainly as add-on therapy to inhaled corticosteroids and long-acting β_2 agonists.

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DRUGS FOR BRONCHIAL ASTHMA – PHARMACOLOGY

Clinical use of β_2-adrenoceptor agonists as bronchodilators

- Short-acting drugs (**salbutamol** or **terbutaline**, usually by inhalation) to prevent or treat wheeze in patients with reversible obstructive airways disease.
- Long-acting drugs (**salmeterol, formoterol**) to prevent bronchospasm (e.g. at night or with exercise) in patients requiring long-term bronchodilator therapy.

Clinical use of theophylline

- As a second-line drug, in addition to steroids, in patients whose *asthma* does not respond adequately to β_2-adrenoceptor agonists. Intravenously (as **aminophylline ,** a combination of theophylline with ethylenediamine to increase its solubility in water) in *acute severe asthma.*

Clinical use of inhaled muscarinic receptor antagonists (e.g. ipratropium)

- For *asthma,* as an adjunct to β_2-adrenoceptor antagonists and steroids.
- For some patients with *chronic obstructive pulmonary disease,* especially long-acting drugs (e.g. **tiotropium**).
- For bronchospasm precipitated by β_2-adrenoceptor antagonists.

For clinical uses of muscarinic receptor antagonists in other organ systems

Clinical use of glucocorticoids in asthma

- Patients who require regular bronchodilators should be considered for glucocorticoid treatment (e.g. with inhaled **beclometasone**).
- More severely affected patients are treated with high-potency inhaled drugs (e.g. **budesonide**).
- Patients with acute exacerbations of asthma may require intravenous **hydocortisone** and oral **prednisolone** .
- A 'rescue course' of oral **prednisolone** may be needed at any stage of severity if the clinical condition is deteriorating rapidly.

Prolonged treatment with oral prednisolone , in addition to inhaled bronchodilators and steroids, is needed by a few severely asthmatic patients.

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DRUGS FOR PEPTIC ULCERS- INTRODUCTION & CLASSIFICATION

These are the drugs which counteract acidity by various mechanisms.

Classification:

Reduction of gastric acid secretion

- **H2 antihistaminics:** Cemetidine, Ranitidine, Famotidine, Roxatidine
- **Proton pumlt inhibitors:** Omeprazoie, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole
- **Anticholinergics:** Pirenzepine, Propantheline, Oxvyphenonium
- **Prostaglandin analogues:** Misoprostol

Neutralization of gastric acid (Antacids)

- **Systemic antacids:** Sodium bicarbonate, Sodium citrate
- **Nonsystemic antacids:** Mgnesium hydroxide, Magnesium trisilicate, Aluminium hydroxide, Magaldrate, Calcium carbonate

Ulcer protectives: Sucralfate, Colloidal, bismuth subcitrate (CBS)

Anti- H. pyloric drugs: Amoxicillin, Clarithromycin, Metronidazole, Tinidazole, Tetracycline

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DRUGS FOR PEPTIC ULCERS- PHARMACOLOGY

Antacids:

Mechanism of action

- As the name implies, they are antiacid and raise pH.
- Sodium bicarbonate is the simplest:
  $HCO3^- + H^+ \rightarrow CO2 + H2O$
- Magnesium hydroxide and aluminium hydroxide are also used:
  $Al(OH)3 + 3HCl \rightarrow AlCl3 + 3H2O$
  $Mg(OH)2 + 2HCl \rightarrow MgCl2 + 2H2O.$

Histamine H2 receptor antagonists:

Mechanism of action

Antagonism of histamine H2 receptors which are coupled via adenylyl cyclase to increase cyclic adenosine monophosphate (cAMP) which activates the proton pump.

Proton pump inhibitors (PPIs):

Mechanism of action

- Irreversible inhibition of the proton pump (H+/K+-ATPase)
- PPIs are activated in an acidic environment which helps selectivity.
  Helicobacter pylori eradication

Anti- H. pylori drugs:

Most peptic ulcers are due to infection with *H. pylori.*

- Eradication is the most effective treatment for long-term cure of ulcers with low relapse rates.
- A variety of combination therapies: 'triple therapy'.

Anticholinergic drugs:

Atropinic drugs reduce the volume of gastric juice without raising its pH unless there is food in stomach to dilute the secreted acid.

Prostaglandins:

PGE2 and PGI2 are produced in the gastric mucosa and appear to serve protective role by inhibiting acid secretion and promoting mucus + HCO3- secretion.

Ulcer protective agents:

Some agents, termed cytoprotective, are said to enhance endogenous mucosal protection mechanisms and/or to provide a physical barrier over the surface of the ulcer.

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EMETICS AND ANTIEMETICS- INTRODUCTION & CLASSIFICATION

Emetics:

These are drugs used to evoke vomiting

Classification:

Drugs acting on CTZ: ApomorPhine

Drugs reflexly acting on CTZ: Ipecacuanha

Antiemetics:

These are drugs used to prevent or suppress vomiting.

Classification:

Anticholinergics: Hyoscine, Dicvclomine

H1 antihistaminics: Promethazine, Diphenhydramine, Dimenhvdrinate, Doxylamine, Cyclizine, Meclozine, Cinnarizine.

Neuroleptics (D2 blockers): Chlorpromazine, Prochiorperazine, Haloperidol, etc.

Prokinetic drugs: Metoclopramide, Domperidone, Cisapride, Mosapride, Tegaserod

5-HT3 antagonists: Ondansetron, Granisetron

Adjuvant antiemetics: Corticosteroids, Benzodiazepines, Cannabinoids.

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EMETICS AND ANTIEMETICS- PHARMACOLOGY

Emetics:

Apomorphine: It acts as a dopamrnergic agonist on the CTZ
Ipecacuanha: It acts by irritating gastric mucosa as well as through CTZ
Powdered musard suspension or strong salts solution: They act reflexly by irritating the stomach.

Antiemetics:

Neuroleptics: Act by blocking dopamine receptors.

5-HT_3 receptor blockers: The specific antagonists of the 5-HT_3 selectively block 5-HT_3 receptors in the periphery.

Prokinetic drugs: One of several substituted benzamides with antiemetic activity, metoclopramide, is highly effective at high doses against the highly emetogenic cisplatin.

Benzodiazepines: The antiemetic potency of lorazepam and alprazolam is low. Their beneficial effects may be due to their sedative, anxiolytic, and amnesic properties. These same properties make benzodiazepines useful in treating anticipatory vomiting.

Corticosteroids: Dexamethasone and methylprednisolone, used alone, are effective against mildly to moderately emetogenic chemotherapy. Their antiemetic mechanism may involve blockade of prostaglandins.

Cannabinoids: Marijuana derivatives, including dronabinol and nabilone, are effective against moderately emetogenic chemotherapy. However, they are seldom first-line antiemetics because of their serious side effects, including dysphoria, hallucinations, sedation, vertigo, and disorientation.

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DRUGS FOR CONSTIPATION- INTRODUCTION & CLASSIFICATION

These are drugs that promote evacuation of bowels. A distinction is sometimes made according to the intensity of action.

Laxative or aperient: milder actiory elimination of soft but formed stools.
Purgative or cathartic: stronger action resulting in more fluid evacuation.
Many drugs in low doses act as laxative and in larger doses as purgative.

Classification:

Bulk forming

Dietary fibres: Bran, Psyllium (Plantago), Ispaghula, Methylcellulose
Stool softeners: Docusates (DOSS), Liquid paraffin

Stimulant purgatives:

- **Diphenylmethanes:** Phenolphthalein, Bisacodyl, Sodium picosulfate
- **Anthraquinones (Emodins)**: Senna, Cascara sagrada

5-H4 Antagonist: Tegaserod
Fixed oil: Castor oil
Osmotic purgatives:
Magnesium salts: sulfate, hydroxide
Sodium salts: sulfate, phosphate, Sodium pottasium tartrate, Lactulose

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DRUGS FOR CONSTIPATION- PHARMACOLOGY

Irritants and stimulants:

Senna is a widely used stimulant laxative. Its active ingredient is a group of sennosides, a natural complex of anthraquinone glycosides. Taken orally, it causes evacuation of the bowels within 8 to 10 hours. It acts directly on nerve fibers in the mucosa of the colon.

Bulk laxatives

The bulk laxatives include hydrophilic colloids. They form gels in the large intestine, causing water retention and intestinal distension, thereby increasing peristaltic activity. Similar actions are produced by methylcellulose, psyllium seeds, and bran.

Saline and osmotic laxatives

Saline cathartics, such as magnesium citrate, magnesium sulfate, sodium phosphate, and magnesium hydroxide, are nonabsorbable salts that hold water in the intestine by osmosis and distend the bowel, increasing intestinal activity and producing defecation in a few hours. Electrolyte solutions containing polyethylene glycol (PEG) are used as colonic lavage solutions. PEG powder for solution is available as a prescription and also an over-the-counter laxative. Lactulose is a semisynthetic disaccharide sugar that acts as an osmotic laxative.

Stool softeners (emollient laxatives or surfactants)

Surface-active agents that become emulsified with the stool produce softer feces and ease passage. These include docusate sodium, docusate calcium, and docusate potassium. They may take days to become effective. They should not be taken together with mineral oil because of the potential for absorption of the mineral oil.

Lubricant laxatives:

Mineral oil and glycerin suppositories are considered to be lubricants. They facilitate the passage of hard stools. Mineral oil should be taken orally in an upright position to avoid its aspiration and potential for lipid or lipoid pneumonia.

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DRUGS FOR DIARRHOEA- INTRODUCTION & CLASSIFICATION

Rational management of diarrhoea depends on establishing the underlying cause and instituting specific therapy (only if necessary), since most diarrhoeas are self-limiting. Majority of enteropathogens are taken care of by motility and other defence mechanisms of the gut.

Therapeutic measures may be grouped into:

- Treatment of fluid depletion, shock and acidosis
    - Oral rehydration: Oral rehydration (ORS)
    - Intravenous rehydration: Mixture of NaCl 85mM, KCI 13 mM, NaHCO3 48mM 1 in 1L of water or 5% glucose
    - Maintenance of nutrition: Diet consisting of milk, boiled potato, rice, chicken soup, banana, sago,
- Drug therapy (antidiarrhoeal drugs)

The relative importance of each is governed by the severity and nature of diarrhoea.

Antidiarrhoeal Drugs

Classification

A. Antimotility agents: diphenoxylate, loperamide

B. Adsorbents: bismuth subsalicylate, methylcellulose, aluminum hydroxide

C. Agents that modify fluid and electrolyte transport: Bismuth subsalicylate

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DRUGS FOR DIARRHEA- PHARMACOLOGY

A. Antimotility agents:

- Two drugs that are widely used to control diarrhea are diphenoxylate and loperamide.
- Both are analogs of meperidine and have opioid-like actions on the gut, activating presynaptic opioid receptors in the enteric nervous system to inhibit acetylcholine release and decrease peristalsis.
- At the usual doses, they lack analgesic effects.
- Side effects include drowsiness, abdominal cramps, and dizziness.
- Because these drugs can contribute to toxic megacolon, they should not be used in young children or in patients with severe colitis.

B. Adsorbents

- Adsorbent agents, such as bismuth subsalicylate, methylcellulose, and aluminum hydroxide are used to control diarrhea.
- Presumably, these agents act by adsorbing intestinal toxins or microorganisms and/or by coating or protecting the intestinal mucosa.
- They are much less effective than antimotility agents. They can interfere with the absorption of other drugs.

C. Agents that modify fluid and electrolyte transport

- Bismuth subsalicylate, used for traveler's diarrhea, decreases fluid secretion in the bowel.
- Its action may be due to its salicylate component as well as its coating action.

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ANTERIOR PITUITARY HORMONES- INTRODUCTION

Hormones of anterior pituitary gland:

Anterior Growth hormone (GH) (somatotropin):

Somatotropin is a large polypeptide that is released by the anterior pituitary in response to growth hormone (GH) releasing hormone produced by the hypothalamus. Secretion of GH is inhibited by another pituitary hormone, somatostatin. GH is released in a pulsatile manner, with the highest levels occurring during sleep. With increasing age, GH secretion decreases, being accompanied by a decrease in lean muscle mass. Human GH is produced synthetically by recombinant DNA technology. GH from animal sources is ineffective in humans. Somatotropin influences a wide variety of biochemical processes; for example, through stimulation of protein synthetic processes, cell proliferation and bone growth are promoted. Increased formation of hydroxyproline from proline boosts cartilage synthesis.

Prolactin:

Prolactin is a peptide hormone similar in structure to GH, and is also secreted by the anterior pituitary. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function.

Adrenocorticotropic hormone (ACTH, Corticotropin): It is a 210 amino acid, two chain glycoprotein (22"k sugar), MW 30000.

Thyroid stimulating hormone (TSH, Thyrotropin): TSH stimulates thyroid to synthesize and secrete thyroxine (T4) and triiodothyronine (T3)

Gonadotropins- Follicle stimulating hormone (FSH) and Luteinizing hormone (LH). The gonadotropins are glycoproteins that are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They find use in the treatment of infertility in men and women. Menotropins are obtained from the urine of menopausal women and contain FSH and luteinizing hormone LH. Chorionic gonadotropin (hCG) is a placental hormone and an LH agonist, to which it is structurally related. It is also excreted in the urine.

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ANTERIOR PITUITARY HORMONES- PHARMACOLOGY

Adrenocorticotropic hormone (corticotropin)

The target organ of ACTH is the adrenal cortex, where it binds to specific receptors on the cell surfaces. The occupied receptors activate G protein coupled processes to increase cyclic adenosine monophosphate (cAMP), which in turn stimulates the rate-limiting step in the adrenocorticosteroid synthetic pathway. This pathway ends with the synthesis and release of the adrenocorticosteroids and the adrenal androgens.

Growth hormone:

Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins insulin-like growth factors I and II (IGF-I and IGF-II).

Thyroid stimulation hormone:

The TSH receptor present on thyroid cells is a G protein coupled receptor which utilizes the adenylyl cyclase-cAMP transducer mechanism to produce its effects In human thyroid cells high concentration of TSH also induces PIP2 hydrolysis The resulting increase in cytosolic Ca2+ and protein kinase C activation may also mediate TSH actions. TSH induces hyperplasia and hypertrophy of thyroid follicles and increases blood supply to the gland, promotes trapping of iodide by thyroid, promotes organification of trapped iodine and its incorporation into T3 and Ta by increasing peroxidase activity, enhances endocytotic uptake of thyroid colloid by the follicular cells and proteolysis of thyroglobulin to release more of T3 and T4.

Gonadotropins: Human menopausal gonadotropin, follicle-stimulating hormone, and human chorionic gonadotropin

Urofollitropin is FSH obtained from menopausal women and is devoid of LH. Follitropin beta is human FSH manufactured by recombinant DNA technology.

Prolactin

Prolactin is a peptide hormone. Its secretion is inhibited by dopamine acting at D_2 receptors. Its primary function is to stimulate and maintain lactation. It decreases sexual drive. The hormone enters a cell, where it activates a tyrosine kinase to promote tyrosine phosphorylation and gene activation.

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POSTERIOR PITUITARY HORMONES- INTRODUCTION

The posterior pituitary gland consists largely of the terminals of nerve cells that lie in the *supraoptic* and *paraventricular* nuclei of the hypothalamus. Their axons form the *hypothalamic-hypophyseal tract*, and the fibres terminate in dilated nerve endings in close association with capillaries in the posterior pituitary gland. Peptides, synthesised in the hypothalamic nuclei, pass down these axons into the posterior pituitary, where they are stored and eventually secreted into the bloodstream. The two main hormones of the posterior pituitary are oxytocin and ADH (vasopressin).

Oxytocin

Oxytocin, originally extracted from animal posterior pituitaries, is now chemically synthesized. Its only use is in obstetrics, where it is employed to stimulate uterine contraction to induce or reinforce labor or to promote ejection of breast milk. To induce labor, the drug is administered intravenously. However, when used to induce milk let-down it is given as a nasal spray. Oxytocin causes milk ejection by contracting the myoepithelial cells around the mammary alveoli.

Vasopressin

Vasopressin (antidiuretic hormone), is structurally related to oxytocin. The chemically synthesized nonapeptide has replaced that extracted from animal posterior pituitaries. Vasopressin has both antidiuretic and vasopressor effects. In the kidney, it binds to the V_2 receptor to increase water permeability and resorption in the collecting tubules. Thus, the major use of vasopressin is to treat diabetes insipidus. It also finds use in controlling bleeding due to esophageal varices or colonic diverticula. Other effects of vasopressin are mediated by the V_1 receptor, which is found in liver, vascular smooth muscle, and other tissues.

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POSTERIOR PITUITARY HORMONES- PHARMACOLOGY

Antidiuretic hormone

Regulation of secretion and physiological role: Antidiuretic hormone released from the posterior pituitary has a crucial role in the control of the water content of the body through its action on the cells of the distal part of the nephron and the collecting tubules in the kidney. The hypothalamic nuclei that control fluid balance lie close to the nuclei that synthesise and secrete ADH.

Antidiuretic hormone receptors

There are three classes of receptor for ADH: V_1, V_2 and V_3. V_2 receptors, which are coupled to adenylate cyclase, mediate its main physiological actions in the kidney, whereas the V_1 and V_3 receptors are coupled to the phospholipase C/inositol trisphosphate system.

Pharmacological actions:

Renal actions: Antidiuretic hormone binds to V_2 receptors in the basolateral membrane of the cells of the distal tubule and collecting ducts of the nephron. Its main effect in the collecting duct is to increase the rate of insertion of water channels into the lumenal membrane, thus increasing the permeability of the membrane to water. It also activates urea transporters and transiently increases Na^+ absorption, particularly in the distal tubule.

Other non-renal actions: Antidiuretic hormone causes contraction of smooth muscle, particularly in the cardiovascular system, by acting on V_1 receptors. The affinity of these receptors for ADH is lower than that of the V_2 receptors, and smooth muscle effects are seen only with doses larger than those affecting the kidney. ADH also stimulates blood platelet aggregation and mobilisation of coagulation factors.

Oxytocin

Action *on the uterus.* Oxytocin contracts the uterus. Oestrogen induces oxytocin receptor synthesis and, consequently, the uterus at term is highly sensitive to this hormone.

Other actions. Oxytocin contracts myoepithelial cells in the mammary gland, which causes 'milk let-down'-the expression of milk from the alveoli and ducts. It also has a vasodilator action. A weak antidiuretic action can result in water retention, which can be problematic in patients with cardiac or renal disease, or preeclampsia.

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CORTICOSTEROIDS- INTRODUCTION AND CLASSIFICATION

- The adrenal gland consists of the cortex and the medulla. The latter secretes epinephrine, whereas the cortex, synthesizes and secretes two major classes of steroid hormones the adrenocorticosteroids, and the adrenal androgens.
- The adrenal cortex is divided into three zones that synthesize various steroids from cholesterol and then secrete them.
- The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone), which are responsible for regulating salt and water metabolism. Production of aldosterone is regulated primarily by the renin-angiotensin system.
- The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol), which are involved with normal metabolism and resistance to stress.
- The inner zona reticularis secretes adrenal androgens (for example, dehydroepiandrosterone).
- Secretion by the two inner zones and, to some extent, the outer zone is controlled by pituitary corticotropin adrenocorticotropic hormone, which is released in response to the hypothalamic corticotropin-releasing hormone. Glucocorticoids serve as feedback inhibitors of corticotropin and CRH secretion.
- Hormones of the adrenal cortex are used in replacement therapy; in the treatment and management of asthma as well as other inflammatory diseases, such as rheumatoid arthritis; in the treatment of severe allergic reactions; and in the treatment of some cancers.

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Subject Incharge- *Miss. Rohini R. Pujari* ***LECTURE SYNOPSIS No.-***

CORTICOSTEROIDS- PHARMACOLOGY

Glucocorticoids

Metabolic actions

- *Carbohydrates*: decreased uptake and utilisation of glucose accompanied by increased gluconeogenesis; this causes a tendency to hyperglycaemia.
- *Proteins*: increased catabolism, reduced anabolism.
- *Lipids*: a permissive effect on lipolytic hormones and a redistribution of fat, as observed in Cushing's syndrome.

Regulatory actions

- *Hypothalamus and anterior pituitary gland*: a negative feedback action resulting in reduced release of endogenous glucocorticoids.
- *Cardiovascular system*: reduced vasodilatation, decreased fluid exudation.
- *Musculoskeletal*: decreasing osteoblast and increasing osteoclast activity.
- *Inflammation and immunity*:
    - *acute inflammation*: decreased influx and activity of leucocytes
    - *chronic inflammation*: decreased activity of mononuclear cells, decreased angiogenesis, less fibrosis
    - *lymphoid tissues*: decreased clonal expansion of T and B cells, and decreased action of cytokine-secreting T cells.
- *Mediators*:
    - decreased production and action of cytokines, including interleukins, tumour necrosis factor-α and granulocyte macrophage colony-stimulating factor
    - reduced generation of eicosanoids
    - decreased generation of IgG
    - decrease in complement components in the blood
    - increased release of anti-inflammatory factors such as interleukin-10 and annexin 1.
- *Overall effects*: reduction in the activity of the innate and acquired immune systems, but also decreased healing and diminution in the protective aspects of the inflammatory response.

Mineralocorticoids

The main endogenous mineralocorticoid is aldosterone. Its chief action is to increase Na^+ reabsorption by the distal tubules in the kidney, with concomitant increased excretion of K^+ and H^+. An excessive secretion of mineralocorticoids, as in Conn's syndrome, causes marked Na^+ and water retention, with a resultant increase in the volume of extracellular fluid, hypokalaemia, alkalosis and hypertension.

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CORTICOSTEROID ANTAGONISTS- INTRODUCTION AND CLASSIFICATION

Several substances have proven to be useful as inhibitors of the synthesis of adrenal steroids:

- Metyrapone
- Aminoglutethimide
- Ketoconazole
- Trilostane
- Spironolactone
- Eplerenone
- Mifepristone

Five pharmacologic agents are useful inhibitors of adrenocortical secretion. *Mitotane*, an adrenocorticolytic agent.

- The other inhibitors of steroid hormone biosynthesis—*metyrapone, aminoglutethimide, ketoconazole,* and *trilostane*.
- Metyrapone, aminoglutethimide, and ketoconazole inhibit cytochrome P450 enzymes involved in adrenocorticosteroid biosynthesis.
- Differential selectivity of these agents for the different steroid hydroxylases provides some degree of specificity to their actions.
- Trilostane is a competitive inhibitor of the conversion of pregnenolone to progesterone, a reaction catalyzed by 3-hydroxysteroid dehydrogenase.
- All of these agents pose the common risk of precipitating acute adrenal insufficiency; thus, they must be used in appropriate doses, and the status of the patient's HPA axis must be carefully monitored.

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CORTICOSTEROIDS ANTAGONISTS- PHARMACOLOGY

Metyrapone: Metyrapone interferes with corticosteroid synthesis by blocking the final step in glucocorticoid synthesis, leading to an increase in 11-deoxycortisol as well as adrenal androgens and the potent mineralocorticoid 11-deoxycorticosterone. The adverse effects encountered with metyrapone include salt and water retention, hirsutism, transient dizziness, and g.i. disturbances.

Aminoglutethimide: This drug acts by inhibiting the conversion of cholesterol to pregnenolone. As a result, the synthesis of all hormonally active steroids is reduced. Aminoglutethimide has been used therapeutically in the treatment of breast cancer to reduce or eliminate androgen and estrogen production. In these cases, it is used in conjunction with dexamethasone. However, it increases the clearance of dexamethasone. Aminoglutethimide may also be useful in the treatment of malignancies of the adrenal cortex to reduce the secretion of steroids. Recent studies indicate it is an aromatase inhibitor.

Ketoconazole: Ketoconazole is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing's syndrome.

Trilostane: Trilostane reversibly inhibits 3Î²-hydroxysteroid dehydrogenase and, thus, affects aldosterone, cortisol, and gonadal hormone synthesis. Its side effects are gastrointestinal.

Mifepristone: At high doses, mifepristone is a potent glucocorticoid antagonist as well as an antiprogestin. It forms a complex with the glucocorticoid receptor, but the rapid dissociation of the drug from the receptor leads to a faulty translocation into the nucleus. Its use is presently limited to the treatment of inoperable patients with ectopic ACTH syndrome.

Spironolactone: This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. It can also antagonize aldosterone and testosterone synthesis. It is effective against hyperaldosteronism. Spironolactone is also useful in the treatment of hirsutism in women, probably due to interference at the androgen receptor of the hair follicle.

Eplerenone: Eplerenone specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the side effect of gynecomastia that is associated with the use of spironolactone. It is approved as an antihypertensive.

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THYROID HORMONES- CLASSIFICATION AND PHARMACOLOGY

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for their normal function. The two major thyroid hormones are triiodothyronine (T3; the most active form) and thyroxine (T4). Although the thyroid gland is not essential for life, inadequate secretion of thyroid hormone (hypothyroidism) results in bradycardia, poor resistance to cold, and mental and physical slowing. If, however, an excess of thyroid hormones is secreted (hyperthyroidism), then tachycardia and cardiac arrhythmias, body wasting, nervousness, tremor, and excess. Heat production can occur.

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with colloid (thyroglobulin), which is the storage form of thyroid hormone.

Regulation of synthesis: Thyroid function is controlled by a tropic hormone, thyroid-stimulating hormone (TSH; thyrotropin). TSH is a glycoprotein, structurally related to LH and FSH, which is synthesized by the anterior pituitar. TSH generation is governed by the hypothalamic thyrotropin-releasing hormone (TRH). TSH action is mediated by cAMP and leads to stimulation of iodide (I^-) uptake. Oxidation to iodine (I_2) by a peroxidase is followed by iodination of tyrosines on thyroglobulin. Condensation of two diiodotyrosine residues gives rise to T4, whereas condensation of a monoiodotyrosine residue with a diiodotyrosine residue generates T3, which is still bound to the protein. The hormones are released following proteolytic cleavage of the thyroglobulin.

Regulation of secretion: Secretion of TSH by the anterior pituitary is stimulated by the hypothalamic TRH. Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone. Most of the hormone (T3 and T4) is bound to thyroxine-binding globulin in the plasma.

Mechanism of action

Both T4 and T3 must dissociate from thyroxine-binding plasma proteins prior to entry into cells, either by diffusion or by active transport. In cell, T4 is enzymatically deiodinated to T3, which enters nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T_4.

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ANTITHYROID DRUGS- CLASSIFICATION AND PHARMACOLOGY

These are drugs used to lower the functional capacity of the hyperactive thyroid gland.

Inhibit hormane synthesis (Antithyroid drugs): Propylthiouracil,Methimazole, Carbimazole.

Inhibit iodide trapping (Ionic inhibitors): Thiocyanates (-SCN), Perchlorates (-ClO4), Nitrates (-NO3).

Inhibit harmone release: Iodine, Iodides of Na and K, Organic iodide.

Destroy thyroid tissue: Radioactive iodine (^{131}I,^{125}I,^{123}I).

Inhibition of thyroid hormone synthesis: The thioamides, propylthiouracil (PTU) and methimazole, are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the coupling of iodotyrosines to form T3 and T4. PTU can also block the conversion of T4 to T3. The thioamides are well absorbed from the gastrointestinal tract, but they have short half-lives. Several doses of PTU are required per day, whereas a single dose of methimazole suffices due to the duration of its antithyroid effect.

Inhibit iodide trapping (Ionic inhibitors): Î²-Blockers that lack sympathomimetic activity, such as propranolol, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. Intravenous administration is effective in treating thyroid storm. An alternative in patients suffering from severe heart failure or asthma is the calcium-channel blocker, diltiazem. Other agents used in the treatment of thyroid storm include PTU iodides, and glucocorticoids.

Blockade of hormone release: A pharmacologic dose of iodide inhibits the iodination of tyrosines, but this effect lasts only a few days. What is more important, iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. Today, iodide is rarely used as the sole therapy. However, it is employed to treat potentially fatal thyrotoxic crisis (thyroid storm) or prior to surgery, because it decreases the vascularity of the thyroid gland. Iodide is not useful for long-term therapy, because the thyroid ceases to respond to the drug after a few weeks. Iodide is administered orally.