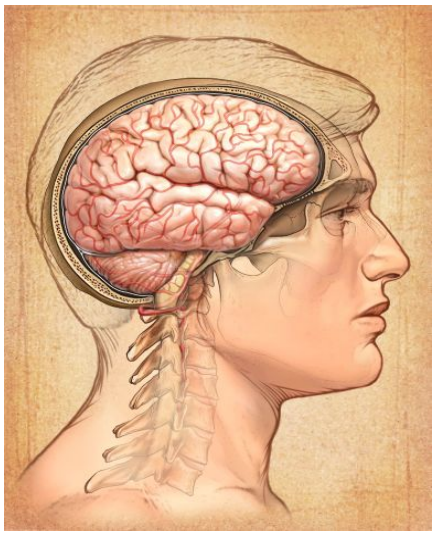
Module 14 – CNS Drugs Part I

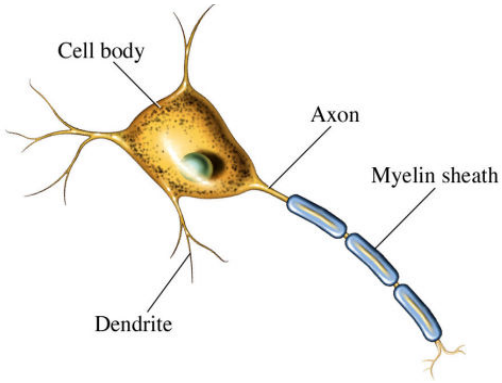
14.1 – Introduction to Neuropharmacology

- Neuropharmacology is the study of how drugs affect the function of the central nervous system.
- There are many disorders of the central nervous system and most of them have a component that is mediated by a biochemical imbalance.
- In neuropharmacology we attempt to treat this biochemical imbalance with drugs.
- Unfortunately the drugs treat the symptoms of disease but not the cause.



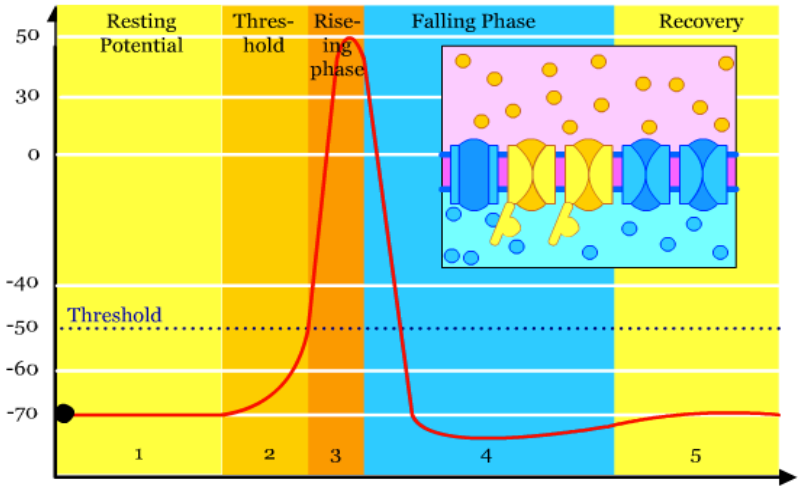
The Brain

- The brain is composed of literally millions of neurons.
- Neurons are cells in the brain that act to process and transmit signals and information.
- Neurons are excitable cells that transmit information by electrical and chemical signaling.
- The start of information transfer begins at the dendrite, which receives a signal from another neuron.
- This causes action potentials (electrical signaling) to propagate along the axon of the neuron.
- When the action potential reaches the pre-synaptic nerve terminal, it causes release of neurotransmitters (chemical signaling) which pass the signal along to the next neuron, via a synapse (see below)



Action Potentials

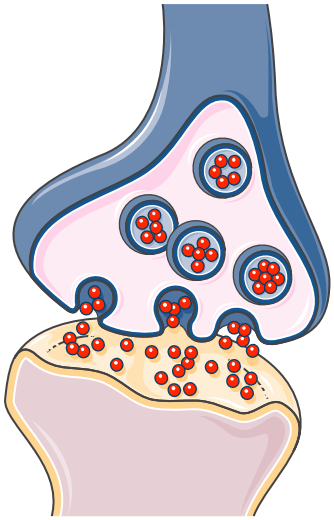
- Action potentials play a key role in cell-to-cell communication in neurons.
- The resting membrane potential of cells is approximately -70 mV. This means that the inside of the cell is negative with respect to the outside.



- During depolarization, positively charged Na^+ ions enter the cell through voltage gated Na^+ channels.
- The Na^+ channels then close and potassium channels open allowing potassium to leave the cell during repolarization.
- The current overshoots resting membrane potential and then returns to baseline (-70 mV).

Synapse

- This picture represents what occurs at a synapse.
- Once an action potential reaches the pre-synaptic nerve terminal, it causes influx of calcium.
- Calcium influx causes vesicles containing neurotransmitters to fuse with the pre-synaptic membrane.
- The vesicles release neurotransmitters into the synaptic cleft (the space between the neurons).
- The neurotransmitters bind to receptors on the post-synaptic nerve membrane and the signal continues.



Neurotransmitters in the CNS

- Neurotransmitters are chemicals that transmit a signal across a synapse.
- Neurotransmitters can be broken down into classes as summarized below:

Monoamines

Norepinephrine – Depression and Anxiety
Epinephrine – Anxiety
Dopamine – Parkinson's and Schizophrenia
Serotonin – Depression and Anxiety

Amino Acids

Excitatory – glutamate (Alzheimer's) and aspartate (Alzheimer's).
Inhibitory – GABA (Anxiety) and glycine (Anxiety).

Other

Acetylcholine – Alzheimer's and Parkinson's.

Basic Mechanisms of CNS Drug Action

- Drugs can act to treat CNS disorders in several ways.
- These include:

1. Replacement – the drug acts to replace neurotransmitters that are low in diseases.
2. Agonists/Antagonist – A drug that directly binds to receptors on the post-synaptic membrane.
3. Inhibiting neurotransmitter breakdown – Neurotransmitter metabolism is inhibited.
4. Blocking Reuptake – Neurotransmitter reuptake into the pre-synaptic neuron is blocked.
5. Nerve stimulation – The drug directly stimulates the nerve causing it to release more neurotransmitter.

14.2 Parkinson's Disease

- Parkinson's disease (PD) was first described in 1817 by James Parkinson.
- We now know that Parkinson's disease is caused by a progressive loss of dopaminergic neurons in the substantia nigra of the brain.
- Although progressive loss of dopaminergic neurons is a normal process of aging, patients with PD lose 70-80% of their dopaminergic neurons.
- Without treatment, PD progresses in 5-10 years to a state where patients are unable to care for themselves.

Symptoms

PD is a chronic movement disorder. Patients have distinct symptoms which include:

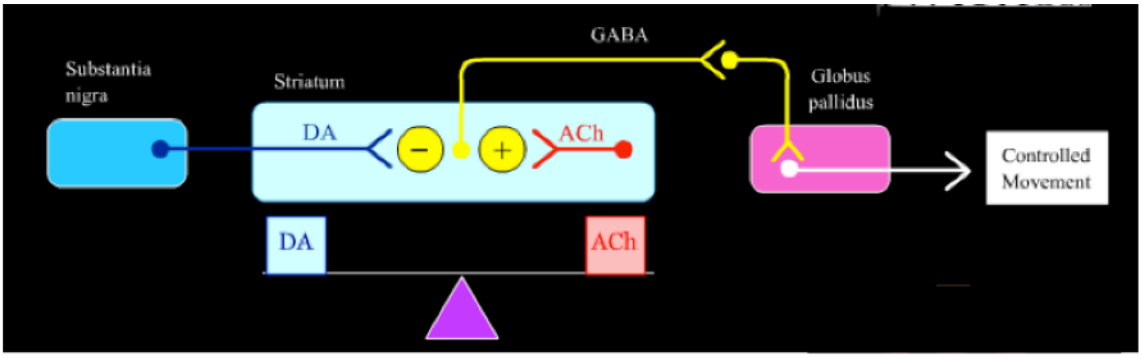
1. Tremor – mostly in the extremities including hands, arms, legs, jaw and face.
2. Rigidity – due to joint stiffness and increased muscle tone.
3. Bradykinesia – slowness of movement, especially slow to initiate movements.
4. Masklike face – patients can't show facial expression and have difficulty blinking and swallowing.
5. Postural Instability – balance is impaired, patients have difficulty balancing while walking.
6. Dementia – Often develops later in disease.

Pathophysiology

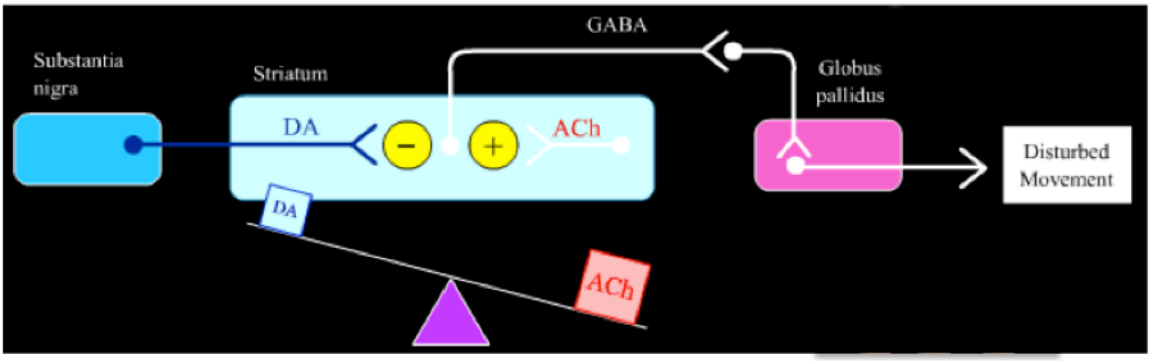
- PD is a chronic movement disorder that is caused by an imbalance between acetylcholine and dopamine in the brain.
- In healthy patients there is a normal balance of acetylcholine and dopamine, which results in normal GABA release.
- The symptoms of Parkinson's arise because:
  1. Dopamine release is decreased, therefore there is not enough dopamine present to inhibit GABA release.
  2. There is a relative excess of acetylcholine compared to dopamine, which results in increased GABA release.
  3. Excess GABA release causes the movement disorders observed in PD.

Pathophysiology

Healthy



Parkinson's Disease



Etiology

- The etiology of PD is largely idiopathic (i.e. unknown) but there are some factors thought to be associated with development of the disorder:
  1. Drugs – A by-product of illicit street drug synthesis produces the compound MPTP. MPTP causes irreversible death of dopaminergic neurons.
  2. Genetics – Mutation in 4 genes (alpha synuclein, parkin, UCHL1, and DJ-1) is known to predispose patients to PD.
  3. Environmental Toxins – Certain pesticides have been associated with PD.
  4. Brain Trauma – Direct brain trauma from injury (i.e. boxing, accidents) is linked with increased risk for developing PD.
  5. Oxidative Stress – Reactive oxygen species are known to cause degeneration of dopaminergic neurons. There is a link between diabetes induced oxidative damage and PD.

14.3 Drug Treatment of Parkinson's Disease

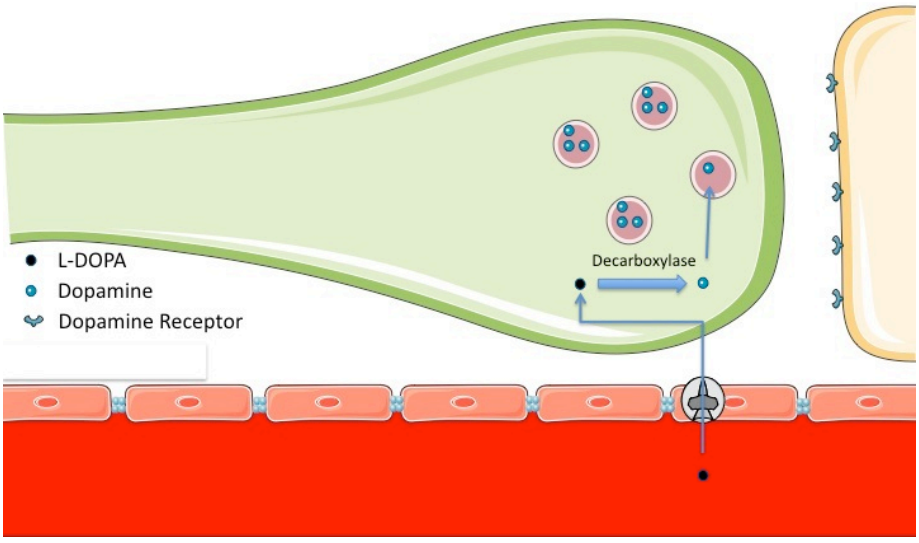
- The ideal treatment for PD would be to reverse the degeneration of dopaminergic neurons. Unfortunately, no such treatment exists.
- Therefore we treat the symptoms of PD by trying to improve the balance between dopamine and acetylcholine.
- Drug treatment of PD improves the dopamine acetylcholine balance by either:
    1. Increasing dopamine
    2. Decreasing acetylcholine

<u>Agents that Increase Dopamine Neurotransmission</u>

- There are 5 different major classes of drugs that act by increasing dopamine neurotransmission:
    1. Dopamine Replacement
    2. Dopamine Agonist
    3. Dopamine Releaser
    4. Catecholamine-O-Methyltransferase Inhibitor
    5. Monoamine oxidase-B (MAO-B) inhibitor

1. <u>Dopamine Replacement – Levodopa (L-Dopa)</u>

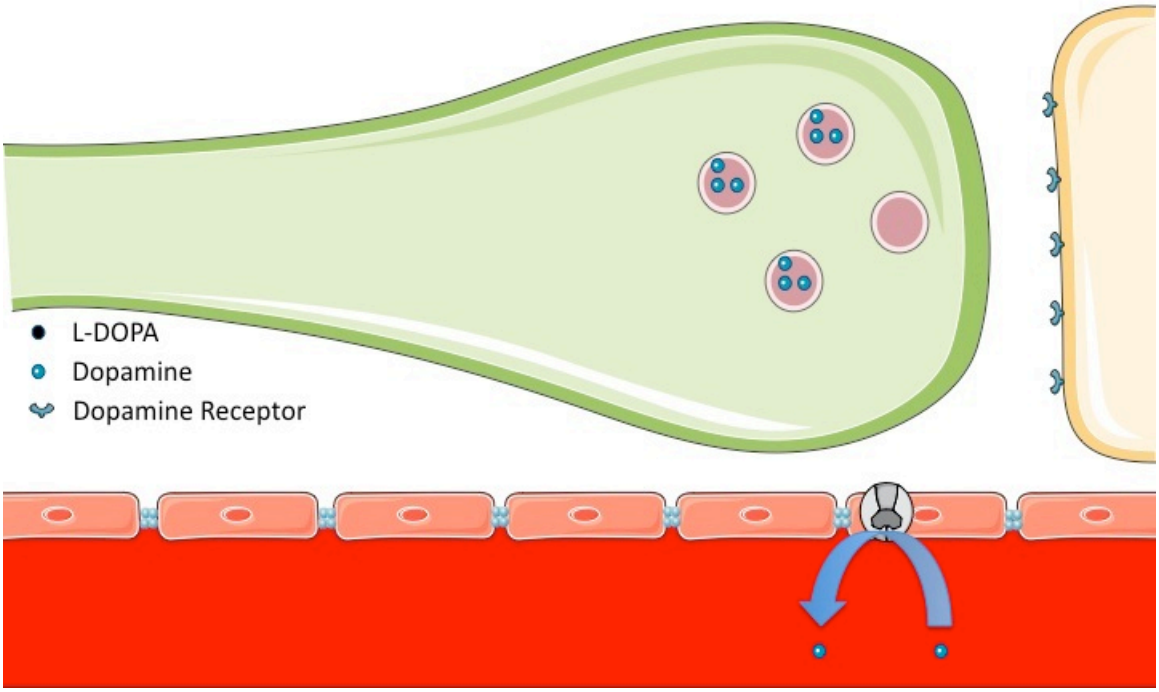
- Levodopa is the most effective drug for treating PD.
- Unfortunately, the beneficial effects of L-DOPA decrease over time as the disease progresses.
- L-DOPA crosses the blood brain barrier by an active transport protein.
- L-DOPA is inactive on its own but is converted to dopamine in dopaminergic nerve terminals.
- Conversion of L-DOPA to dopamine is mediated by decarboxylase enzymes in the brain.
- The cofactor pyridoxine (vitamin B6) speeds up this reaction.



Why not just give dopamine?

- In contrast to L-DOPA, dopamine:

    1. Does not cross the blood brain barrier.
    2. Has a very short half-life in blood.

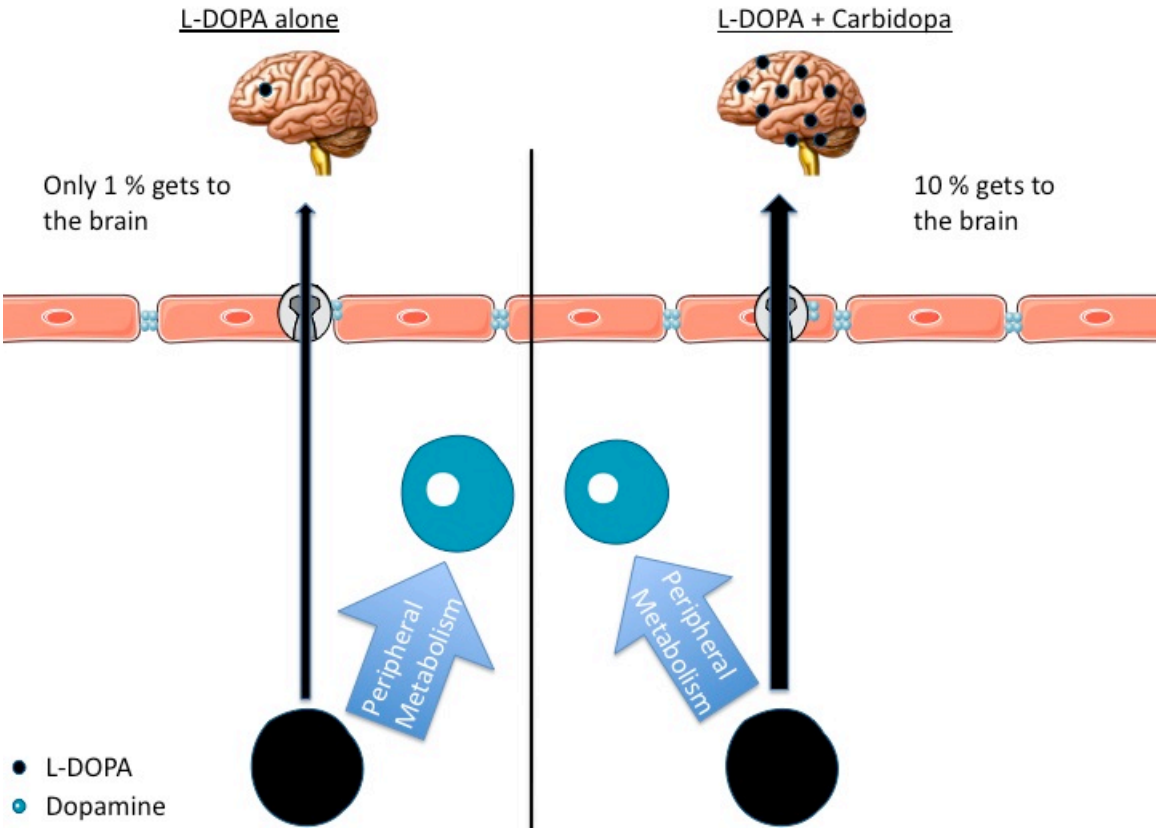


L-Dopa – Adverse Effects

- L-DOPA has several side effects including:
    - Nausea and vomiting – due to dopamine mediated activation of the chemoreceptor trigger zone in the medulla.
    - Dyskinesias – abnormal involuntary movements.
    - Cardiac dysrhythmias – conversion of L-DOPA to dopamine in the periphery can result in activation of cardiac beta 1 receptors. *(review Module 8)*
    - Orthostatic hypotension – rapid drop in blood pressure when a patient stands up.
    - Psychosis – 20% of patients will develop hallucinations, vivid dreams/nightmares and paranoid thoughts.

L-Dopa – Peripheral Metabolism

- Only approximately 1 % of the total L-DOPA dose reaches the brain.
- The remaining L-DOPA is metabolized in the peripheral tissue (mostly in the intestine) before reaching the brain.
- For this reason, L-DOPA is almost always given with carbidopa, a decarboxylase inhibitor that inhibits the peripheral metabolism of L-DOPA.
- When carbidopa is combined with L-DOPA, approximately 10% of L-DOPA reaches the brain.
- Carbidopa allows a lower dose of L-DOPA to be administered and decreases the incidence of cardiac dysrhythmias and nausea and vomiting.



Patients taking L-DOPA may experience two types of loss of effect:

1) Wearing Off – Gradual loss of effect.
2) On-Off – Abrupt loss of effect.

Wearing Off

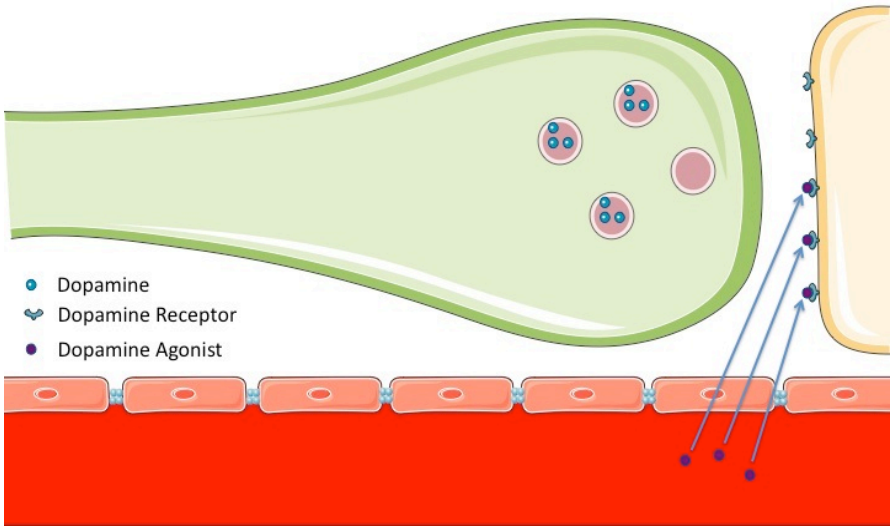
- Usually occurs at the end of the dosing interval and indicates that drug levels might be low.
- Can be minimized by:
    1. Shortening the dosing interval.
    2. Give a drug that inhibits L-DOPA metabolism (i.e. a COMT inhibitor).
    3. Add a dopamine agonist to the therapy.

On-Off

- Can occur even when drug levels are high.
- Can be minimized by:
    1. Dividing the medication into 3-6 doses per day.
    2. Using a controlled release formulation.
    3. Moving protein-containing meals to the evening.

2. Dopamine Agonist

- Produce their effects by directly activating dopamine receptors on the post-synaptic cell membrane.
- Not as effective as L-DOPA but are often used as first line treatment for patients with milder symptoms.

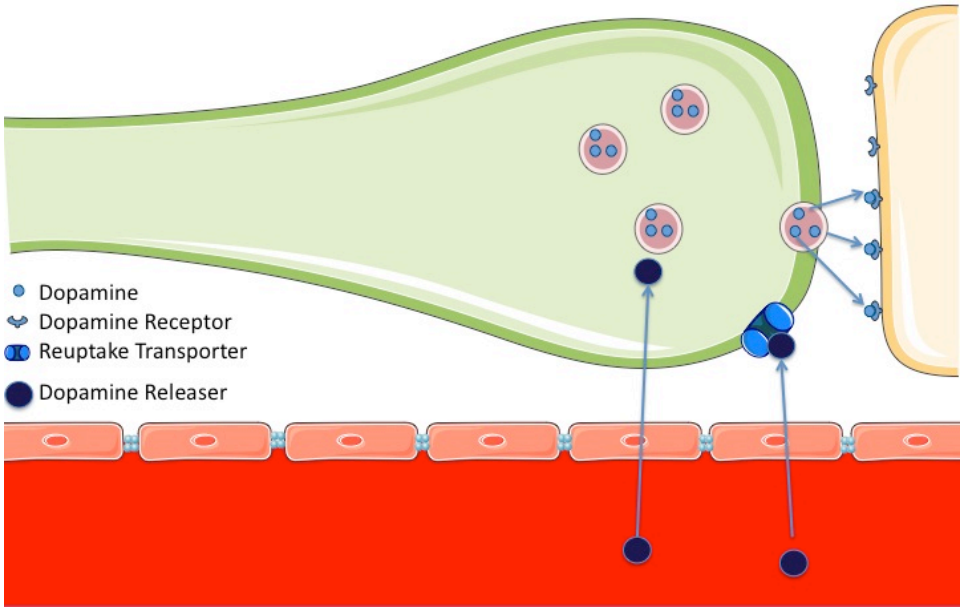


Adverse Effects

- Hallucinations
- Daytime drowsiness
- Orthostatic hypotension

3. Dopamine Releaser

- Acts to stimulate release of dopamine from dopaminergic neurons and in addition, it also blocks dopamine reuptake into pre-synaptic nerve terminals. It also blocks NMDA receptors.
- Response develops rapidly, usually within 2-3 days.
- Not as effective as L-Dopa, so usually used in combination with L-Dopa or alone only in mild PD.
- Blockade of NMDA receptors is thought to decrease dyskinesia side effect of L-Dopa.
- Adverse effects include dizziness, nausea, vomiting, lethargy and anticholinergic side effects.



4. Catecholamine-O-Methyltransferase Inhibitor (COMT)

- COMT is an enzyme that adds a methyl group to both dopamine and L-DOPA.
- Methylated dopamine and L-DOPA are inactive and do not activate dopamine receptors.
- Inhibiting COMT results in a greater fraction of L-DOPA that is available to be converted into dopamine.
- COMT inhibitors are only moderately effective in treating symptoms of PD and are often combined with L-Dopa.
- Adverse effects are similar to those experienced with L-DOPA including nausea, orthostatic hypotension, vivid dreams and hallucinations.

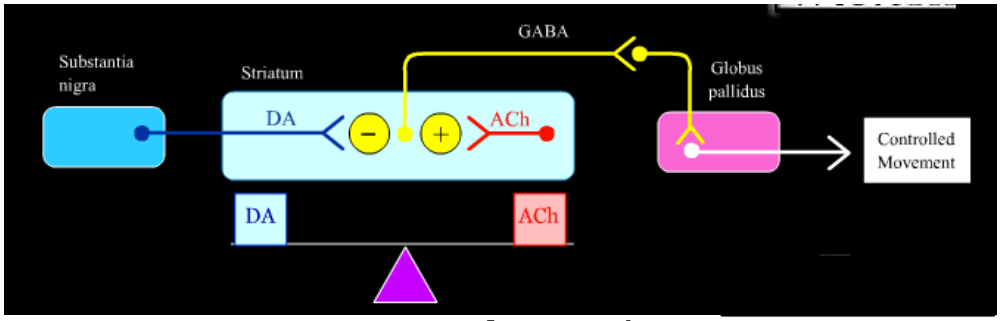
5. Monoamine oxidase-B (MAO-B) inhibitor

- MAO-B is an enzyme that metabolizes dopamine and L-DOPA through oxidation, therefore inactivating them.
- MAO-B is present in both the periphery and in the brain.
- Inhibiting oxidative metabolism of L-DOPA allows more conversion to dopamine in the brain.
- Similarly, inhibition of dopamine metabolism allows more dopamine to remain in nerve terminals and be released following an action potential.
- MAO-B inhibitors are only moderately effective in treating symptoms of PD and are often combined with L-Dopa.
- Adverse effects include insomnia, orthostatic hypotension and dizziness.
- At therapeutic doses, MAO-B inhibitors used to treat Parkinson's do not inhibit MAO-A in the liver and therefore do not cause hypertensive crisis when patients eat tyramine-containing foods (*review Module 11*).

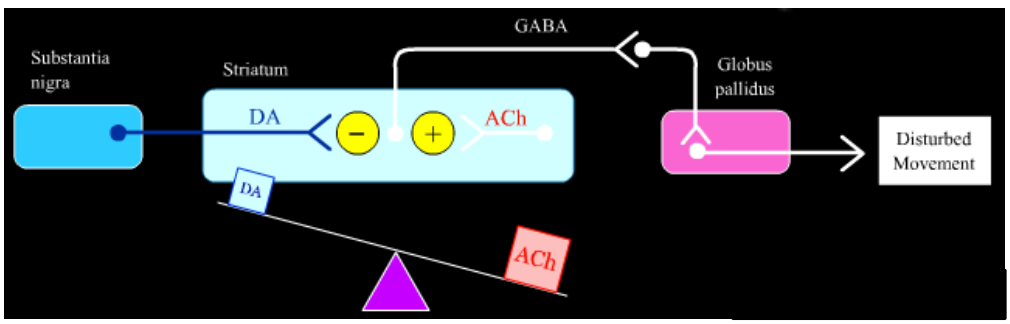
What about Acetylcholine?

- We must remember that the symptoms of PD are due to the relative imbalance of dopamine (to little) and acetylcholine (too much).
- The relative excess of acetylcholine in PD causes diaphoresis (excess sweating), salivation and urinary incontinence.

Healthy

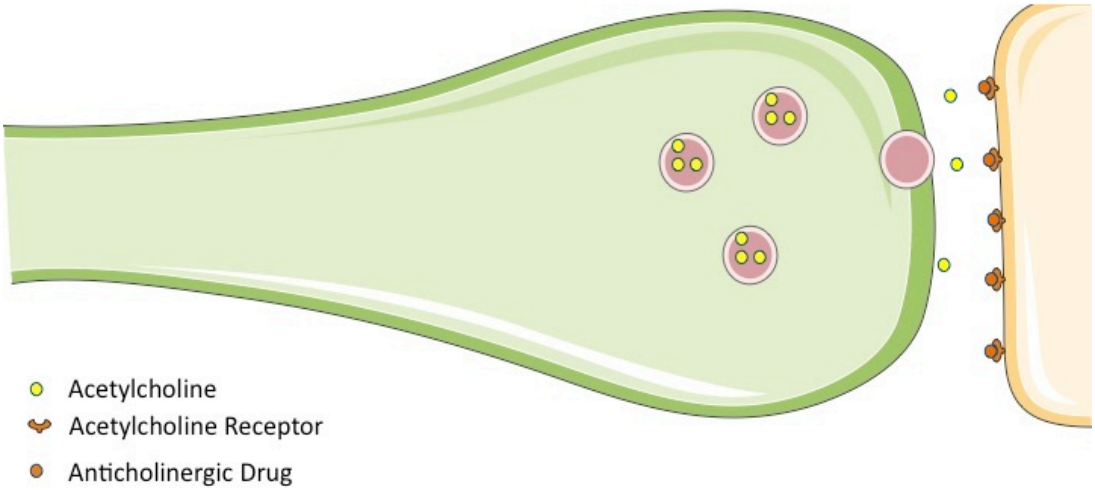


Parkinson's



Anticholinergic Drugs

- Anticholinergic drugs block the binding of acetylcholine to its receptor and are also called cholinergic antagonists.
- Anticholinergic drugs may increase the effectiveness of L-Dopa.
- In doing so these drugs decrease the incidence of diaphoresis, salivation, and incontinence.
- In the figure you can see anticholinergic drugs (orange dots) are blocking the binding of acetylcholine (yellow dots) to the receptor.

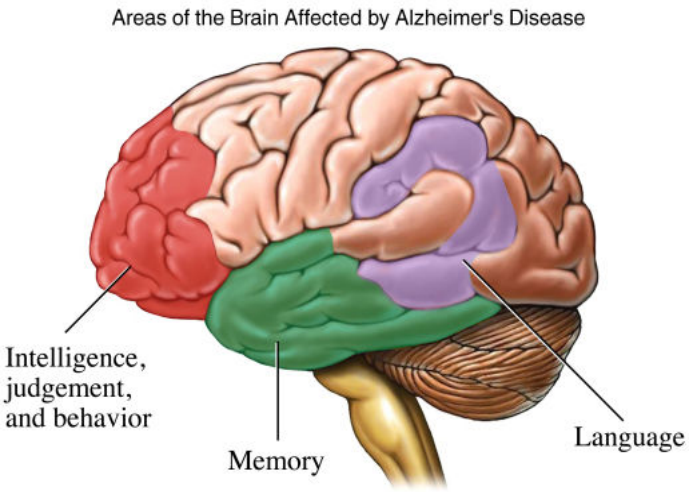


Adverse Effects

- Typical anticholinergic side effects include:
  Dry mouth, blurred vision, urinary retention, constipation, tachycardia.

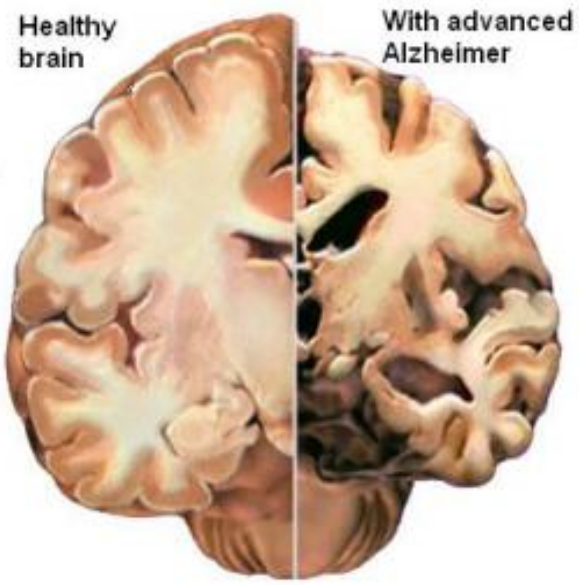
- Elderly patients may experience severe CNS side effects such as hallucination, confusion and delirium so anticholinergic drugs are usually reserved for younger patients only.

14.4 Alzheimer's Disease



- Alzheimer's disease is an irreversible form of progressive dementia and is the most common form of dementia.
- Over 500,000 Canadians have Alzheimer's disease.
- Approximately 1 in 11 people over the age of 65 has Alzheimer's disease.
- Women account for almost 75% of all current cases of Alzheimer's.
- Alzheimer's costs Canadian's over $15 billion dollars per year.
- Symptoms of Alzheimer's disease include memory loss, problems with language, judgment, behavior and intelligence.
- Early symptoms of disease include confusion, memory loss and problems conducting routine tasks.
- As disease progresses, patients have difficulty performing daily living activities including eating, bathing, speaking and controlling bowel and bladder function.

<u>Pathophysiology</u>



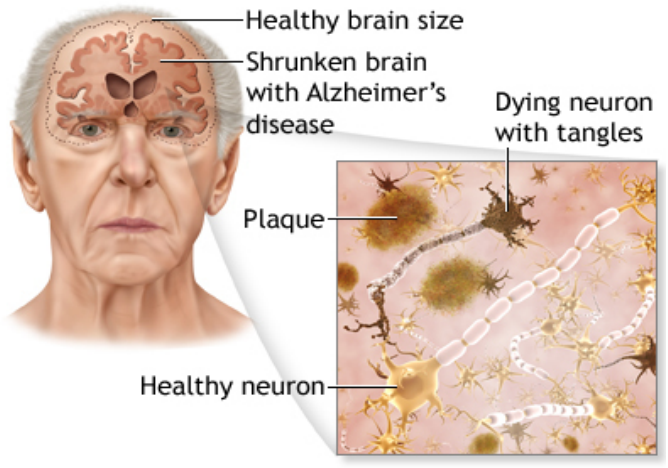
- The pathophysiology of Alzheimer's is characterized by a degeneration of cholinergic neurons in the hippocampus early in disease, followed by degeneration of neurons in the in the cerebral cortex.
- Alzheimer's is linked to decreased cholinergic nerve function.
- Patients with advanced Alzheimer's have only 10% of the cholinergic function of healthy subjects.

Diagnosis

- A definitive diagnosis of Alzheimer's cannot be given until after death when a brain sample is analyzed.
- The hallmarks of Alzheimer's are neurofibrillary tangles and neuritic plaques.

Neurofibrillary tangles

- Form inside neurons when microtubule arrangement is disrupted.
- The cause is abnormal production of a protein called tau. Tau is responsible for forming cross-bridges between microtubules keeping their structure.



Neuritic Plaques

- Found outside of neurons and are composed of a core of a protein fragments called beta amyloid.
- Beta amyloid has been shown to kill hippocampal cells and causes Alzheimer's like symptoms when injected into monkeys.

Etiology

- The cause of Alzheimer's disease is usually unknown.
- Approximately 20% of cases are thought to run in families (i.e. genetically determined).
- There is some evidence that mutations in DNA can be a cause for developing Alzheimer's disease.
- For example, patients with two copies of the apolipoprotein E4 (ApoE4) are at increased risk for developing Alzheimer's. It appears that ApoE4 promotes formation of neuritic plaques by binding to beta amyloid, therefore promoting deposition.
- There is also an increased incidence of Alzheimer's disease in patients with mutations in the amyloid precursor protein gene. This gene is involved in the production of beta-amyloid, a component of neuritic plaques.
- Head injury is also a risk factor for developing Alzheimer's.

14.5 Drug Treatment of Alzheimer's Disease

- Drug treatment of Alzheimer's disease shows only minimal improvement in symptoms.
- There are currently only two classes of drugs used to treat Alzheimer's:

    1. Cholinesterase inhibitors – Inhibit the breakdown of acetylcholine.
    2. NMDA receptor antagonists – Block NMDA mediated increases in intracellular calcium.

1. Cholinesterase inhibitors

- These drugs inhibit the metabolism of acetylcholine by the enzyme acetylcholinesterase.
- This allows more acetylcholine to remain in the synaptic cleft to exert its actions.
- Cholinesterase inhibitors are only able to enhance cholinergic neurotransmission in the remaining healthy neurons.
- Cholinesterase inhibitors display minimal benefit on some measures of memory.
- Cholinesterase inhibitors are only effective in approximately 25% of patients.

Adverse Effects

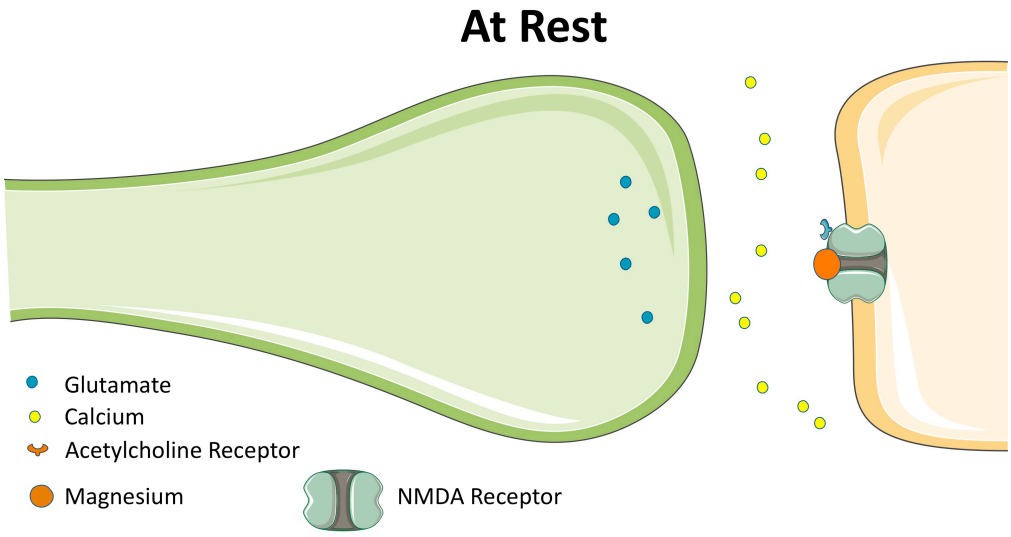
- Common adverse effects of cholinesterase inhibitors include:
    - Nausea and vomiting
    - Diarrhea
    - Insomnia

2. NMDA receptor antagonists

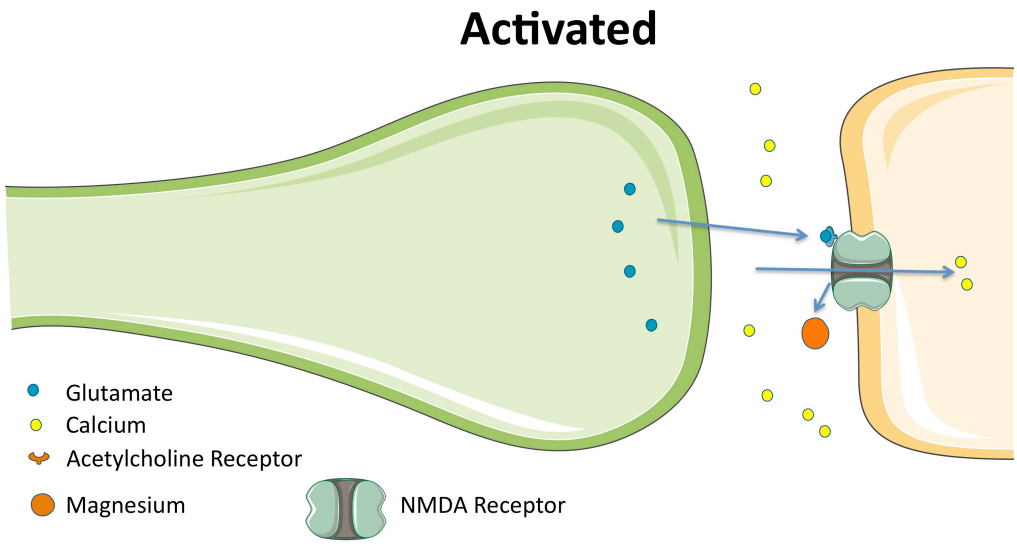
The NMDA Receptor

- The NMDA receptor is a calcium channel that is blocked by magnesium at rest.
- When glutamate binds to the NMDA receptor, the magnesium dissociates allowing calcium to enter the post-synaptic neuron.
- When the glutamate leaves the receptor, magnesium returns to block the entry of calcium.
- Normal calcium influx is thought to be important in the process of learning and memory.
- In Alzheimer's disease, there is excess glutamate release so the NMDA receptor remains open allowing excess calcium to enter the cell.

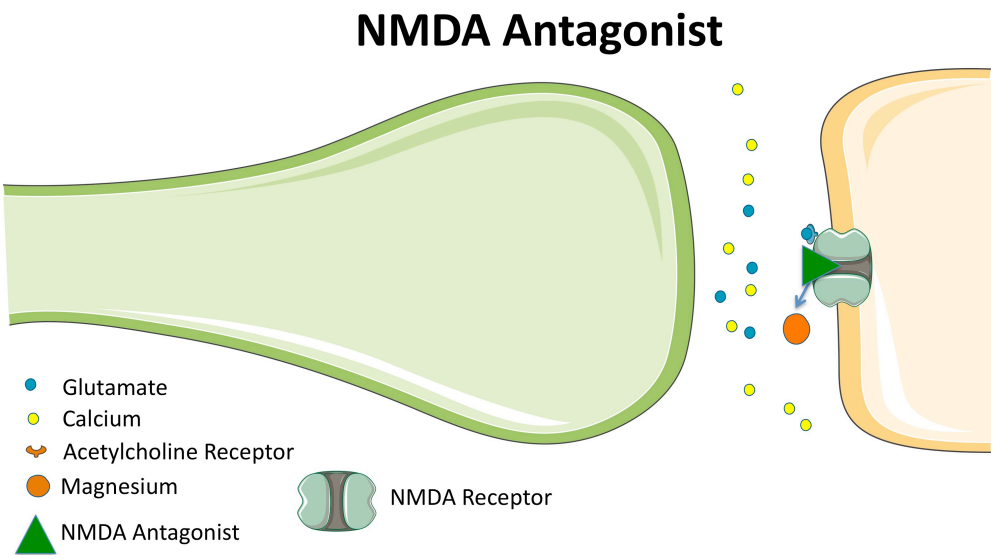
- Excess calcium is detrimental in two ways:
    1. It is actually detrimental to learning and memory (it overpowers the normal calcium signal).
    2. It causes degradation of neurons (too much calcium is toxic)



At rest a magnesium molecule blocks the NMDA receptor not allowing calcium to enter the post-synaptic neuron.



Binding of glutamate causes dissociation of magnesium allowing calcium to enter the post-synaptic neuron.



In Alzheimer's disease, excess glutamate is released from neurons. This causes prolonged opening of the NMDA receptor and excess calcium influx into the post-synaptic neuron. NMDA receptor antagonists block calcium influx into the post-synaptic neuron.

Adverse Effects

- NMDA antagonists are well tolerated.
- Side effects observed in clinical trials had the same incidence as patients taking placebo.

14.6 Schizophrenia

- Schizophrenia makes it hard to tell the difference between real and unreal experiences, to think logically, to have normal emotional responses, and to behave normally in social situations.
- In contrast to popular belief and this picture, patients with schizophrenia usually do not have multiple personalities and are usually not violent.
- Schizophrenia is a common mental disease that affects approximately 1% of the world's population.
- Schizophrenia usually begins in adolescence or early adulthood (16-30 years old).

Symptoms

- Symptoms of schizophrenia can be divided into positive or negative symptoms.
- Positive symptoms are ones that exaggerate or distort normal neurological function.
- Negative symptoms are ones where there is a loss of normal neurological function.

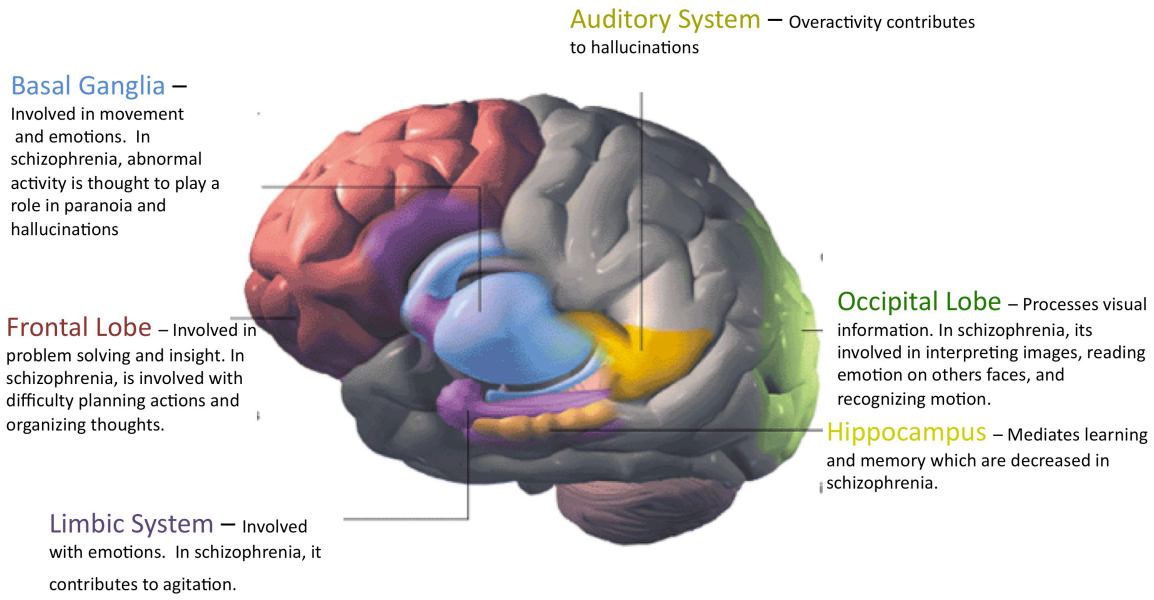
Positive Symptoms	Negative Symptoms
Delusions	Social Withdrawal
Hallucinations	Poverty of Speech
Agitation	Poor Self Care
Paranoia	Poor Insight
Combativeness	Poor Judgment
Disorganized Speech	Emotional Withdrawal
Disorganized Thinking	Blunted Affect
	Lack of Motivation

Etiology

- The cause of schizophrenia is largely unknown. Here are a few factors known to increase the risk for developing schizophrenia:

1. **Family history:** 10% of schizophrenics have a parent with the disease. If both parents have schizophrenia, there is a 25% chance their children will have it.
2. **Drug abuse:** Methamphetamine (crystal meth), phencyclidine (PCP – angel dust) and lysergic acid diethylamide (LSD) use are all known to cause schizophrenia.
3. **Low birth weight:** Babies born at less than 5.5 pounds have an increased risk of developing schizophrenia.
4. **Low IQ:** The lower a person's IQ, the greater the risk they have of developing schizophrenia.

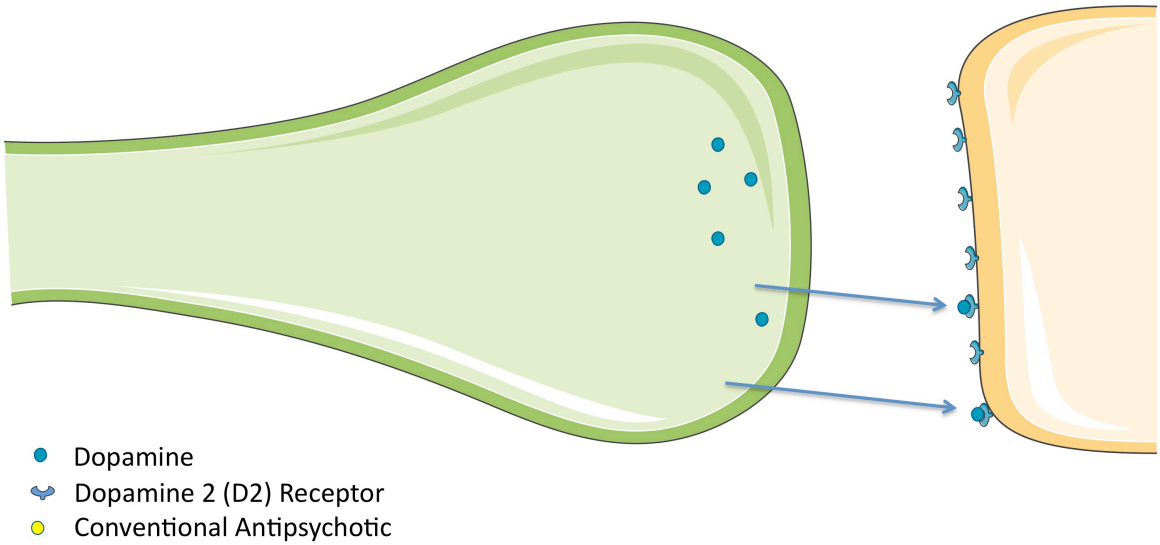
Brain Regions Affected by Schizophrenia



Pathophysiology

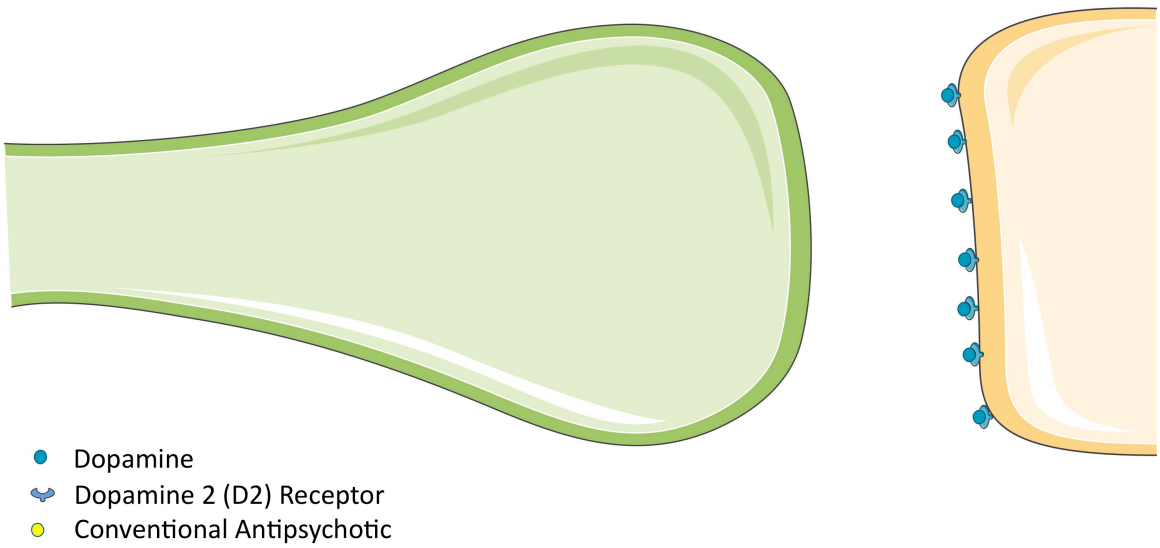
- Usually schizophrenia is thought of as a disorder with increased dopaminergic nerve transmission.
- Drugs that block dopaminergic nerve function decrease some of the positive symptoms of schizophrenia.
- Schizophrenia and Parkinson's are often thought of as on the opposite ends of the dopamine continuum because in schizophrenia there is excess dopamine and in Parkinson's there is too little dopamine.
- Further, drugs used to treat Parkinson's disease may cause schizophrenia like side effects.
- Although the dopamine hypothesis is helpful, it is too simple. The neurotransmitters 5-HT (also called serotonin) and glutamate also play a role in schizophrenia.
- **5-HT (serotonin)** – Patients with schizophrenia have a decreased number of 5-HT_{2A} and an increased number of 5-HT_{1A} receptors in the frontal cortex. These changes are thought to play a role in the symptoms patients with schizophrenia experience.
- **Glutamate** – Glutamate binds to and activates the NMDA receptor. PCP (angel dust) is a strong antagonist of the NMDA receptor and causes many of the symptoms of schizophrenia. Patients with schizophrenia have a decreased number of NMDA receptors in some regions of their brain.

NORMAL DOPAMINE NEUROTRANSMISSION



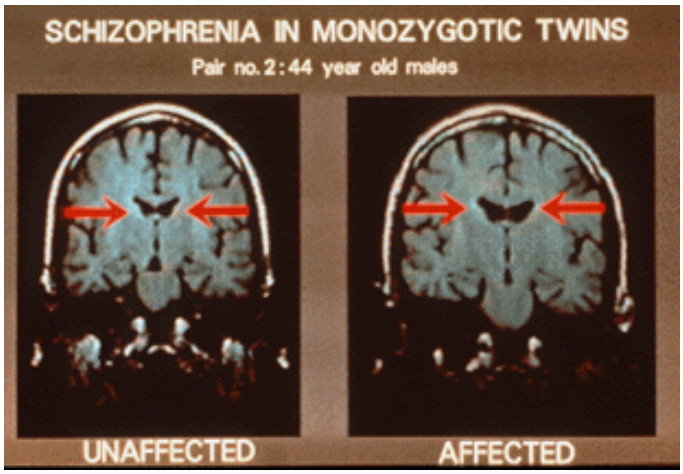
During normal dopamine neurotransmission some dopamine is released and binds to D2 receptors.

DOPAMINE NEUROTRANSMISSION IN SCHIZOPHRENIA



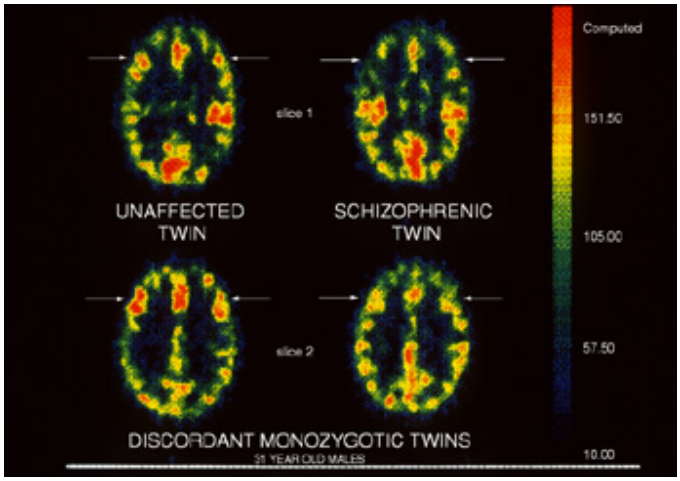
In schizophrenia there is increased dopaminergic neurotransmission and therefore increased binding of dopamine to D2 receptors.

Diagnosis



- There is no definitive test for schizophrenia.
- Diagnosis is usually made by a psychiatrist after interviewing the patient and family.
- The psychiatrist may evaluate several things before diagnosing schizophrenia:

1. Changes in function from before illness.
2. Developmental background.
3. Family history.
4. Response to medication.
5. Brain scans – some changes are typical in schizophrenics. In the top image the schizophrenic twin has enlarged ventricles. In the bottom image the schizophrenic twin has decreased frontal lobe brain activity.



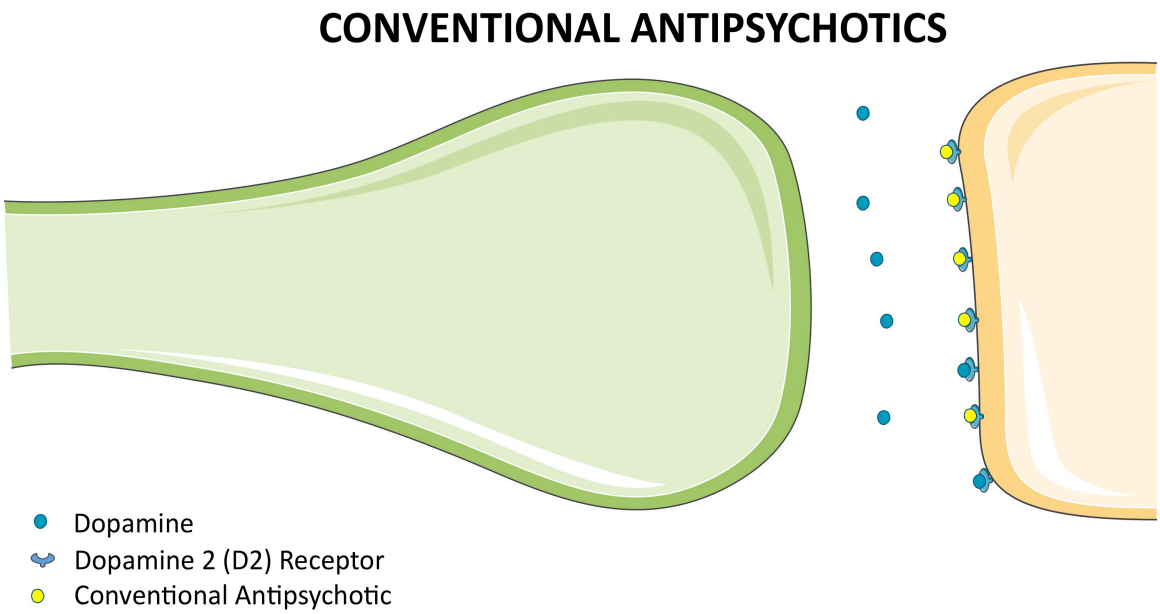
**Brain scans do not provide a definitive diagnosis of schizophrenia

14.7 Drug Treatment of Schizophrenia

- The basis for treating the symptoms of schizophrenia is blocking dopamine and/or serotonin neurotransmission in the brain.
- Drugs used to treat schizophrenia can be classified as conventional antipsychotics or atypical antipsychotics.
- Conventional and atypical antipsychotics differ in their mechanism of action and side effect profile.
- Although it was once thought the atypical antipsychotics would take over the market, both conventional and atypical antipsychotics are in use today.

Conventional Antipsychotics

- Conventional antipsychotics act primarily by blocking dopamine 2 (D2) receptors primarily in the mesolimbic area of the brain.
- To a lesser degree, they also block receptors for acetylcholine, histamine, and norepinephrine.
- The potency of conventional antipsychotics is directly proportional to their ability to inhibit D2 receptors.
- These drugs are more effective at treating the positive symptoms of schizophrenia than the negative symptoms.
- Initial effect of drugs may be seen in as few as 1 or 2 days but substantial improvement in symptoms usually takes between 2 and 4 weeks.



Conventional antipsychotics block the binding of dopamine to D2 receptors.

Adverse Effects

- There are several adverse effects of conventional antipsychotics including:

    1. Extrapyramidal Symptoms
    2. Sudden high fever
    3. Anticholinergic effects
    4. Orthostatic Hypotension
    5. Sedation
    6. Skin reactions

Extrapyramidal Symptoms

- Extrapyramidal symptoms (EPS) deserve special mention. They are movement disorders that resemble the symptoms of Parkinson's disease.
- EPS are due to blockade of D2 receptors and four types of EPS occur:

    1. **Acute dystonia** – Involuntary spasm of the muscles in the face, tongue, neck or back. Typically occurs early in therapy.
    2. **Parkinsonism** – Bradykinesia, mask-like faces, rigidity, and stooped posture are common. May treat with an anticholinergic drug to help relieve these symptoms. L-Dopa must be avoided.
    3. **Akathesia** – Pacing, squirming, and a desire to continually be in motion. Typically occurs early in treatment.
    4. **Tardive Dyskinesia** – Occurs in about 20% of patients on long-term therapy. Is irreversible so early detection is essential. Symptoms include involuntary twisting and writhing of the face and tongue along with lip-smacking. Patients developing tardive dyskinesia should be switched to an atypical antipsychotic.

Atypical Antipsychotics

- Atypical antipsychotics block both dopamine D2 receptors and 5-HT_{1A} and 5-HT_{2A} receptors.
- Despite having some activity to block D2 receptors, the affinity is very low. Therapeutic action is attributed to blockade of 5-HT receptors.
- Compared to conventional antipsychotics, atypical antipsychotics have:

    1. The same efficacy versus positive symptoms of schizophrenia,
    2. A much greater efficacy versus negative symptoms of schizophrenia.
    3. A much lower risk of developing extrapyramidal symptoms, especially tardive dyskinesia. This is attributable to decreased D2 receptor blocking activity.

Adverse Effects

- Sedation
- Orthostatic hypotension
- Weight gain (sometimes severe)
- Risk of developing type II diabetes
- Anticholinergic effects.