6.1.4

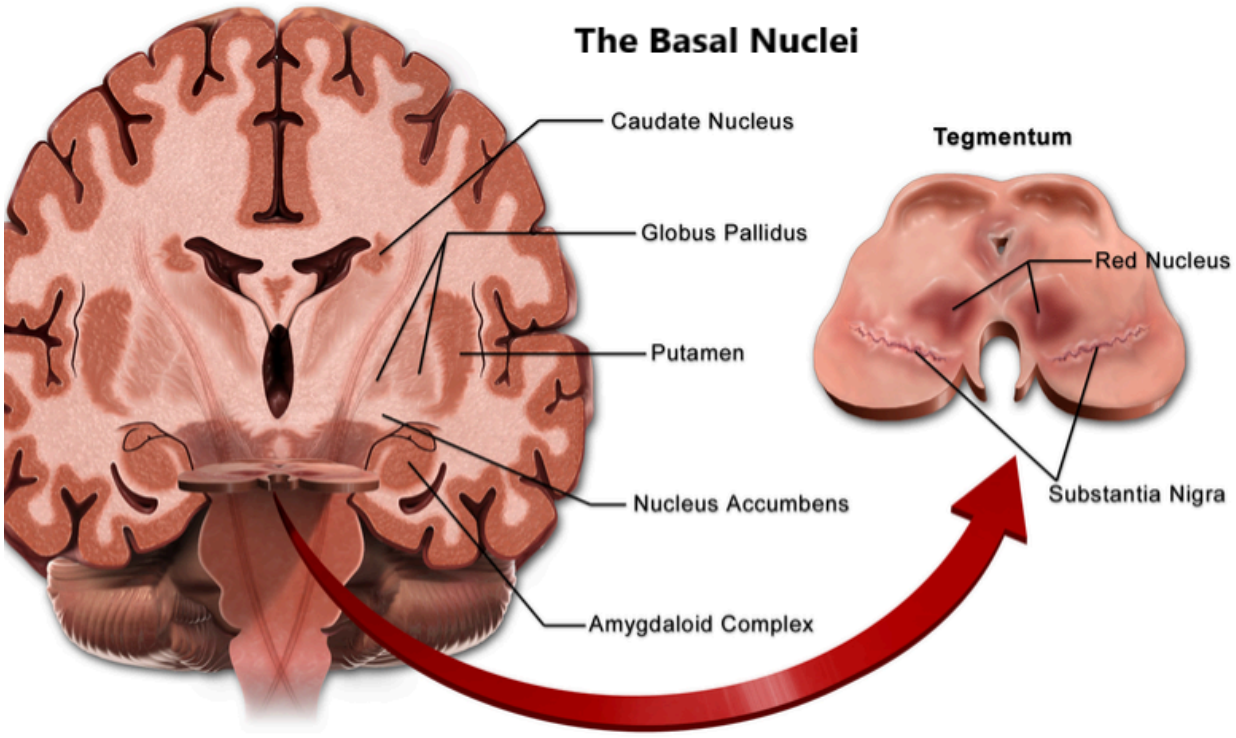
Parkinson’s Disease (PD)

Watch the video Parkinson's Disease (**Note that from 11:23 on, the video is mostly for your information only.**)

Parkinson’s Disease (PD) is a common neurodegenerative disease second only to Alzheimer’s disease in occurrence. It is more common in men. PD occurs due to degeneration of dopaminergic neurons of the **substantia nigra** that are important in regulating movement. This degeneration results in decreased **dopamine** release.

PD is caused by both genetic and environmental factors. Genetic mutations such as in the PINK1, parkin, or alpha synuclein genes have been tied to the development of PD. Environmental factors like exposure to pesticides (especially paraquat) and contaminated heroine that contains the toxin known as MPTP increase a person’s chance of getting Parkinson’s. A history of head injuries is also correlated with the development of PD.

The basal nuclei (or ganglia) of the midbrain are important components of neural circuits responsible for the planning, organizing, and coordination of motor movement. The basal nuclei are the combined structures of the caudate nucleus, putamen (both of which make up the striatum), globus pallidus, and the substantia nigra. Substantia nigra means “black substance.” It consists of dopaminergic neurons that release dopamine. Dopamine has an inhibitory effect in the circuits as they project onto the striatum. Dopamine acts to inhibit the activity of antagonistic muscles and thus facilitates purposeful movement. The striatum consists mainly of cholinergic neurons that produce acetylcholine which acts as an excitatory neurotransmitter to instigate movement.



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The symptoms of PD begin to occur when 80% of dopaminergic neurons of the substantia nigra have died, causing an imbalance between excitatory ACh and inhibitory dopamine. Those with basal nuclei disorders such as Parkinson's disease show an increase in muscle tone and uncontrolled movements at rest. Common symptoms of PD include:

1. **Resting tremor:** this is the most common symptom and involves the tremor of the finger against the thumb and shakiness of the hand while at rest.
2. **Cogwheel rigidity:** resistance to passive movement during examination when the doctor attempts to move the elbow joint through its range of motion and a ratchet-like start and stop movement is elicited.
3. **Bradykinesia:** slowness of movement.
4. **Akinesia:** a mask-like facial expression that arises due to the loss of the ability to move muscles voluntarily.
5. **Postural instability:** Unsteadiness that increases the risk of falls whether standing or sitting.

The central triad of PD includes resting tremor, rigidity, and bradykinesia. The acronym **TRAP** is commonly used to remember symptoms of PD and stands for tremor, rigidity, akinesia, and postural instability.

Patients with PD are prone to falls, drooling, and slow speech because of muscle weakness and muscle rigidity in the throat, tongue, and palate. Autonomic symptoms include lacrimation, dysphagia, orthostatic hypotension, issues with thermal regulation, constipation, impotence, and urinary incontinence. Cognitive dysfunction presents later in disease progression for some of those with PD. **Lewy bodies** are abnormal aggregates of protein remnants that develop inside some nerve cells involved with PD. A major component of this aggregate is the protein alpha-synuclein. The changes in alpha-synuclein that come with PD cause it to form aggregates that are toxic to neurons. These aggregates can be released by neurons and taken up by others, allowing them to spread to other brain areas.

Because acetylcholine and dopamine are out of balance in PD patients, medications used to treat PD work to increase dopamine or decrease acetylcholine. Simply treating a patient with dopamine for PD is ineffective because dopamine cannot pass the blood-brain barrier (BBB). **Levodopa** (or L-dopa) is a precursor of dopamine that has been the

cornerstone of PD pharmaceutical therapy because it can cross the blood-brain barrier. Once levodopa is in the brain, it is converted into dopamine in the remaining substantia nigra neurons by the enzyme **dopa-decarboxylase**. However, levodopa can be converted into dopamine in the periphery before it crosses the BBB by peripheral dopa-decarboxylase. This premature conversion is undesirable because it decreases the amount of levodopa that can reach the brain. Additionally, excessive dopamine in the periphery causes symptoms such as nausea, vomiting, tachycardia, and high blood pressure. These symptoms occur because dopamine is a catecholamine like norepinephrine and epinephrine and thus will bind and activate adrenergic receptors. Excess dopamine is also known to cause gastrointestinal issues because there are many dopamine receptors in GI tissues.

To prevent the conversion of levodopa into dopamine prematurely, levodopa is always administered with a dopa-decarboxylase inhibitor called **carbidopa**. Carbidopa cannot cross the blood-brain barrier. Because of this characteristic, carbidopa inhibits the conversion of levodopa to dopamine in the periphery but allows levodopa to be converted to dopamine in the brain where it is needed. There are additional enzymes that break down levodopa in the periphery, so various other medications that inhibit these enzymes are also used with pharmaceutical treatment. Medications that inhibit the breakdown of dopamine in the brain are also important to keep dopamine levels elevated. Dopamine receptor agonists that act like dopamine in the brain are another medication option that is used.

The importance of exercise in the treatment of PD cannot be overemphasized. It is believed that exercise causes the release of growth factors for neurons. Experts agree that exercise is just as important as medication and using them together provides the best outcomes for improving symptoms and mobility.

Deep brain stimulation may also be used for patients who suffer from symptoms despite optimal medical therapy. Deep brain stimulation involves surgery and the placement of a device that can deliver electrical stimulation to neurons in and around the thalamus and basal nuclei. However, this surgery doesn't reverse neuronal degeneration and PD will continue to progress.