Parkinson's Network of Mt. Diablo

Parkinson's Disease: Transmitters and Proteins
January 19, 2022

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Parkinson's Disease (PD) is the second most common neurodegenerative disease (after Alzheimer's disease) in the United States, affecting an estimated one million people and one percent of the US population over 60 years of age. The primary pathological change in PD is the death of dopaminergic nerve cells (neurons) of the brainstem, neurons that release the neurotransmitter dopamine (DA). These neurons normally project to the basal ganglia within the brain and the loss of DA leads to movement disorders characterized by muscle rigidity, resting tremor, and difficulty initiating movements (bradykinesia). Recent research has found that aggregation of the protein α-synuclein (αSyn) is thought to be one of the pathogenic factors in the genesis of PD and in other diseases, which include multiple system atrophy and Lewy body disease. Dopaminergic neurons of the brainstem appear particularly vulnerable to the effects of αSyn aggregates.

Parkinson's Disease is much more than a disorder of movement and many of those with PD have multiple symptoms (Figure 1) that appear several years before the tremors and muscle rigidity that characterize the disease. These early symptoms often include sleep disorders, constipation, and loss of the ability to smell (anosmia).

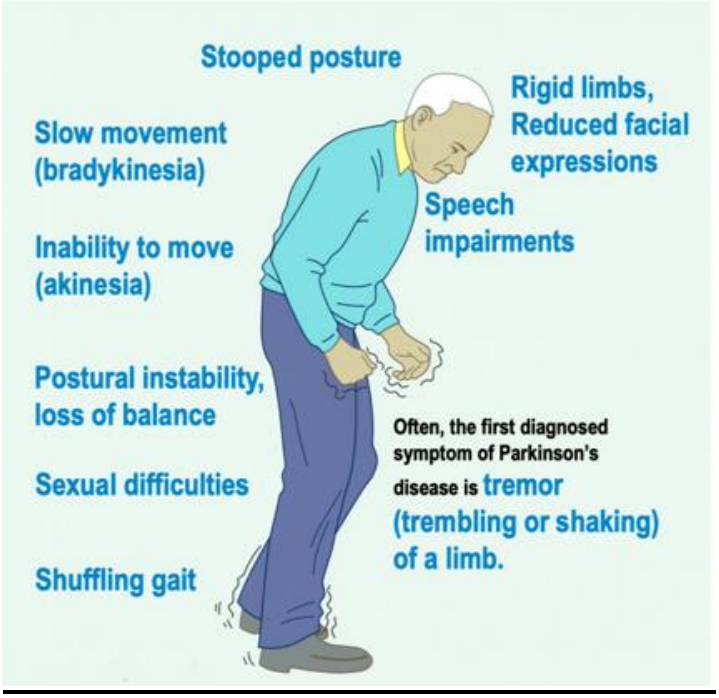

Figure 1. The complex symptomatology of Parkinson's Disease.

The Basal Ganglia

The basal ganglia are a large group of neurons deep within the brain (Figure 2) that play a major role in movement functions. Neurons of the basal ganglia receive input from wide regions of the cerebral cortex and other brain regions, process this information, and then project back to the motor cortex to influence the generation of movements.

Patients with basal ganglia diseases, (including PD) often exhibit involuntary movements. In PD, the most common involuntary movement is that of **resting tremor**, a continuous tremor at rest characterized by alternating flexion and contraction of muscles, such as seen in the "pill rolling" movements of the fingers. These tremors are diminished during voluntary movement of the affected part. For instance, a person whose hand has an involuntary tremor while at rest, can reach for a cup of coffee and the tremor disappears, only to reappear after he replaces the cup of coffee on a table.

Note that people with movement disorders due to diseases of the basal ganglia are not paralyzed. They can move, but their movements are often abnormal.

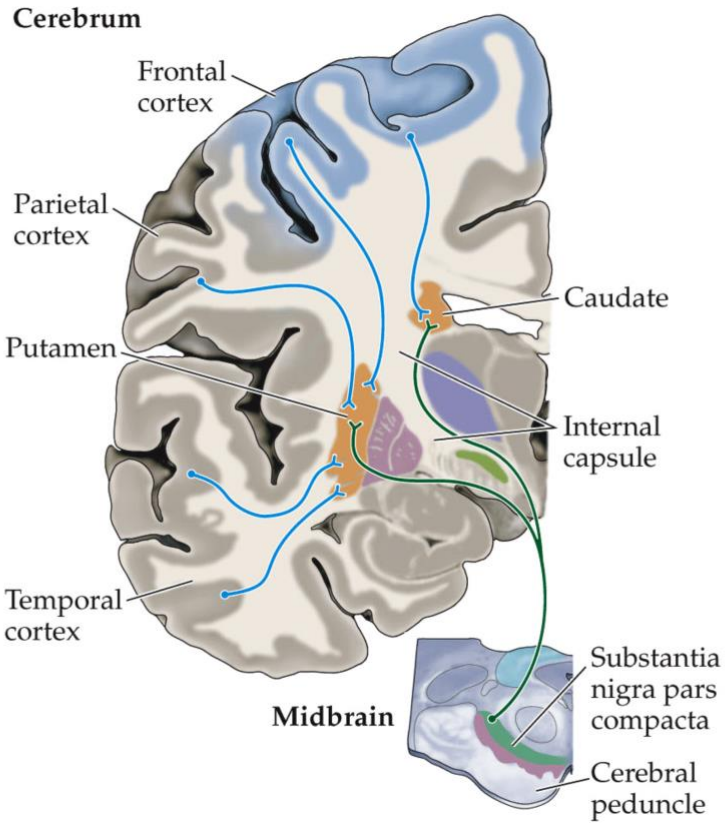

Figure 2. A diagrammatic view of the basal ganglia (orange and purple), a group of millions of neurons deep in the brain. In this view (termed a *coronal* section), imagine that you are looking at the person from the front. One half of his brain (the right half) is shown. The neurons of the folded cerebral cortex that covers the surface of his brain are connected (blue lines) to various regions of the basal ganglia (orange and purple). Note the connections in green between the substantia nigra and the basal ganglia. These latter connections contain the neurotransmitter dopamine and degenerate in Parkinson's disease. (From Purves: *Neuroscience*).

It is known that the **intestinal microbiota** influence brain development, modulate behavior, and contribute to neurological disorders. The microbes of the gut may participate in the pathogenesis of PD. A recent study examined mice that produce excess amounts of α-synuclein in their brains. These mice have motor impairments that mimic those of human PD. Antibiotic treatment of the mice improved their motor behavior, while microbial re-colonization of the gut led to renewed motor deficits. Furthermore, if these mice were raised germ-free, administration of fecal microbiota to the mice from PD-affected human patients increased physical impairments (Figure 3) compared to microbiota transplants from healthy human donors. These findings reveal that gut bacteria influence movement disorders in mice and suggest that alterations in the human intestinal microbiome represent a risk factor for PD.

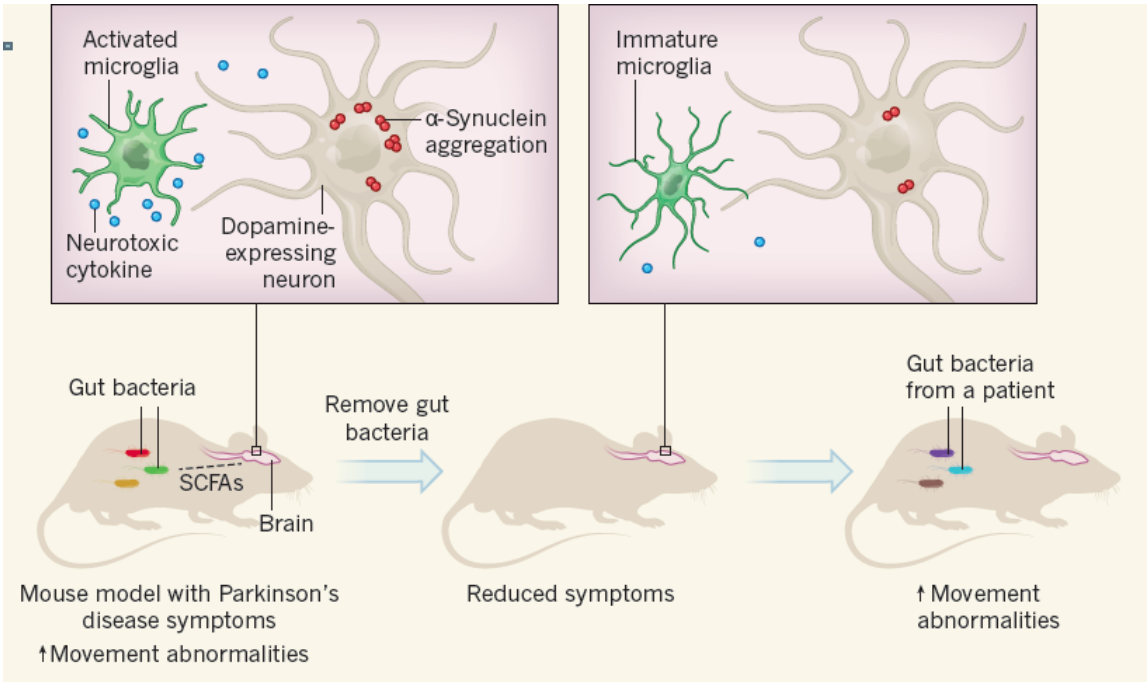

Figure 3. In a mouse model of PD, the animals have high levels of human α-synuclein protein in their brains and have disease characteristics that include movement abnormalities and α-synuclein aggregation in neurons that contain the neurotransmitter dopamine. In these mice there is an immune response in the brain that activates microglial cells that produce neurotoxic cytokine molecules. When gut bacteria were removed, the severity of the disease symptoms was reduced. *From:* T.R. Sampson *et al,* "Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease." Cell. **167**: 1469–1480, 2016.

A study published in 2015 described a group of patients who had severe gastrointestinal ulcers that were treated by cutting the nerves (vagus nerves) to the intestine several years before in order to reduce the amount of acid secreted by the stomach. Surprisingly, over decades, this group of patients had a significant reduction in the incidence of Parkinson's disease compared to the general population of age-matched subjects. Subsequent studies in mouse models of PD have shown that there is a high concentration of abnormal α-synuclein protein in the intestine and that this protein can move by retrograde axonal transport in vagus nerves from the intestine to the brain. This suggests that, at least in some cases, the genesis of PD may be in the intestine.

Treatments for PD.

1-Drug therapies are designed to replace the loss of dopamine (DA) by giving the precursor of DA, L-DOPA, that passes into the brain (DA does not) and is taken up by the dopaminergic neurons that convert L-DOPA to dopamine and increase their dopamine production and storage. This treatment may be supplemented with synthetic drugs that act on DA receptors in the basal ganglia.

2-Deep brain stimulation (DBS) with fine-wire electrodes placed in the basal ganglia to activate neurons that have lost their DA input. DBS is primarily used to improve the symptoms of muscle rigidity.

3- Tissue transplantation to replace the lost dopaminergic neurons of the substantia nigra with viable neurons that produce DA. The transplanted tissue is injected directly into the basal ganglia. These techniques originally used midbrain tissues from aborted fetuses, but fetal cell–based therapies have been considered impractical because of ethical issues and difficulty in producing a defined cell product of DA-producing neurons. A major recent advance has been the ability to convert the skin cells of a PD patient to DA synthesizing neurons using the induced pluripotent stem cell (iPSC) technique (to be described in the lecture). When these cells are injected into the brain, they release DA, improving the patient's PD symptoms, and do not elicit an immune response, because they are derived from the patient's own tissues.

Schweitzer, J.S. *et al* "Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease." New Engl. J. Med. **382:** 1926-1932, 2020.

4-The development of new drugs that reduce the accumulation of α-synuclein in neurons, thus attacking a fundamental cause of the disease. Several of these drugs are presently in clinical trials and will be described in lecture.