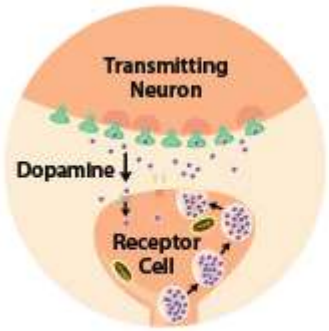
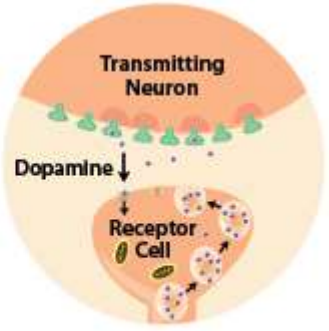
Antiparkinsonism Agents



Healthy Patient



Parkinson's Patient

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Parkinsonism

- Parkinsonism, as a clinical entity, was first described by James Parkinson in 1817.

- It is a syndrome having the features of akinesia, muscular rigidity, tremor, excessive salivation, seborrhoea, mood changes (especially depression), and liver damage that may be present in certain patients.

- Normally the high concentrations of dopamine in basal ganglia of the brain is reduced in the case of Parkinson's disease.

- Parkinson's disease is characterized by dopamine deficiency.

Definition

Parkinson's disease is degenerative disorder of the CNS dopaminergic neurons which shows mainly motor and sometimes cognition (thinking) related symptoms.

Movement-related (motor)

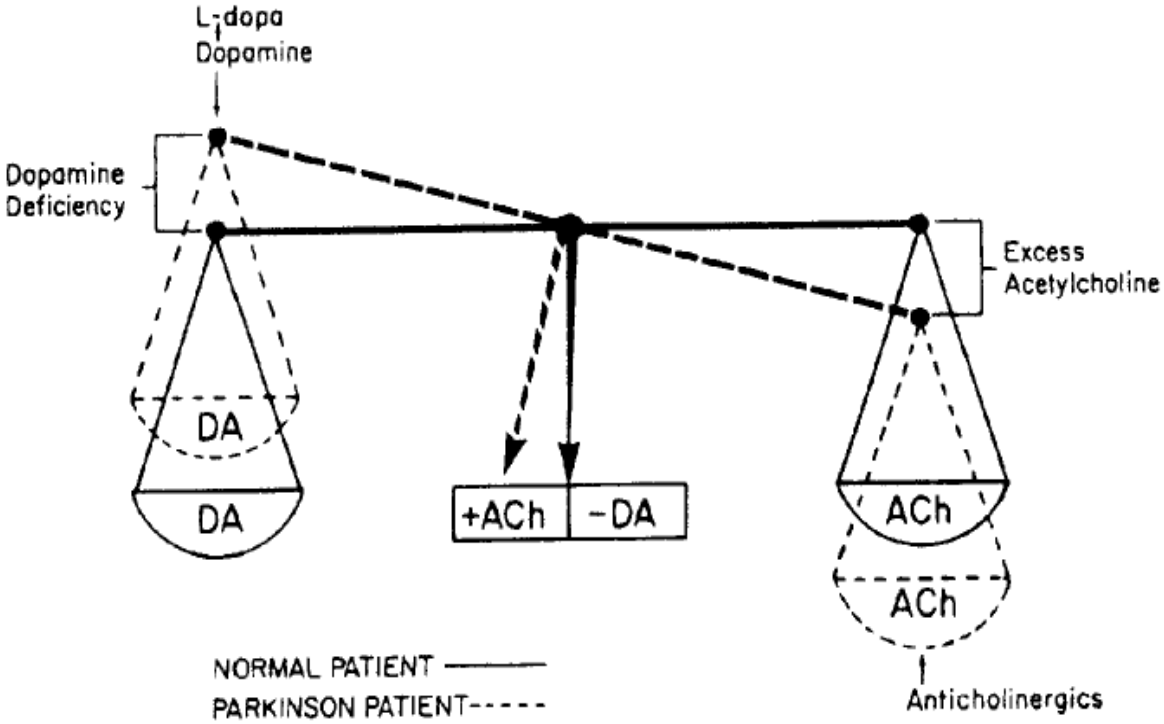
shaking, rigidity, slowness of movement and difficulty with walking

Cognitive problems

Dementia

1. MEDICINAL CHEMISTRY OF DRUG THERAPY OF PARKINSON'S DISEASE (PD)

- Therapeutic goal: symptomatic relief through restoration of balance between neurotransmission by ACh and DA in the basal ganglia



Schematic representation of the imbalance between the excitatory neurotransmitter acetylcholine (Ach) and the inhibitory neurotransmitter dopamine (DA) in the basal ganglia.

Causes

• Parkinson is caused due to imbalance of dopamine(DA) and acetylcholine (Ach) .

• Ach and DA need to be balanced for smooth movement. DA causes muscle relaxation while Ach causes contraction.

• Reduction of DA, in the basal ganglia results in imbalance of those two and causes motor disorders.

• In some cases, at later stages of the disease reduction of Ach which is also involved in learning and attention leads to dementia

CLASSIFICATION

The drugs used in the treatment of parkinsonism can be classified as follows:

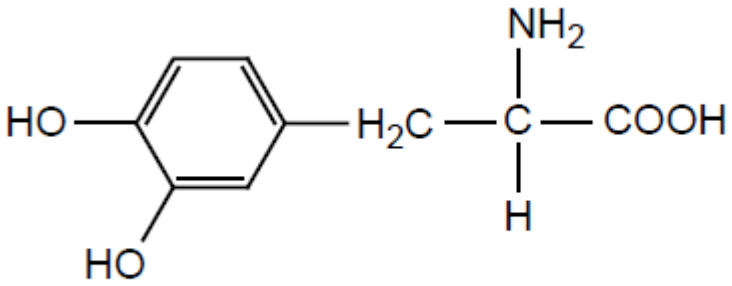
1. Drugs that increase brain levels of dopamine-Ex. Levodopa
2. DOPA decarboxylase inhibitors-ex. Carbidopa
3. Dopamine releasers- Ex. Amantidine
4. Anticholinergic agent- Ex. Trihexyphenydyl,
5. Phenothiazine anaologues- Ex. Ethopropazine

CLASSIFICATION

6. Miscellaneous drugs

- Antidepressants: Amitriptyline, trazadone
- α- tocopherol (vitamine E)
- Glutamate release inhibitor: Lamotrigine
- Glutamate receptor antagonist: Remacemide
- Glial-derived neurotrophic factor: GDNF
- Benztropine
- Orphenadrine citrate
- Chlorphenoxamine HCl

1. Drugs that increase brain levels of dopamine-Ex. Levodopa

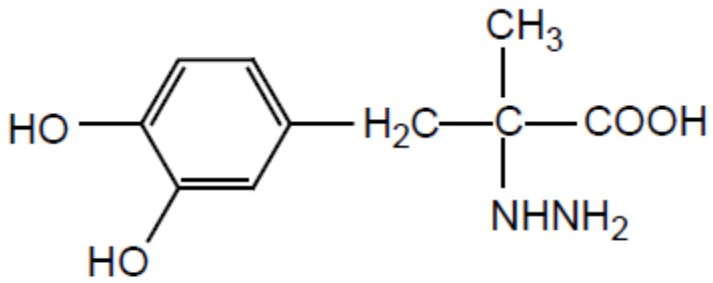


2-Amino-3-(3,4-dihydroxyphenyl) propanoic acid

Mechanism of action: External DA can't cross BBB but the prodrug L-dopa can. L-Dopa is dopamine with acid group to create an amino acid functional group. The blood brain barrier has Amino Acid Transporter which allows penetration of L-dopa, *even though Ldopa is less lipophillic than DA*

- In the brain it gets metabolized into dopamine by the enzyme DOPA decarboxylase.
- Thus, L-DOPA is used to increase dopamine concentrations in the brain which is lowered in Parkinson

2. DOPA decarboxylase inhibitors-ex. Carbidopa



3-(3,4-Di-hydroxyphenyl)-2-hydrazinyl-2-methylpropanoic acid

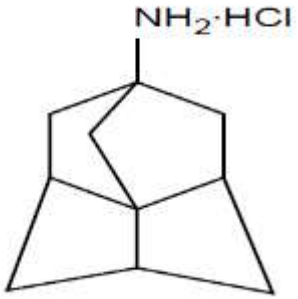
Mechanism of action:

It is a Dopamine decarboxylase inhibitors.

• It's purpose is to increase efficacy of L-Dopa by preventing it's peripheral metabolic degradation and thus allowing more L-Dopa to penetrate the brain

• While Dopamine decarboxylase exists both inside and outside the brain, Carbidopa only blocks metabolism outside the brain cause it can't penetrate the brain.

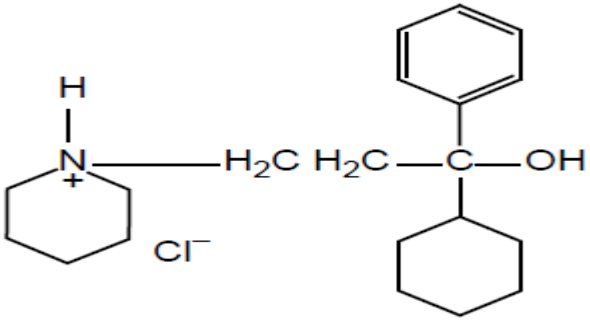
3. Dopamine releasers- Ex. Amantidine



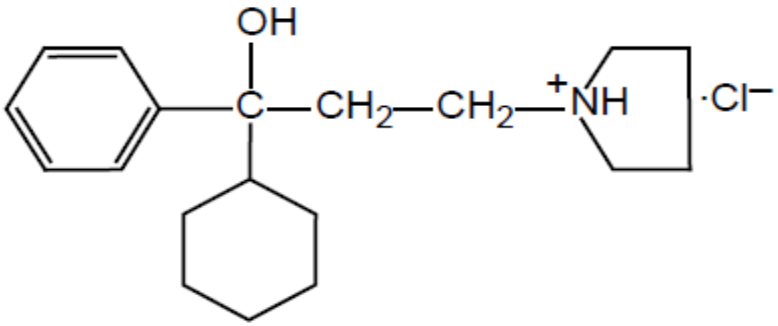
Mechanism of action:

Amantadine appears to act by promoting presynaptic synthesis and release of dopamine in the brain. It acts on glutamate receptors through which dopaminergic system exerts the possible influence on regulating the D1 and D2 receptors.

4. Anticholinergic agents- Ex. Procyclidine, Trihexyphenidyl HCl



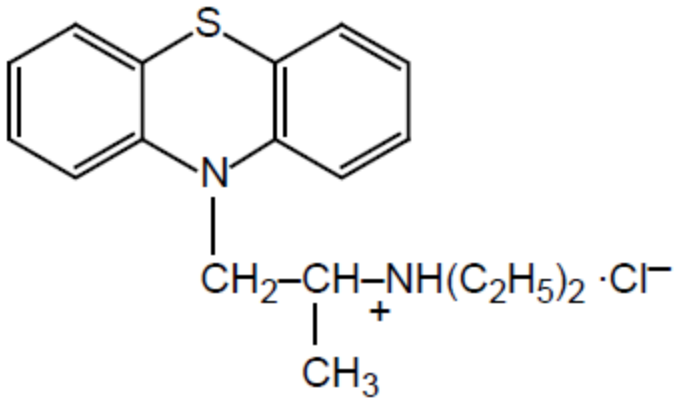
Trihexyphenidyl HCl



Procyclidine HCl

- **Mechanism of action:**
- Anticholinergic medicines block cholinergic nerve impulses that help control the muscles of the arms, legs and body by inhibiting binding of acetylcholine with it's receptors
- Anticholinergic medicines decrease levels of acetylcholine to achieve a closer balance with dopamine levels.

5. Phenothiazine Derivatives: Ex.Ethopropazine



10-[2-(Diethylamino)propyl]phenothiazine hydrochloride

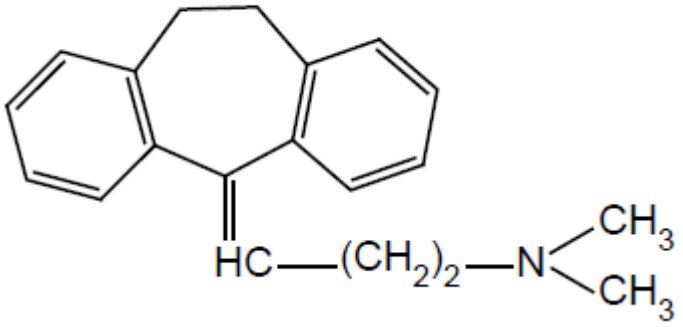
Mechanism of action:

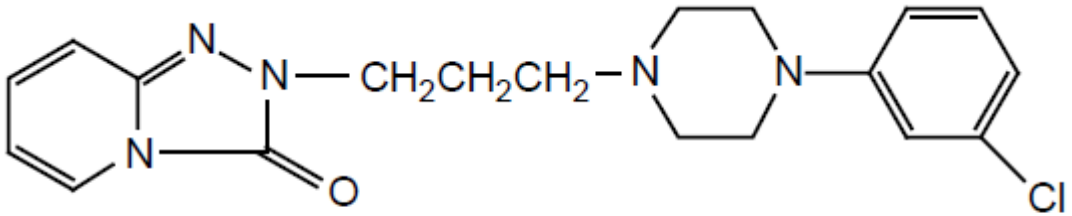
These drugs act by reducing the unbalanced cholinergic activity in the striatum of parkinsonian patients.

6. Miscellaneous drugs

1. Antidepressants: Amitriptyline, trazadone

a. Amitryptyline





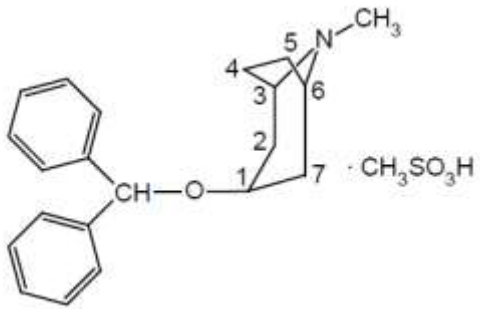
2-{3-[4-(3-Chlorophenyl)-1-piperazinyl]propyl} 1,2,4-triazolo pyridin-3-one.

6. Miscellaneous drugs

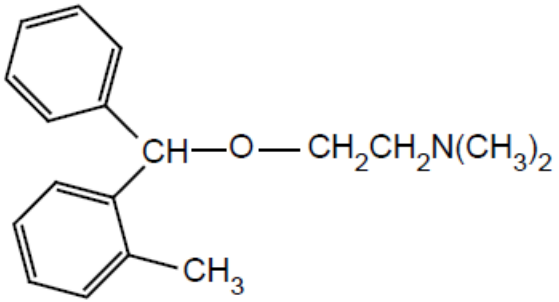
2. Glutamate release inhibitor: Lamotrigine

3, 5-Diamino-6-(2, 3-dichlorophenyl)-1, 2, 4-triazine

3. Benztropine



•Orphenadrine citrate



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Thank you