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Module -5.

Pharmacology of drugs acting on Central Nervous System.

⑧ Psey Psychopharmacological agents :→

The psychopharmacological agent. or psychotropic drugs are those which are having primary effects on psyche (mental processes) and are used for treatment of psychiatric disorders.

- It is an important to make an attempt to characterise the primary abnormality because specific drugs are now available.

1). Antipsychotics Drugs :→

The antipsychotic drugs (neuroleptics) are used primarily to treat schizophrenia, but they are also effective in other psychotic and manic states

Classification :→

First generation antipsychotic (low potency).

- Chlorpromazine
- Thioridazine

First generation antipsychotic (high potency)

- Triflupromazine, Perphenazine
- Fluphenazine, Haloperidol
- Pimozide, Loxapine
- Prochlorperazine, Thiothexine

Second generation antipsychotic :→

- Aripiprazole
- Olanzapine
- Ziprasidone
- Quetiapine
- Lurasidone
- Asenapine
- Iloperidone
- Lozapine

Eirst-generation antipsychotics:→

Antipsychotic effects reflect competitive blocking of dopamine D_2 receptors.

First-generation antipsychotics are more likely to be associated with movement disorders

known as extrapyramidal symptoms (EPS), particularly drugs that bind tightly to dopaminergic neuro-receptors, such as haloperidol.

Second-generation antipsychotic drugs:→

The second-generation antipsychotic drugs (also called "atypical" antipsychotics) have a lower incidence of EPS than the first-generation agents but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine & perhaps other receptors.

✓ Mechanism of action:→

→ Most of the second generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly $5\text{-}HT_{2A}$ receptors.

→ Clozapine has high affinity for D_1, D_4, $5\text{-}HT_2$ muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D_2 receptor antagonist. Risperidone blocks $5\text{-}HT_{2A}$ receptors to a greater extent than it does D_2 receptors, as does olanzapine.

→ The second-generation antipsychotic aripiprazole is a partial agonists at D_2 and $5\text{-}HT_{1A}$ receptors, as well as an antagonist of $5HT_{2A}$ receptors.

→ Quetiapine blocks D_2 receptors more potently than $5\text{-}HT_{2A}$ receptors but is relatively weak at ~~binding~~ blocking ~~at~~ either receptor. Its low risk for EPs may also be related to the relatively short period of time it binds to the D_2 receptor.

2). Anti-Depressants ⇒

These are drugs which can elevate mood in depressive illness.

Classification :→

I) Reversible inhibitors of MAO-A (RIMAs):

•) Moclobemide, Clorgyline

II) Tricyclic antidepressants (TCAs):-

A) NA + 5HT reuptake inhibitors:-

•) Imipramine, Amitriptyline, Trimipramine, Doxepin, Dothiepin, Clomipramine.

B) Predominantly NA reuptake inhibitors:-

•) Desipramine, Nortriptyline, Amoxapine, Reboxetine.

III) Selective serotonin reuptake inhibitors (SSRIs) :->

•) Fluoxetine, Fluvoxamine, Paroxetine, ~~Sero~~ Sertraline, Citalopram, Escitalopram, ~~Dapo~~ Dapoxetine.

IV) Serotonin and noradrenaline reuptake inhibitors (SNRIs) →

Venlafaxine, Duloxetine.

VI. Atypical antidepressants :- (Bipolar disorder)

Trazodone, ~~Mirtazapine~~ Mianserin, Mirtazapine, Bupropion, Tianeptine, Amineptine, Atomoxetine.

↳ Adverse Effects of Antidepressants :-

1). Anticholinergic : dry mouth, bad taste, constipation, epigastric distress, urinary retention (especially in males with enlarged prostate), blurred vision, palpitation.

2). Sedation, mental confusion and weakness, especially with amitriptyline & more sedative congers.

3). Increased apetite & weight gain is noted with most TCAs and trazodone, but not with SSRIs, SNRIs and bupropion.

4). ~~Seat~~ Sweating (despite antimuscarinic action) and fine tremors are relatively common

→ Adverse Effects of Antipsychotics :-

Antipsychotics are very safe drugs in single or infrequent doses: deaths from overdose are almost unknown. However, side effects are common and often limit their use.

3). Anti-anxiety :→

Anxiety :- It is an emotional, unpleasant state, in nature, associated with uneasiness, discomfort and concern or fear about some defined or undefined future threat. Some degree of anxiety is a part of normal life.

Antianxiety drugs :→ These are ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of interfering with normal mental or physical functions.

Classification :→

1) Benzodiazepines :→) Diazepam
) Chlordiazepoxide
) Oxazepam
) Lorazepam, Alprazolam.

2). Azapirones :→ •) Buspirone
•) Gepirone
•) Ispapirone. Hydroxyzine.

3). Sedative antihistaminic :→ Hydroxyzine.

4). β blocker :→ Propranlol.

Adverse Effects of anti-anxiety :→

1). Chlordiazepoxide : It was the first BZD to be used clinically. oral absorption is slow. A smooth long lasting effect is produced. It is preferred in chronic anxiety states. BZD used to cover alcohol withdrawl. Its t½ is 6-12 hours, but active metabolites are produced which extend the duration of action. Its convulsant action is weak. Daily dose- 25-100mg.

Diazepam : It is quickly absorbed, produces a brief intial phase of strong action followed by prolonged milder effect due to a two phases plasma

concentration decay curve $t_{1/2}$ 1 hr, elimination phase $t_{1/2}$ 20-30 hours. Daily dose → 5-30 mg.

2) Oxazepam :- It is slowly absorbed, being relatively polar, its penetration in brain is also slow. The plasma $t_{1/2}$ is about 10 hours. It is metabolized only by glucuronide conjugation, therefore no active metabolite is produced. Daily dose → 30-60 mg in 2-3 divided portions.

4) Anti-manic :→ It is also known as Bipolar disorders.

Lithium is a small monovalent cation. In 1949, it was found to be sedative in animals and to exert beneficial effects in manic patients.

Action & Mechanism :→

CNS :→ Lithium has practically no acute effects in normal individuals as well as in bipolar patients. It is neither sedative nor euphoriant, but on prolonged administration, it acts as a mood stabilizer in bipolar disorder.

a) 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. However, relative to Na^+ and K^+ concentration, the concentration of Li^+ associated with therapeutic effect is very low.

b). Lithium decreases the presynaptic release of NA and DA in the brain of treated animals without affecting 5-HT release. This may correct any imbalance in the turnover of brain mono-amines.

Adverse effects of Anti-manics :→

1). Nausea, vomiting and mild diarrohea occur initially, can be minimized by starting at lower ~~doses~~ doses.

2) Thirst and polyuria are experienced by most, some fluid retention may occur initially, but clears later.

3). Fine tremors are ~~noted~~ noted even at therapeutic concentrations.

1). Hallucinogens :→

These are drugs which alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis. The important drugs are described below:

Lysergic acid diethylamide (LSD) :→

It is the most potent hallucinogen (psychedelic), 25 – 50 µg produces all the effects. In addition to the mental effects, it produces pronounced central sympathetic stimulation. Its action appears to involve serotonergic neuronal systems in brain.

Lysergic acid amide :→ A close relative of LSD but 10 times less potent, found in morning glory (Ipomoea Violace) seeds.

Phencyclidine :→ It is an anticholinergic, which activates σ receptors in brain causing disorientation, distortion of body image, hallucinations and an anaesthetic like state. Ketamine is a closely related

compound with lower hallucinogenic potential. It is used in anaesthesia.

* Cannabinoids :-

9 Δ Tetrahydrocannabinol (9 Δ THC) →

It is the active principle of Cannabis Indica (Marijuana), which has been the most popular recreational and ritualistic toxicant used for millennia. Its use has spread worldwide. The following are the various forms in which it is used :→

Bhang :→ The dried leaves is generally taken by oral route after grinding and making a paste. It acts slowly.

Ganja :→ The dried female inflorescence is more potent and is smoked; effects are produced almost instantaneously.

Charas :→ is the dried resinous extract from the flowering tops and leaves most potent and is usually smoked along with tobacco also called hashish.

B]. Drugs used in Parkinsons disease :→

These drugs that have a therapeutic effect in Parkinsons disease (PD).

Parkinson disease is a progressive degenerative Disorder. The most consistent lesion in PD is degeneration neurones in the substania nigra pars compacta (SN–PC) and the nigrostriatal (dom dopaminergic tract).

this results in the deficiency of dopamine (DA) in the striatum which controls muscle tone and coordinates movements. PD is characterized by rigidity, tremor and hypokinesia.

Classification :→

I Drugs affecting brain dopaminergic system :→

a) Dopamine precursor :→ Levodopa (1-dopa).

b) Peripheral decarboxylase inhibitors :→ Carbidopa, Benserazide.

c) Dopaminergic agonists :→ Bromocriptine,

Ropinirol, Pramipexole.

d). MAO-B inhibitor: Selegiline, Rasagiline

e). COMT inhibitors: Entacapone, Tolcapone
(Catechol-o-methyltransferase)

f). Glutamate (NMDA) receptor antagonists
(Dopamine facilitators): Amantadine

II). Drugs affecting brain Cholinergic system:

a) Central anticholinergics: Trihexyphenidyl (Benzhexol), Procyclidine, Biperiden.

b). Antihistamines: Orphenadrine, Promethazine.

Levodopa:→

→ It is inactive by itself, but is the immediate precursor of the transmitter DA. More than 95% of an oral dose is decarboxylated in the peripheral tissues (mainly gut and liver).

→ about 1-2% of administered levodopa crosses to the brain, is taken up by the surviving dopaminergic neurones, converted to DA

which is stored and released as a transmitter.

→ Marked symptomatic improvement occurs in parkinsonian patients. Hypokinesia and rigidity resolve first, later tremor as well. Secondary symptoms of posture, ~~gait~~, handwriting, speech, facial expression, mood, self care and interest in life are gradually normalized.

Levodopa + Carbidopa :→

Benefits of the Combination are :→

1). The plasma $t_{1/2}$ of levodopa is prolonged and its dose is reduced to approximat-ely $1/4^{th}$.

2). Systemic Concentration of DA is reduced, nausea and vomiting are not prominent - therapeutic doses of levodopa can be attained quickly.

3) Cardiac Complications are minimized.

4) Pyridoxine reversal of levodopa effect does not occur.

→ Improvement in parkinsonian symptoms occurs within 1/2 - 1 hr of an oral dose of bromocriptine and lasts for 6-10 hours.

Drugs used in Alzheimer's Disease:→

Dementia of the Alzheimer type has three distinguishing features :→

a). accumulation of senile plaques (β-amyloid ~~or~~ accumulations).
b). Formation of numerous neurofibrillary tangles, and
3). Loss of cortical neurons, particularly cholinergic neurons.

→ Current therapies aim to either improve cholinergic transmission within the CNS or prevent ~~excitatory~~ excitotoxic actions resulting from overstimulation of NMDA - glutamate receptor-s in ~~set~~ selected areas of the brain.

Acetylcholinesterase Inhibitors :→

a). The reversible ACHE inhibitors approved for the treatment of mild to moderate Alzheimer's disease include donepezil, ~~gala~~

galantamine, and rivastigmine.

•) All of them have some selectivity for AChE in the CNS, as compared to the periphery. Galantamine may also augment the action of acetylcholine at nicotine receptors in the CNS.

•) Rivastigmine is hydrolyzed by AchE to a carbamylate metabolite and has no interactions with drugs that alter the activity of CYP450 enzymes.

•) Common adverse effects includes nausea, diarrohea, vomiting, anorexia, tremors, bradycardia, & muscle cramps.

NMDA Receptors :=>

→ Excess intracellular Ca^{2+} can activate a no number of processes that ultimately damage neurons and lead to apoptosis.

→ Memantine, is an NMDA receptor antagonist indicated for moderate to severe Alzheimer's disease.

→ It acts by blocking the NMDA receptor and limiting Ca^{+} influx into the neuron, such that toxic intracellular levels are not achieved.

→ Memantine is well tolerated, with few dose-dependent adverse events. Expected side effects, such as confusion, agitation & restlessness

CNS Stimulants

These are drugs whose primary action is to stimulate the CNS to improve specific brain functions.

Caffeine → Out of ~~these~~ three naturally occuring methylxanthies, only caffeine is used as CNS stimulant.

Caffeine has poor water solubility is rapidly but irregularly absorbed after oral administration. It is <50% bound to plasma proteins, distributed all over the body, and nearly completely metabolized in liver by demethylation and oxidation. Metabolites are excreted in urine; plasma $t_{1/2}$ is 3-6 hours in adults.

Uses are :→

1) Migraine :- Caffeine is used in combination with ergotamine for treatment of migraine attack. It appears to benefit by augmenting constriction of cranial vessels and by enhancing absorption of ergotamine from the g.i.t.

2). Apnoea in preature infants is as alternative to theophylline.

I]. Amphetamine :→ i) They exert potent CNS stimulant actions. Maximal selectivity is exhibited by dextroamphetamine and methamphetamine which in the usual doses produce few pt peripheral effects.

ii). The central actions of amphetamines are largely mediated by release of NA from adrenergic neurones in the brain. Amphetamine also inhibits neuronal reuptake of DA.

iii). The cortical effects include alertness, increased concentration and attention span, euphoria, talkativeness, increased work capacity.

iv). High dose produce ~~sleep~~ euphoria, restlessness, insomnia, aggression, panic, marked excitement which may progress to mental confusion, delirium, hallucinations and an acute psychotic state.

Mechanism of action :→

These drugs enter the nerve ending by active transport and displace DA/NE from storage vesicles by altering their pH. They have some property to inhibit DA metabolism by inhibiting MAO-B in the nerve ending.

Adverse Effects :→

a). Tolerance :→ Tolerance develops rapidly to peripheral sympathomimetic and anorexic effects.

b). Psychic dependence :→ Amphetamine produces high psychic dependence and rarely physical dependence. Withdrawal

Opioid Analgesics and Antagonists

Drugs having agonistic activity, especially on μ-receptors are used as analgesics. Morphine is the prototype drug in this category. Other morphine agonists and mixed agonists-antagonists have actions similar to morphine with few modifications.

Classification :→

1) Natural opium of alkaloids :- Morphine, Codiene.

2) Semisynthetic opiates :- Diacetylmorphine (Heroin), Pholcodiene, Ethylmorphine.

3) Synthetic opioids :→ Pethidine (Mepericidine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol.

a) Morphine :→

Mechanism of action :→

↳ Morphine and other opioids exert their major effects by interacting stereospecifically with opioid receptors on the membranes of certain cells in the CNS and other anatomic structures, such as the gastrointestinal (GI) tract and the urinary bladder.

↳ ~~Morphine~~ Morphine also acts at κ receptors in lamina I and II of the dorsal horn of the spinal cord. It decreases the release of substance P, which modulates pain perception in the spinal cord.

↳ Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli.