Unit-V Pharmacology of drugs acting on Central Nervous system-

Psychopharmacological Agents:-

These are the drugs used to treat CNS condition or psychiatric disorders related to behaviour of a person.

They are sub-classified as -

(i) Antipsychotics.
(ii) Anti-depressants
(iii) Anti-anxiety agents
(iv) Antimanics
(v) Hallucinogens

Antipsychotics (neuroleptics)

These agents/drugs are useful in all types of functional psychosis especially schizophrenia.
eg- Delusions, Hallucinations, thought disorder, abnormal, disorganised behaviour, withdrawal from social contacts.
→ drugs having salutary therapeutic effect in psychoses (all eg)

Antipsychotic Drugs
(Neuroleptic drugs)

- Phenothiazines
  - Aliphatic side chain
    - Chlorpromazine
    - Triflupromazine
  - Piperidine side chain
    - Thioridazine
  - Piperazine side chain
    - Trifluoperazine
    - Fluphenazine
- Thioxanthine
  - Flupenthixol
- Other heterocyclic compounds
  - Pimozide
  - Loxapine
  - Levosulpiride
- Butyrophenones
  - Haloperidol
  - Trifluperidol
  - Penfluridol
- Atypical antipsychotics
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Aripiprazole
  - Ziprasidone
  - Amisulpiride
  - Zotepine

Mechanism of Action:-

All antipsychotics (except- clozapine) drugs act as antagonist at dopamine D_2 receptor blocking action. (good correlation)

⇒ Phenothiazines and thioxanthenes also block D_1, D_3 and D_4 receptors, but there is no correlation of such blockade with their antipsychotic potency.

⇒ Atypical antipsychotics have a high affinity for 5-HT_2 receptors, but have antagonistic action on α_1, Ach M_1, histamine H_1 &

dopamine D_2 receptors. (CTZ = chemoreceptor trigger zone) for emesis. (108)

⇒ Dopaminergic blockade in pituitary lactotropes causes hyperprolactinemia, while that in CTZ is responsible for the antiemetic action.

* CTZ = chemoreceptor trigger zone for emesis, also commonly known as the area postrema (AP) is located within the dorsal surface of the medulla oblongata, on the floor of the fourth vertricle of the brain.

Pharmacological Action:- The pharmacological actions of Chlorpromazine are:

(1.) Action on CNS: Anti-psychotic drugs reduce spontaneous motor activity and in large dose cause catalepsy a state in which animal becomes immobile even when placed in an unnatural position.

⇒ Phenothiazine potentiates the action of analgesic drugs like morphine and prolongs hexobarbitone sleep in animals.

(2) Anti-emetics- Chlorpromazine depress the CTZ and thus act as a powerful anti-emetic. It combats the effect of apomorphine (a dopamine agonist) on the CTZ in the medulla.

⇒ It however is no effective in vomiting

due to vestibular stimulation or that caused by local GI irritation.

③ Action on ANS: The drug act as an autonomic suppressant, because of its α adrenergic blocking action, it blocks certain action of adrenaline and nor-adrenaline.

⇒ It also produce moderate inhibition of action of acetylcholine and 5-HT.

⇒ Neuroleptics have varying degrees of α adrenergic blocking activity which may be graded as —

CPZ > triflupromazine > thioridazine > clozapine > fluphenazine > haloperidol > trifluoperazine > pimozide, ie. more potent compounds have lesser α blocking activity.

④ Action on CVS: Chlorpromazine sometimes produce orthostatic hypotension particularly in the elderly; it is probably due to inhibition of centrally mediated pressor reflexes along with adrenergic blocking agents.

⑤ Endocrine system:- Chlorpromazine can suppress oestrous cycle in animals, block ovulation and can produce amenorrhoea and galactorrhoea due to elevation of serum prolactin level in women.

- The action is due to blocking of dopamine

action on the hypothalmus and pituitary.

Pharmacokinetics-

Oral absorption of CPZ is somewhat unpredictable and bioavailability is low. More consistent effects are produced after i.m or i.v. administration.

* It is highly bound to plasma as well as tissue proteins.

⇒ Volume of distribution, therefore, is large (20 L/Kg)

⇒ It is metabolized in liver, mainly by CYP 2D6 into number of metabolites.

⇒ The elimination $t_{1/2}$ is variable, but mostly is in the range of 10-30 hours.

Clinical Uses of antipsychotic drugs

(1) They are used to treat Schizophrenia. It is effective in controlling symptoms of acute schizophrenia. Long term antipsychotic treatment is often effective in preventing recurrence of schizophrenic attacks and this is major factor in allowing schizophrenic patients to lead normal lives.

(2) Anxiety- Antisychotics have antianxiety

action but should not be used for simple anxiety because they produce psychomotor slowing, emotional blunting, autonomic and extrapyramidal side effect.
Benzodiazepines are the primary drug used in anxiety.

③ As antiemetics- the typical neuroleptics are potent antiemetics. They control a wide range of drug and disease induced vomiting at doses much lower than those needed in psychosis.

④ other uses-
- To potentiate hypnotics, analgesics and anaesthetics
- It is also used in pre-anaesthetic medication.
- Tetanus: CPZ is an alternative drug to relieve skeletal muscle spasm.

Adverse effects-
- CNS ⇒ Drowsiness, lethargy, mental confusion;
- CVS ⇒ Postural hypotension, palpitation, inhibition of ejeculation are due to α adrenergic blockade.
- Anticholinergic ⇒ Dry mouth, blurring of vision, constipation, urinary hesitancy in elderly.
- Endocrine ⇒ Hyperprolactinemia.
- weight gain often occurs due to long term antipsychotic therapy, sugar and lipid may tend to rise.

Antidepressants

These are drugs which can elevate mood in depressive illness.

⇒ Depression is the most common cause of effective disorders.

⇒ Depression is mainly due to deficiency of amines (NA, 5HT, Dopamine) etc.

- There are two types of Depression:

① Unipolar Depression — in which mood swings are always in the same direction.

② Bipolar Affective Disorder — In this, depression alternate with mania. Mania, is most respects is exactly the opposite, with excessive enthusiasm and self confidence.

Symptoms —

① sleep disturbance,

(ii) Feeling of guilt,

(iii) Ugliness and

(iv) loss of libido

- But the major drawback of depression is that it leads to suicidal tendency.

Anti-depressants

- Reversible inhibitors of MAO-A (RIMAs)
  - Moclobemide
  - Clorgyline
- Selective serotonin reuptake inhibitors (SSRIs)
  - Fluoxetine
  - Fluvoxamine
  - Paroxetine
  - Sertraline
  - Citalopram
  - Escitalopram
  - Dapoxetine
- Atypical anti depressants
  - Trazodone
  - Nian serine
  - Mirtazapine
  - Bupropion
  - Amoxapine
  - Tianeptine
  - Amineptine
- Tricyclic antidepressants (TCAs)
  - NA + 5-HT reuptake inhibitors
    - Imipramine
    - Amitriptyline
    - Trimipramine
    - Doxepin
    - Dothiepin
    - Clomipramine
  - Predominantly NA reuptake inhibitors
    - Desipramine
    - Nortriptyline
    - Reboxetine
  - Serotonin and noradrenalin reuptake inhibitors (SNRIs)
    - Venlafaxine
    - Desvenlafaxine
    - Duloxetine

Mechanism of antidepressant action-

⇒ The TCAs and related drugs inhibit NET and SERT which mediate active reuptake of biogenic amines NA and 5-HT into their respective neuron and thus potentiate them by increasing their availability in the synaptic cleft.

⇒ ~~Monoaminergic hypothesis of depression (MAO)~~

① Tricyclic Anti-Depressants

→ Depression is due to:

1. Drugs
2. Alcohal
3. Vitamin deficiency.

Mechanism of Action –

① Inhibit reuptake of nor-adrenaline (NA) and serotonin (5-HT) → Increase the availability of amines → reduce depression.

② Block the muscarinic chalinergic (Ach) and histamine (H_1).

⇒ The term monoamines include → NA, 5-HT & DA.

• Most of the amines is taken back by the neurons (which secreted the monoamine), a process called as reuptake.

⇒ Monoamines reuptake ~~is~~ can be inhibited by TCAD.

⇒ The TCAD cause MARI effect → increase the local availability of NA as well as 5HT → relief of depression.

(2) Selective Serotonin Re-uptake Inhibitors-

↳ Drug that inhibit 5-HT uptake.

Mechanism of Action-

→ Fluoxetine blocks specifically the reuptake of 5 HT in the brain serotoninergic neurons but has no effect on NA or DA reuptake.

(3) Monoamino Oxidase Inhibitors -

The enzyme, MAO, has two subtypes -

(I) MAO-A,

(II) MAO B.

Both the type of MAO cause degradation of monoamines (eg NA, DA & 5-HT).

⇒ MAO-A is found in the gut, liver, CNS etc.

⇒ MAO-B is restricted to CNS and blood platelets alone.

Anti-anxiety Drugs

These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind.

Antianxiety ~~Drug~~ Drug

- Benzodiazepines
  - Diazepam
  - Oxazepam
  - Lorazepam
  - Clonazepam
  - Clordiazepoxide
  - Alprazolam
- Azepirones
  - Buspirone
  - Gepirone
  - → Ispapirone
- sedative antihistaminic
  - → Hydroxyzine
- β-adrenergic blocker
  - → Propranolol

Mechanism of Action:-

the limbic system incorporates a balanced complex of ~~cerebral cortex~~ excitatory and inhibitory components. The emotional states result partly by:

(1) The nature of the activity generated in the limbic system;

(2) The intensity of the arousal response evoked in the cerebral cortex by the flow of impulses along the ascending reticular system.

⇒ The ~~spontaneous~~ increased activity interaction of

→ The spontaneous increased activity of the limbic neuron is inhibited by benzodiazepines through a probable interaction of BDZs with either GABA or glycine, resulting into pre-synaptic inhibitary process in both brain and spinal cord.

Antimanics

Mania - is a period of elevated, expansive or irritable mood with co-existing symptoms of increased energy and goal-directed activity and decreased need for sleep.

Drug for mania And Bipolar disorder

- Lithium carbonate
- Anti-convulsants
  - → Sodium valproate
  - → Carbamazepine
  - → Lamotrigine
- Atypical antipsychotics
  - → Olanzapine
  - → Risperidone
  - → Quetiapine
  - → Aripiprazole

Mechanism

The mechanism of antimanic and mood stabilizing action of lithium is not known. However, the following mechanism have been proposed:

- Li^+ partly replaces body Na and is nearly equally distributed inside and outside the cells, this may affect ionic fluxes across brain cells or modify the property of cellular membranes and associated with therapeutic effect o is very low.
- Lithium decreases the presynaptic release of NA and DA in the brain to treated animals without affecting 5-HT release. this may correct any imbalance in the turnover of brain ~~to~~ monoamines.

Hallucinogens

→ Psychotomimetics, Psychedelics, Psychodysleptics, Psychotogens.

These are drugs which alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis.
many natural products having hallucinogenic property have been discovered.

Classification

- Indole Amines
  - → lysergic acid diethylamide
  - → lysergic acid amide
  - → Psilocybin
  - → Harmine
  - → Bufotenin
- Phenylalkyl amines
  - → mescaline
  - → Ecstasy
  - → Yaba
- Arylcyclohexyl Amines
  - → Phencyclidine
- Cannabinoids
  - → Tetra-hydrocannabinal

Various form of Cannabinoids-
→ Bhang, Ganja, charas

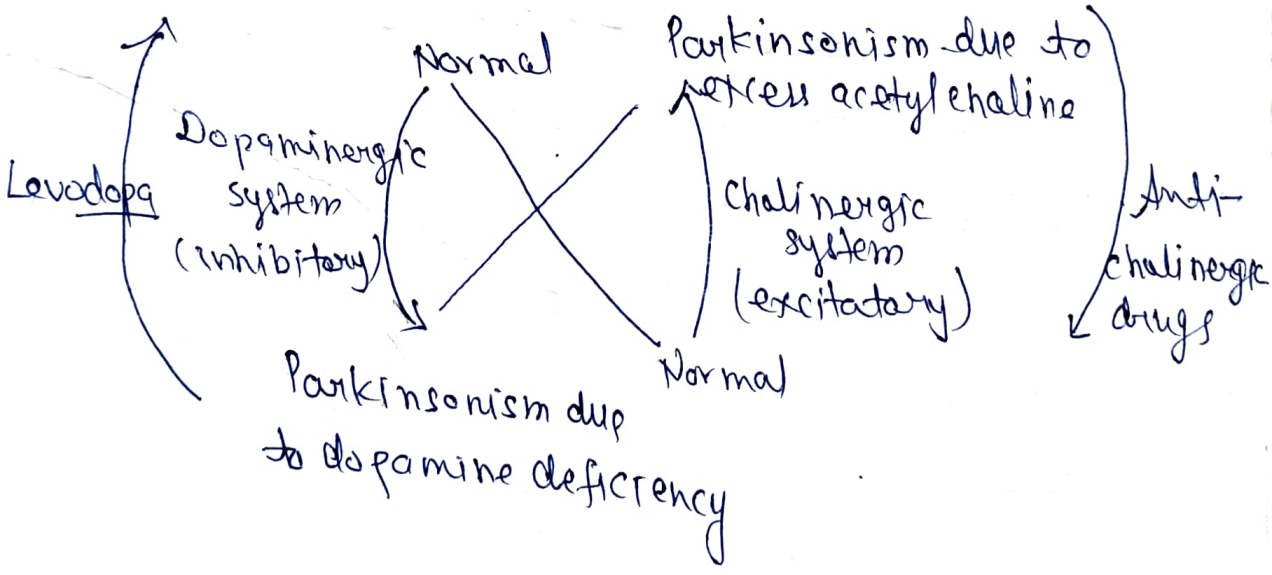
Cannabis produces potent analgesic, anti-emetic, anti-inflammatory and many other pharmacological action

Drugs Used in Parkinson's disease

↳ Anti-Parkinsonian Drugs.

Tremor, rigidity and bradykinesia/akinesia that characterize the ~~symptrom~~ sydrome known as Parkinson's disease.

Parkinson's disease is a progressive degene-rative disorder, mostly affecting older people.
→ First described by James Parkinson in 1817.
→ caused due to deficiency of Dopamine or excess of Acetylcholine in the brain.



Antiparkinsonian Drugs

- Drugs affecting brain dopaminergic system
  - Dopamine precursor
    - → Levodopa
  - Dopaminergic agonists
    - → Bromocriptine
    - → Ropinirole
    - - Pramipexole
  - Comt inhibitors
    - → Entacapone
    - - Tolcapone
  - Peripheral decarboxylase inhibitors
    - → Carbidopa
    - → Benserazide
  - MAO-B inhibitors
    - → Selegiline
    - - Rasagiline
  - Glutamate agonist
    - → Amantadine
- Drug affecting brain cholinergic system
  - Central anticholinergics
    - → Trihexyphenidyl
    - - Procyclidine
    - - Biperiden
  - Antihistaminics
    - → Orphenadrine
    - → Promethazine.

Drugs Affecting the Dopaminergic System –

Dopaminergic activity can be enhanced by:

1. Levodopa with a peripheral dopa decarboxylase inhibitor;
2. Increasing release of endogenous dopamine;
3. Stimulation of dopamine receptors;
4. Inhibition of catechol-O-methyltransferase (comt);
5. Inhibition of monoamine oxidase type B

⇒ Levodopa & Dopa Decarboxylase Inhibitors –

Mechanism– Parkinsonism can develop due to deficiency of DA in the basal ganglia.

The levodopa after entering the brain is converted into DA. Levodopa is a prodrug, the real drug is dopamine. Levodopa is converted into dopamine by dopa decarboxylase enzyme and cross BBB and give with inhibitors of the peripheral dopa decarboxylase to minimize side effects.

⇒ Increased Release of Endogenous Dopamine

- Amantadine

Mechanism of Action-

Endogenous dopamine release is stimulated by amantadine, which also inhibits reuptake of dopamine into nerve terminals.

⇒ $T_{1/2}$ = 10-30 hours, 95% eliminated by kidney

⇒ Catechol-O-methyl Transferase Inhibitors-

Tolcapone & Entacapone

Mechanism-

Reversible competitive inhibition of COMT, thereby reducing metabolism of L-dopa and increasing its availability within nigrostriatal nerve fibres. It is relatively specific for central nervous system COMT, with little effect on the peripheral COMT, thus causing increased brain concentrations of L-dopa, while producing less of an increase in plasma concentration.

⇒ Monoamine Oxidase Inhibitors - Type B -
(selegiline & Rasagiline)

Mechanism -

There are two forms of MAO, namely type A (substrates

- Type A = Substrates include 5-hydroxytryptamine and tyramine
- Type B = Substrates include phenylethylamine

MAO-B is mainly localized in neuroglia.

⇒ MAO-A metabolizes endogenous adrenaline, noradrenaline and 5-hydroxytryptamine (5-HT), while the physiological role of MAO-B is unclear.

⇒ Inhibition of MAO-B raises brain dopamine level without affecting other major transmitter amines. Because selegiline and rasagiline selectively inhibit MAO-B,

Drug Affecting the Cholinergic System -

Muscarinic Receptors Antagonists -

mechanism -

Non-selective muscarinic receptor antagonism is believed to restore, in part, the balance b/w dopaminergic / cholinergic pathways in the striatum.

Drugs Used in Alzheimer's Disease

Alzheimer's disease is the most common cause of dementia.

- A progressive neurodegenerative disorder which affects older individuals and is the most common cause of dementia.

⇒ Atrophy of cortical and subcortical areas is associated with deposition of β-amyloid protein in the form of extracellular senile (amyloid) plaques and formation of e intracellular neuro-fibrillary tangles made up of "tau" protein followed by neuron loss.

⇒ Symptoms of AD are progressive loss of memory & disordered cognitive function with loss of short-term memory loss that usually proceeds loss of long term memory.

⇒ The loss of cholinergic activity in brain can protein with AD lead to the use of cholinesterase inhibiting drugs which can cross BBB.

⇒ These drugs block degradation of Ach and increase availability of Ach in the synaptic cleft.

Anti-Alzheimer's drug
Cognition Enhancers
(Cerebroactive drugs)

- Cholinergic activators
  - Rivastigmine
  - Donepzile
  - Galantamine
  - Tacrine
- Glutamate (NMDA) antagonist
  - Memantine
- Miscellaneous drugs
  - Piracetam
  - Pyritinal
  - Dihydroergotoxine
  - Citicoline
  - Piribedil
  - Ginkgo biloba

CNS Stimulants

These are drugs whose primary action is to stimulate the CNS globally or to improve specific brain function which may lead to convulsion.

CNS Stimulants

- Convulsants
  - Strychnine
  - Picrotoxin
  - Bicuculline
  - Pentylenetetrazole
- Analeptic (Respiratory stimulants)
  - Doxapram
- Psychostimulants
  - Amphetamines
  - Methylphenidate
  - Atomoxetine
  - Modafinil → Caffeine.
  - Armodafinil
  - Cocaine.

Use -

① In analgesic mixture: Caffeine benefits headache probably allaying fatigue and boredom.
- It has no analgesic action of its own.

② migraine: Caffeine is used in combination with ergotamine for treatment of migraine attacks.

Nootropics.

Nootropics → also called → smart drug,
memory enhancers,
neuro enhancers,
cognitive enhancers,
intelligence enhancers,
motivational &
stress managment drug ⇒ that improve one or more aspects of mental function.

⇒ The most commonly used class of drug is stimulants, such as caffeine. These drugs are purportedly used primarily to treat cognitive or motor function difficulties attributable to disorders such as Alzheimer's disease, Parkinson's disease; Huntington's disease and ADHD.

⇒ Several factors positively and negatively influence the use of drug to increase

cognitive performance.

Opioid Analgesics and Antagonists

Analgesic – A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

⇒ Analgesics can be divided into three groups

Ⓐ Opioid / Narcotic / morphine-like analgesics.

Ⓑ Non-opioid / non-narcotic / aspirine-like / antipyretic or antiinflammatory analgesics.

Ⓒ Adjuvant analgesics: Anticonvulsants, viz – gabapentin pregabalin, carbamazepine etc

Opioid Analgesics

Opium– A dark brown, resinous material obtained from poppy (*Papaver somniferum*) capsule.

⇒ It contains two types of alkaloids –

(1) Phenanthrene derivatives –
- (i) Morphine (10% in opium)
- (ii) Codeine (0.5% in opium)
- (iii) Thebaine (0.2% in opium) (non-analgesics)

② Benzoisoquinoline derivatives -

(i) Papaverine (1%)
(ii) Noscapine (6%) } Non-analgesics

Opioid Analgesics

Natural opium alkaloids	Semi-synthetic opioids	Synthetic opioids
→ Morphine	→ Diacetylmorphine (Heroin)	→ Pethidine
→ Codeine	→ Pholcodine	→ Methadone
	→ Ethylmorphine	→ Fentanyl
		→ Remifentanil
		→ Tramadol
		→ Tapentadol

Opioid Receptors

① μ (mu)-receptor — are thought to be responsible for most of the analgesic effects of opioids, and for some major unwanted effects (eg. respiratory depression, euphoria, sedation and dependence). Most of the opioid analgesics are μ-receptor agonists.

② κ (kappa) - receptors contribute to analgesia at the spinal level and may elicit sedation and dysphoria: they produce relatively few unwanted effects and do not contribute to dependence.

③ δ (Delta) :- receptors are probably more important in the periphery but may also contribute to analgesia.

Opioid Antagonists :-

Three opioid antagonists are in use:

Naloxone
Naltrexone
Nalmefene.

⇒ ① Naloxone – It is N-allylnor-oxymorphone and a competitive antagonist on all types of opioid receptors. It blocks μ receptor at much lower doses than those needed to block κ or δ receptor.

⇒ Naloxone is the drug of choice for morphine poisoning.

② Naltrexone – It is chemically related to naloxone and is another pure opioid antagonist, that is devoid of subjective and other agonistic effects, but very high doses have caused unpleasant feelings in some individuals. More potent than naloxone.

③ Nalmefene – This pure opioid antagonist lacks hepatotoxicity of naltrexone, has higher oral bioavailability and is longer acting.

Drug Abuse

It is defined as ~~a disease that~~ the excessive use of psychoactive drugs such as alcohal, heroin pain medication on CNS can illegal drug.

- It can lead to physical, social or emotional harm.

⇒ The phrases substance abuse and drug abuse are often applied to use of an illegal or illicit chemical substance (eg: heroin).

⇒ The two major patterns of drug abuse are.

ⓐ Continuous use: The drug is taken regularly, the subject wishes to continuously remain under the influence of the drug. eg - Opioids, alcohal, sedatives.

ⓑ Occasional use - The drug is taken off and on to obtain pleasure or high, reaction or enhancement of sexual experience, eg - Cocaine, alcohal, cannabis etc.

Unit II General Pharmacology

Pharmacodynamics - is the study of biochemical and physiological effects of drugs on the body or on microorganisms or parasites within or on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

Principles of Drug Action :-

Drug (except those gene based) do not impart new functions to any system, organ or cell; they only alter the pace of ongoing activity.

The basic types of drug action can be broadly classed as:

① Stimulation :- It refers to selective enhancement of the level of activity of specialized cells.
e.g. adrenaline stimulates heart, pilocarpine stimulate salivary gland.

② Depression :- It means selective diminution of activity of specialized cells. eg. barbiturates depress CNS, quinidine depress heart, omeprazole decrease or depresses gastric acid secretion.

③ Irritation :- This connotes a non-selective, often noxious effect and is particularly applied to less specialized cells (epithelium, connective tissue)