

# **Neurodegenerative Diseases**

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# Overview

- Most drugs that affect the central nervous system (CNS) act by altering some step in the **neurotransmission process**.
- Drugs affecting the CNS may act **presynaptically**: influencing the production, storage, release, or termination of action of neurotransmitters.

# Overview

- Drugs affecting the CNS may act **postsynaptically**: may activate or block postsynaptic receptors.
- Common neurodegenerative disorders: Parkinson's and Alzheimer's disease occur as a result of neurodegenerative processes.

# Neurodegenerative Diseases

- Neurodegenerative diseases of the CNS include Alzheimer's disease and Parkinson's disease.
- These devastating illnesses are characterized by the **progressive loss of selected neurons** in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both.

# Neurodegenerative Diseases

- Alzheimer's disease is characterized by the loss of cholinergic neurons in the nucleus basalis of Maynert, whereas Parkinson's disease is associated with a loss of dopaminergic neurons in the substantia nigra.
- The most prevalent of these disorders is Alzheimer's disease.

# Parkinson's Disease

- Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia, and postural and gait abnormalities.

# Parkinson's disease

- Progressive neurological disorder caused by progressive loss of *dopamine* in the CNS causing
- tremor
- muscle rigidity
- bradykinesia (slowness in initiating and carrying out voluntary movements )
- postural gait abnormalities

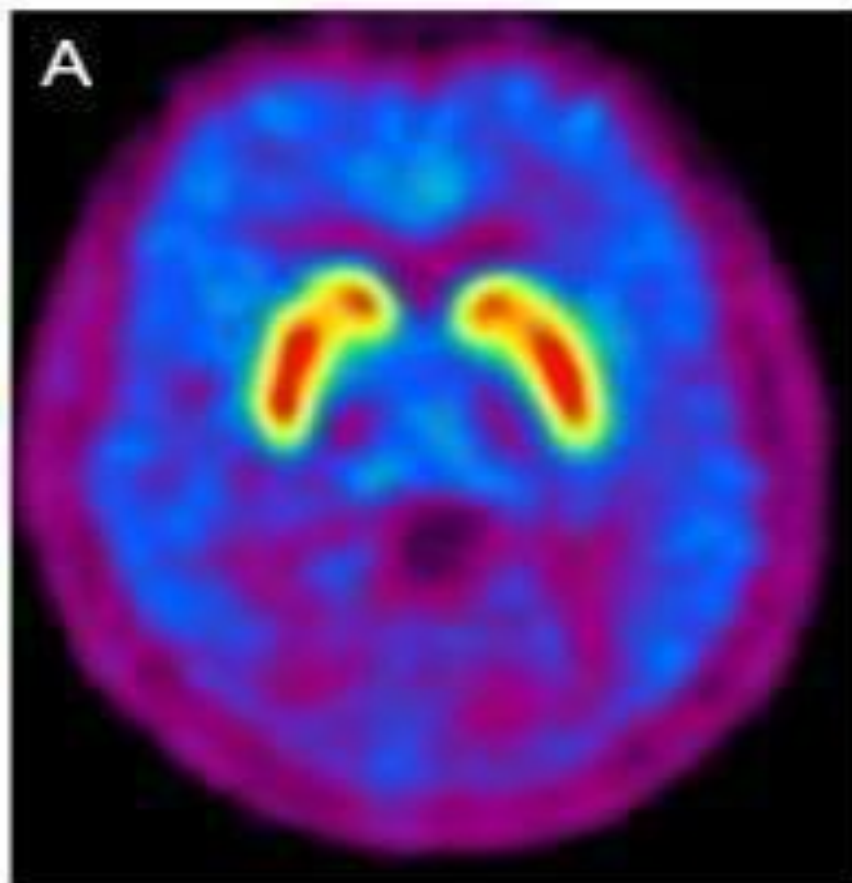
# Etiology

- The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum— parts of the brain's basal ganglia system that are involved in motor control.

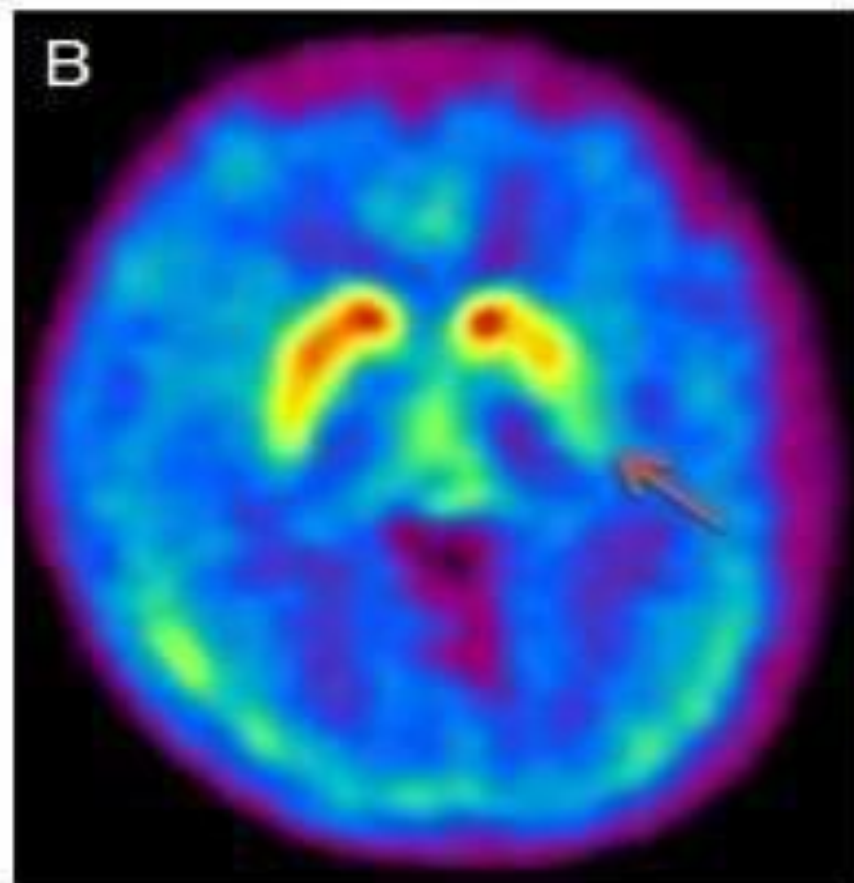


- The loss of dopamine neurons in the substantia nigra is evidenced by diminished overall uptake of dopamine precursors in this region

Control



PD Patient



- **Goal of pharmacotherapy for parkinson's disease** is to increase the ability of the patient to perform normal activities of living (ADLs).

# Strategy of treatment

- In addition to an abundance of **inhibitory dopaminergic neurons**, the neostriatum is also rich in **excitatory cholinergic neurons** that oppose the action of dopamine.

# Strategy of treatment

- Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons.

# Strategy of treatment

- Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct [dopamine/acetylcholine balance](#).

# Drugs Used in Parkinson's Disease

- Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease.

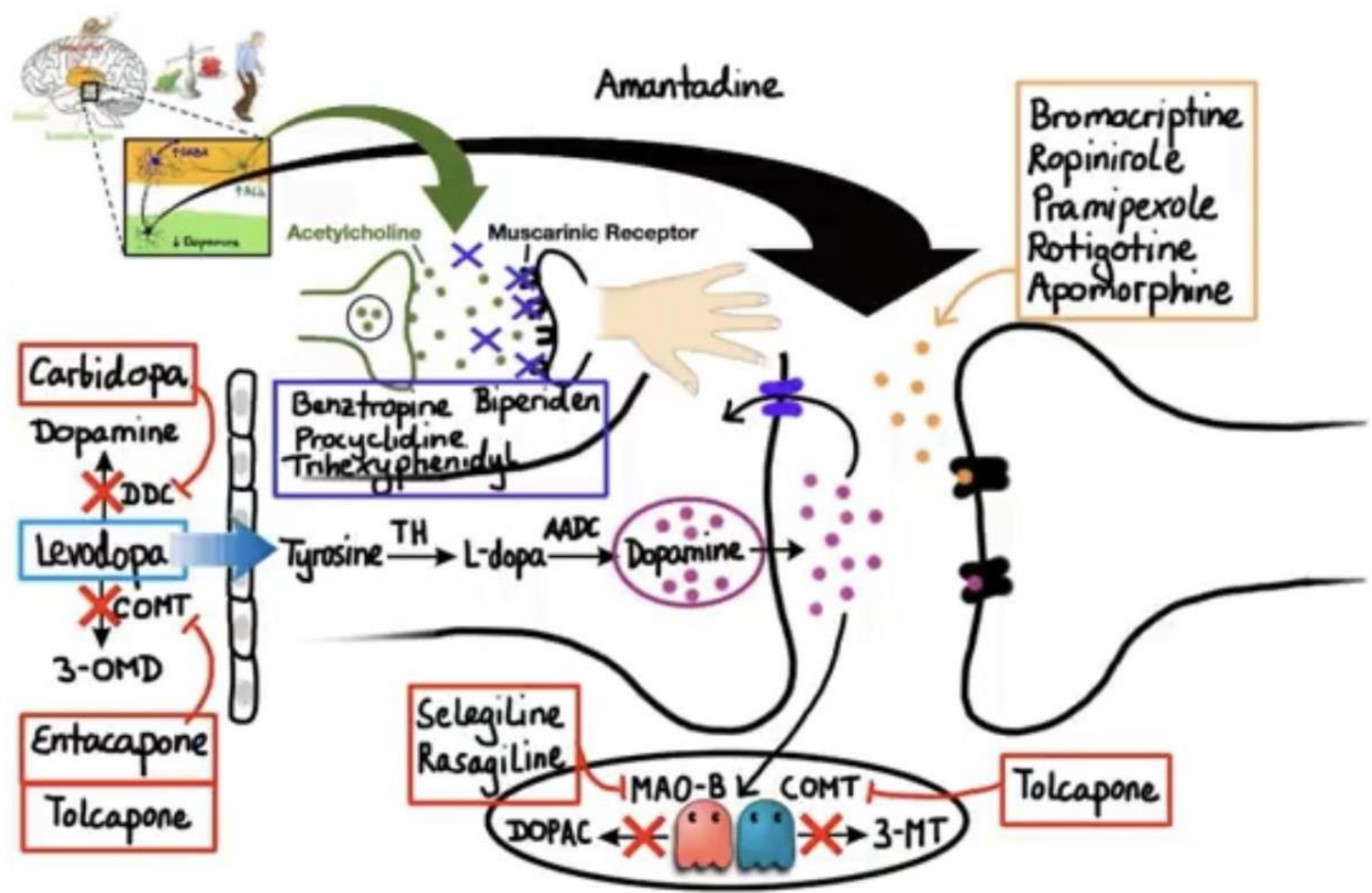
# **Parkinsonism Drugs/ Antiparkinsonism agents**

- Given to restore balance of dopamine and acetylcholine in specific regions of the brain



# Dopaminergics

- Either
- restore dopamine function
- stimulate dopamine receptors located within the brain



# Anti-cholinergics

- Inhibit the action of acetylcholine in the brain
- Used early in the course of therapy for Parkinsonism disease

# Treating Parkinsonism with Anti-Cholinergics

- By blocking the effect of acetylcholine, anticholinergics inhibit the overactivity of this neurotransmitter in the corpus striatum of the brain
- Anticholinergics such as atropine were the first agents used to treat parkinsonism
- Although anticholine act on the CNS, autonomic effects such as ***dry mouth, blurred vision, tachycardia, urine retention, and constipation*** are still troublesome

# Treating Parkinsonism with Anti-Cholinergics

- The centrally acting anticholinergics are not as effective as levodopa at relieving severe symptoms of Parkinsonism.
- They are used early in the course of the disease when symptoms are less severe, in patients who cannot tolerate levodopa and in combination therapy with other parkinsonism drugs

# Antimuscarinic agents

- All of these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers.
- They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis.

# Antimuscarinic agents

- Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission.
- Adverse effects are similar to those caused by high doses of *atropine*—for example, papillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth.

# Alzheimer's Disease

Causes, Effects, and Treatments



# Alzheimer's Disease

- Degenerative brain disorder
- 4 million Americans
- 10% of all people over 65
- 50% of all people over 85
- 19 million people are family members of an Alzheimer's patient
- 22 million people worldwide will be diagnosed by 2025

# The History of Alzheimer's

- Alois Alzheimer in 1906 performed an autopsy
- “Peculiar formations”
- “Dense bundles”

# Functioning Brain

- Cerebrum- 2 hemispheres
  - Higher order functioning- reasoning, planning, analyzing, creating
  - Lobes
    - Frontal
    - Parietal
    - Temporal
    - Occipital

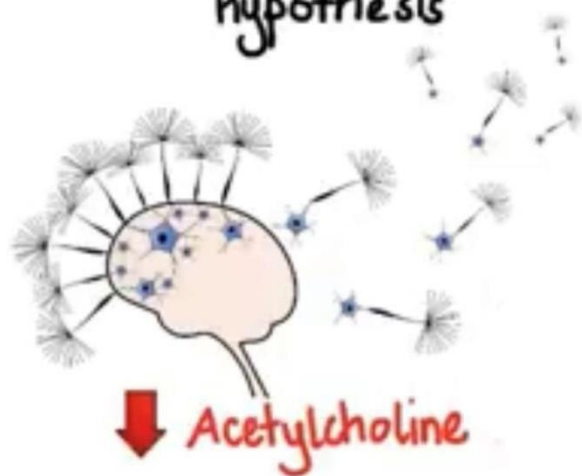
# Functional Brain

- Hippocampus
  - Part of limbic system
  - Role in memory formation
    - Sorts and sends new info to correct part of brain to be stored and recalled when necessary

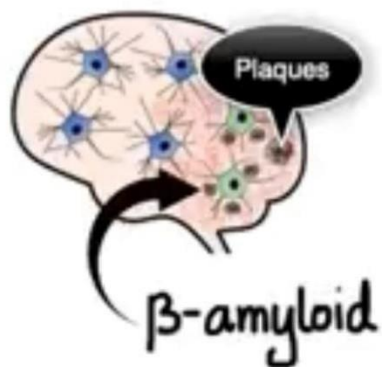
# Neurons

- Basic unit of nervous system- nerve cells
- Stimulus causes neuron to send an electric impulse through the cell body to the tip of the axon where neurotransmitters carry the signal across the synapse to the next neuron

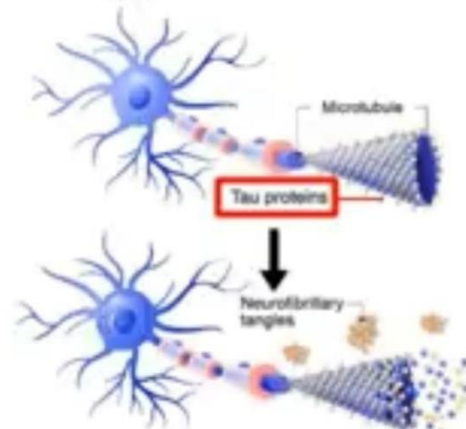
### Cholinergic hypothesis



### Amyloid hypothesis



### Tau hypothesis



# What Alzheimer's does

- Neuron degeneration
  - First in hippocampus
  - Spreads to frontal, parietal, temporal lobes
  - Loss in basal nucleus of Meynert
  - Goes on to rest of brain
  - Brain mass shrinks

# What Alzheimer's Does

- Amyloid plaques
  - Abnormal build-up of a protein called beta-amyloid
- Neurofibrillary tangles
  - Threads of protein tau begin to twist and structure of cell collapses
- Do plaques and tangles cause Alzheimer's or are they a result of the disease?



# BETA-AMYLOID PLAQUES

# AMYLOID PLAQUES

- Plaques form when specific protein in the neuron cell membrane is processed differently

- When these fragments clamp together they become toxic and clamp to neuron
- As more fragments are added these oligomers increase in size and become insoluble eventually forming **BETA-AMYLOID PLAQUES**

# TAU PROTEIN AND NEUROFIBRILLARY TANGLES

# NORMAL TAU PROTEIN

- Neurofibrillary tangles are made when a protein called tau is modified.
- In normal brain cells, tau stabilizes structures critical to the cell's internal transport system.
- Nutrients and other cellular cargo are carried up and down the structures called microtubules to all parts of the neuron.

# In ALZHEIMER'S DISEASE

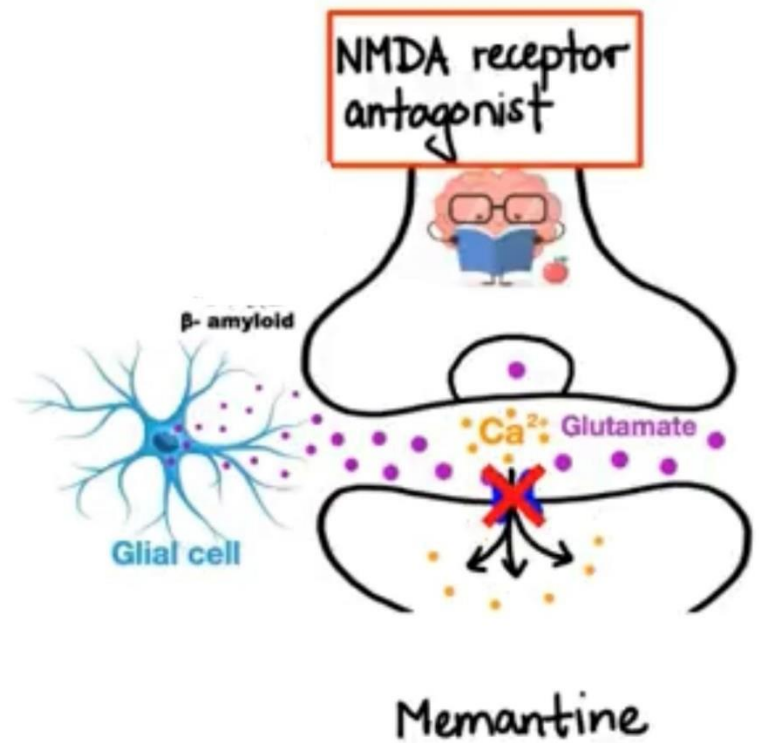
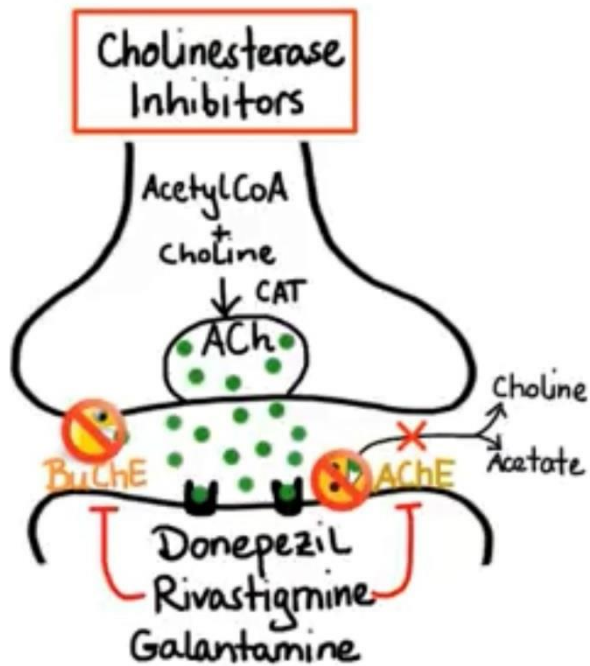
- abnormal tau separates from the microtubules, causing them to fall apart.
- Strands of this tau combine to form tangles inside the neuron, disabling the transport system and destroying the cell.

- Neurons in certain brain regions disconnect from each other and eventually die, causing memory loss.
- As these processes continue, the brain shrinks and loses function.

# Signs and Symptoms

- Severe memory loss
- Confusion
- Inability to formulate abstract thoughts
- Difficulty concentrating
- Difficulty carrying out routine or complex tasks
- Personality changes
- Paranoid or bizarre behavior





# The future of Alzheimer's

- Currently, Alzheimer's disease is treatable, but incurable.
- Researchers are, however, feeling ever closer to pin-pointing the specific causes and biological basis of the disease, which will lead to a possible cure.

# THANK YOU

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