Central Nervous System

- Most of the drugs that affect the central nervous system (CNS) act by altering some steps in the neurotransmission process.

- They may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters.

- Other agents may activate or block postsynaptic receptors.

- Several major differences exist between the neurons in ANS and those in the CNS, for example CNS communicates using 10 different neurotransmitters (ANS has norepinephrine and ACT).

Central Nervous System

- Most of the neurons in the CNS receive both excitatory and inhibitory potentials.

- Thus, several types of neurotransmitters may act on the same neuron, but each binds to its own specific receptors.

- The overall resultant action is due to the summation of individual actions of various neurotransmitters on the neurons.

Neurodegenerative diseases

- Include Alzheimer, Parkinson, Huntington diseases.
- Alzheimer affect some 4 millions Americans while Parkinson is affecting 1.5 millions Americans.
- They are devastating (destructive) illness, characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movements, cognition or both.
- For example Alzheimer characterized by loss of cholinergic neurons, where as Parkinson is associated with a loss of dopaminergic neurons.

Parkinson

- Characterized by tremors, muscular rigidity, bradykinasia (slow in the voluntary movements). most patient are over 65 years old.

- The cause is unknown for most patients, rare to be secondary to viral encephalitis.

- Two main events are happened in this devastating disease:

  (1) Dopaminergic system appears to serve as a tonic , sustaining influence on the motor activity, rather than participating in specific movements.

Parkinson

Dopaminergic neuron makes thousand of synaptic contacts and modulates the activity of a large number of cells.

In Parkinson patients these nerves fire tonically rather than in response to specific muscle movements or sensory input.

(2) Degenerating of the neurons responsible to release dopamine.

Thus, the normal inhibitory influence of dopamine on the cholinergic neurons is significantly diminished, which result in the overproduction of ACT. This trigger abnormal signaling, resulting in loss of muscles movements

Parkinson

- Therapy aimed to restoring dopamine and antagonizing the excitatory effect of cholinergic neurons, this restoring the balance between dopamine/ACT balance in the CNS.

Levodopa and Carbidopa

- Levodopa is a metabolic precursor of dopamine. And used to restore the dopamine level in brain.
- In the new patient, the therapeutic response is consistent,
- while in advanced cases, the number of neurons decrease and fewer cells are capable of taking up Levodopa and converted to dopamine for subsequent storage and release. Subsequently, motor control fluctuation developed. The phenomena that called “wearing off”
- Relief provides by Levodopa is only systemic, and it lasts only while the drug is present in the body.

Levodopa and Carbidopa

- Dopamine itself does not cross the blood brain barriers, but its immediate precursor Levodopa is readily transport into the CNS and converted to dopamine in the brain.

- Large doses is required, because much of the drug is decarboxylated to dopamine by dopamine decarboxylase in the peripheral, resulting in side affects.

- To solve that, Levodopa is combined with Carbidopa, which is a dopamine decarboxylase inhibitor that does not cross the blood brain barriers.

- Thus Carbidopa, diminishes the metabolism of the Levodopa in the peripheral tissues, and increase the availability of Levodopa to the CNS (lower the dose four to five folds).

Levodopa and Carbidopa

- In two third of patient the combination is reduce the severity of the disease in the first few years, then a decline in response is experienced during the third to fifth year of therapy (“wearing off”)

- Adverse effect:

  (1) dopamine stimulate the emetic centre and may cause Nausea, vomiting.

  (2) dopamine has an action on the heart, and may cause tachycardia and ventricular extrasystolic.

  (3) over activity of dopamine in the receptors in the brain may produce Hallucination, confusion and abnormal involuntary movements may occur, dyskinesia.

Selegiline

- is a drug used for the treatment of early-stage Parkinson disease.
- Has been found to increase the dopamine level in the brain by selective inhibitor of dopamine metabolism.
- Selegiline exhibits little therapeutic benefit when used independently, but Enhances the action of Levodopa, and when administered together, Selegiline substantially reduce the required dose of Levodopa.
- When given at high doses, place the patient at high risk of hypertension.

Catechol-O-methyltransferase (COMT) inhibitors

- When peripheral dopamine decarboxylase activity is inhibited by Carbidopa, a significant concentration of 3-O-methyldopa is formed and compete with Levodopa for active transport into the CNS.

- Inhibition of COMT by **Entacapone** and **Tolcapone** leads to decrease the plasma concentration of 3-O-methyldopa, increase the central uptake of dopamine.

- Both of these agents have been demonstrated to reduce the symptoms of “wearing off” phenomena seen in patient on Levodopa-Carbidopa.

Catechol-O-methyltransferase (COMT) inhibitors

- Their adverse effect includes diarrhea, postal hypotension, hallucination and sleep disorders.

- Tolcapone produce hepatic necrosis and only used with patient in whom other mediators are failed.

Dopamine receptors agonist

- This group includes
  (1) two older agents, Bromocriptine and Pergolide.
  (2) two newer agents, Ropinirole and Pramipexole.

- These agents has longer duration of action than that of Levodopa, thus have been effective in patients exhibiting fluctuation in their response to Levodopa.

- Initial therapy with the newer agents is associated particularly with less risk of developing dyskinesias and motor fluctuations in compare to Levodopa.

- These agents are ineffective in patient who have shown no therapeutic response to Levodopa.

Bromocriptine and Pergolide

- Are dopamine receptors agonists, Pergolide being more potent.
- Their side effects are similar to that of Levodopa, however the Hallucination, confusion are more common, while dyskinesia is less frequent.
- Series cardiac problems may develop, particularly with patients with myocardial infarction.
- In addition, both agents have the potential to cause pulmonary fibrosis

Ropinirole and Pramipexole

- They alleviate the deficit in both patients who have never treated with Levodopa and in patients with advanced Parkinson disease taking Levodopa.

- They may delay the need to employ Levodopa in advanced Parkinson, and may decrease the dose of Levodopa in advanced Parkinson.

- Pramipexole interact with Cimitidine, which inhibit the renal secretion of Pramipexole and result in a 40 % increase in the half life of Pramipexole.

- Their main side effect are nausea, hallucination, and hypotension.

Amantadine

- It was accidentally discovered that antiviral drug Amantidine (effective in the treatment of influenza) has an antiparkinsonism action.

- It cause an increase in the release of dopamine, blocking cholinergic receptors, block some of the NDMA glutamate receptors.

- Adverse effect includes restlessness, agitation, hallucination.

- Amantadine is less officious than Levodopa and tolerance develops more readily, However, it has lower side effects.

Antimuscarinic agents

- Blockage of the cholinergic transmission and produce effects similar to rise of dopaminergic transmission
- Much less efficacies than Levodopa and play only an adjuvant role in antiparkinsonism therapy.
- **Benztropine** and **Biperidine** are similar, although individual patient response more favorably to one drug.
- Blocking of the cholinergic transmission produces effects similar to augmentation (rise) of dopaminergic transmission.
- These agents may cause mood change and produce dryness of the mouth and visual problems. Interfere with the gastrointestinal peristalsis. And are contraindicated in glaucoma.

Drugs used to treat Alzheimer disease

- Pharmacological intervention for Alzheimer disease is only palliative (calming) and provides modest short-term benefit.

- None of the current therapeutic agents alter the underlying neurodegenerative process.

- Current therapeutics are aimed at either

  (1) improving cholinergic transmission within the CNS

or

  (2) preventing the excitotoxicity actions of NMDA glutamate receptors in selected brain areas.

Acetylcholinesterase inhibitors

- Many studies have linked the progressive loss of cholinergic neuron and, presumably cholinergic transmission within the cortex, to the memory loss that hallmark (trademark) symptoms of Alzheimer disease.

- Inhibition of Acetylcholinesterase within CNS will improve cholinergic transmission,

- Examples on this group are **Donepezil**, and **Galantamine**.

- At best these agents provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer disease.

- Common adverse effect include anorexia, muscles gramps, and diarrhea

NDMA receptors antagonist

- Over stimulation of glutamine receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons, and is suggested as a mechanism for neurodegenerative processes.

- Antagonist of NDMA glutamine receptors are often neuroprotective, preventing the loss of neurons following ischemic and other injuries.

- Memantine is an example and has shown to prevent or slow the rate of memory loss in Alzheimer dementia, even in patient with moderate to sever cognitive losses.

- Memantine is well tolerated, with few dose related adverse effects, which include confusion and restlessness.