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Deborah Cabin and Her Role in the Research of Parkinson's Disease

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Deborah Cabin received her PhD in physiology from Johns Hopkins University in 1996. She has worked in research labs across America investigating genetic diseases and now is a professor in structural and functional neuroscience at the University of Montana. Her interest in Parkinson's disease is a result of the complexity and mystery it presents to researchers. Since 2006, Deborah has made truly remarkable discoveries regarding the causes of the disease, focusing in particular on a protein which is suspected to contribute significantly to the development of Parkinson's disease (PD). Her research aims to identify the normal role of this protein, the mechanisms by which it leads to diseases, and to provide a progressive mouse model to widen the scope of PD research.

What is Parkinson's disease?

Parkinson's disease is a hereditary neurological disorder which is polygenetic and multifactorial. This means that mutations in an individual's DNA lead to the disease by impacting the peripheral and central nervous system. The combination of several effected genes (polygenetic), with multiple environmental factors (multifactorial) cause the expression of PD (1). PD is x-linked, and symptoms appear later in life, around age 40. The most apparent symptom of Parkinson's disease is hypokinesia, which includes slow movement, difficulty initiating movement, rigidity (increased muscle tone), and tremors of the hands and jaw. Impaired movement is caused by the loss of the neurotransmitter dopamine in the circuit that allows the basal ganglia (more specifically, the substantia nigra) to communicate with the striatum and area 6 of the motor cortex (2). The substantia nigra is a cell group in the mid-brain that uses dopamine as a neurotransmitter and innervates the putamen (an area found in the striatum). These two areas of the brain are essential for planning movement; the motor cortex is located where signals encoding for *what* action is desired are converted into signals that specify *how* the action will be executed. This is how the circuit works normally: When an action is desired, excitatory inputs are sent from the motor cortex to the basal ganglia. These inputs then project inhibitory neurons through the substantia nigra, activating cells in the putamen, which send more inhibitory signals to the thalamus. The net reduction of inhibition removes the suppression from the neurons in the thalamus, causing them to fire and to send movement-

strategy information back to area 6 of the motor cortex (3). Area 6 of the motor cortex, or M1, is essential for the planning and execution of movement for both sides of the body. The neurotransmitter dopamine facilitates the motor loop by activating the cells in the putamen, allowing for the movement of information from the substantia nigra to the thalamus and eventually back to the motor cortex (fig.1) (2).

For patients with Parkinson's disease, the loss of dopamine in this circuit results in abnormal nerve-firing patterns and severely reduced capacity for planning, thus, executing complex and simple movements. But the question is: why does the degeneration of dopaminergic neurons take place?

A hallmark of Parkinson's disease is the presence of Lewy bodies in the cell bodies of an affected person's neurons. Lewy bodies are peculiar deposits of the brain protein alpha-synuclein, whose normal function and role in causing PD was unknown before Dr. Cabin's research.

The normal function of alpha-synuclein in neurons

Dr. Cabin and her research team at University of Montana needed to identify the normal function of α-syn so as to be able to better identify its role in the formation of Lewy bodies and ultimately its contribution to Parkinson's disease. Using recombined homologous stem-cell implants, they were able to generate mouse-models that completely lacked the protein (4). For the first time, researchers were able to observe what happens in a brain with no α-syn. Electron microscopy revealed strange behavior in synaptic vesicles in the neurons of the mouse's hippocampus. Synaptic vesicles are tiny hollow spheres located in the axons and axon terminals on either side of a synaptic cleft (where chemical signals are sent and received between neurons) and they store and transport neurotransmitters to neighboring neurons. Normal synaptic vesicles undergo repeated steps of maneuvers, endocytosis, and exocytosis to complete the process of intercellular communication (Fig. 2) (5). Vesicles are formed in the rough endoplasmic reticulum of the soma, and the Golgi apparatus assigns it a neurotransmitter. Proteins embedded in the vesicle membrane concentrate the neurotransmitter while it waits in the "reserve pool" located in the axon. Once the traffic is clear, the vesicle is transported down to the axon terminal where it releases its contents through the synaptic cleft to the next neuron (6). This is how neurons communicate. The strange vesicle behavior observed by Dr. Cabin and her team was that in the mice that lacked α-syn, vesicles in a non-docked position were significantly impaired by a

repetitive high-frequency stimulation of 12.5 Hz for 300 pulses. Also, the replenishment of docked vesicles after depletion took much longer in the mutant mouse synapses than in normal mouse synapses (fig.3). This suggests that α-syn plays an important role in the generation or maintenance of synaptic vesicles found in reserve pools of axon terminals (4). In the case of Parkinson's disease, this makes sense because a neuron's decreased ability to produce normally functioning synaptic vesicles will lead to a breakdown or loss of interneuron communication.

The mechanism by which α-synuclein contributes to disease

From the results of her mutant mouse experiment, Dr. Cabin was able to construct a basic idea of what α-syn *is* and *how* it operates in the formation of Lewy bodies. Furthermore, research was conducted in the attempt to explain why Lewy bodies are a contributing factor to Parkinson's disease. The evidence provided by the experiment (above) suggests that α-syn plays a role in regulating membrane stability in vesicles and thus, overall neural plasticity. Neural plasticity refers to the capacity of brain neurons to change pathways and to adapt to changes in a person's behavior or environment. Neural plasticity is also a required process to recover from a traumatic brain injury (2). Mutations in the gene that code for α-syn production can lead to the misfolding of the protein. Misfolding can cause the loss of normal functionality of α-syn and also to the aggregation of α-syn in the soma of a neuron, also known as a Lewy body (3).

The Lewy body causes the disruption of vesicle formation, oxidative stress, dopaminergic cell loss, and ultimately contributes to the expression of Parkinson's disease (6). Oxidative stress occurs when the cell body is unable to repair damage caused by oxidation (which is a normal result of burning fuel for energy in the cell) at the rate at which it occurs. This imbalance can cause the neuron to become toxic and die (2). When dopaminergic cells die, as discussed, the pathway between the basal ganglia and the thalamus is weakened with each death. Thus, the communication required within the brain to plan and execute movement is severely hindered, and progresses over time.

Final remarks: further research

Dr. Cabin's research of Parkinson's disease provides probable answers to questions that neuroscientists have been asking for decades. Identifying the function of the illusive α-synuclein in normal brains allows us to delve deeper into its function in abnormal brains. However, since it is an almost exclusively human protein which is complex and difficult to isolate, the

development of an affective model for study is very hard to do. Dr. Cabin introduced the use of the mutant human gene A53T alpha-synuclein on embryonic mice, but would like to develop a method (maybe using a prion-like nature of misfolded α-syn) to generate earlier onset of the disease in the mice for further study (3). This would be useful for identifying early bio-markers, and for testing treatment methods. Parkinson's disease affects over 1 million Americans and an estimated 7-10 million people worldwide, and Dr. Cabin's research has undoubtedly raised our knowledge about the disease and its causes to a new level. Dr. Cabin hopes to extend her research to the role α-syn may play in Alzheimer's disease.

Figures

Fig. 1

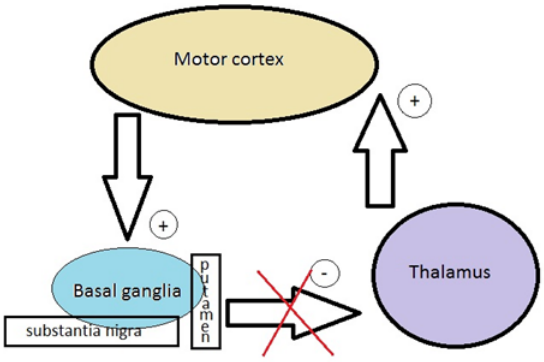


Fig. 2

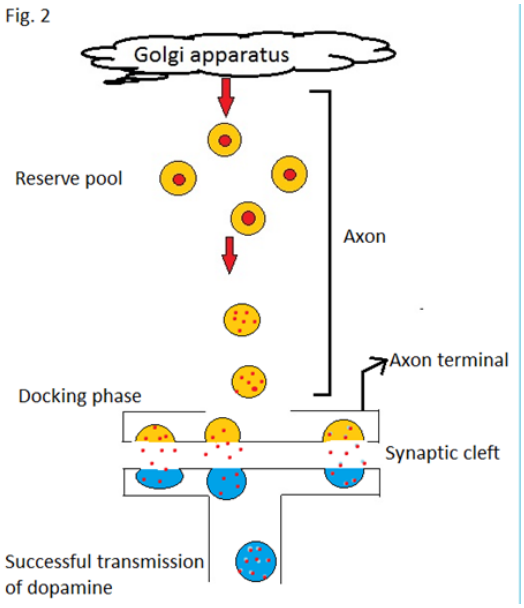
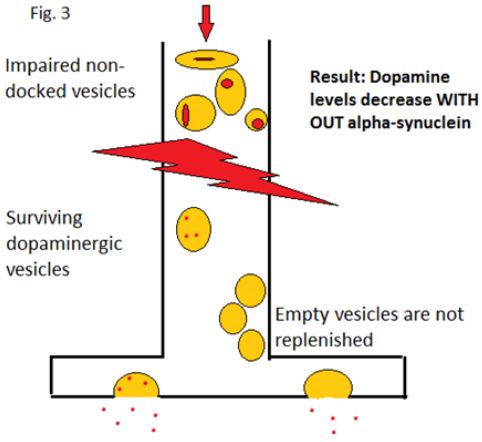


Fig. 3



Resources

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