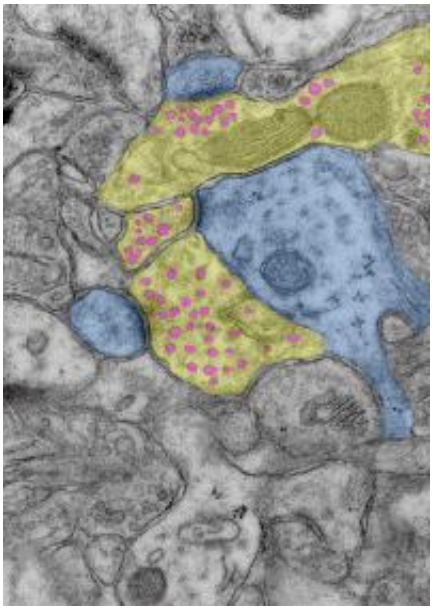
MedicalXpress

Parkinson's disease protein impedes nerve signaling long before brain cells die

October 5 2010, By Jeffrey Norris



UCSF researcher Robert Edwards, MD, has found that release of signaling neurotransmitters at the junction between two nerve cells - called a synapse — is hindered in a mouse model for Parkinson's disease. When a nerve cell "fires," neurotransmitters are released on one side of the synapse from tiny sacs called synaptic vesicles. After release the neurotransmitters bind to receptors on the other side of the synapse. A resultant change in the electrical potential across the cell membrane in the post-synaptic nerve cell determines whether it will fire in turn, propagating the signal through the nerve pathway. In mice with extra copies of genes for the protein called synuclein, fewer vesicles in the pre-synaptic nerve cell release their neurotransmitters when the cell fires. This hinders transmission of the chemical signal across synapses in the nerve pathway. Here the ends of the pre-synaptic cells are shown in green, and the synaptic vesicles that release neurotransmitters are pink. The tips of post-synaptic cells that respond to the neurotransmitters are shown in blue. Credit: Farrukh Chaudhry,Victoria Berge

Parkinson's disease patients have not benefited from any new type of standard treatment in decades. Even so, there have been important discoveries about the disease that may lead to whole new treatment strategies.

Researchers at UCSF, working with nerve cells grown in the lab and with mice, now have discovered an important role for the protein that was first found to be associated with Parkinson's disease more than a decade ago. Researchers had not previously identified a functional role for the protein, called synuclein.

Parkinson's disease runs in families with extra copies of the synuclein gene, and autopsy studies indicate that levels of the protein in brain tissue are elevated in all forms of Parkinson's.

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The new research reveals that abnormally high levels of synuclein in the brain impair the firing of synapses — the transmission of signals between one nerve cell and the next. This happens long before typical disease symptoms appear. The discovery may lead to new drug development aimed at halting the relentless progression of the disease. Current therapy only treats symptoms.

The lead scientist behind the new discovery is UCSF neurologist Robert Edwards, MD, who studies the molecular basis for signaling at synapses and who also treats patients with Parkinson's disease.

“Synuclein is the central protein in Parkinson’s,” Edwards says. “The reason why we think it’s important is because synuclein deposits in the brains of everyone who has Parkinson’s disease.” Synuclein is made by nerve cells – called neurons by scientists – and normally is found at synapses.

But synuclein also deposits in the brain of Parkinson’s patients, suggesting that these aggregates may cause the disease.

“We know that the simple increase in synuclein causes degeneration—the question is whether the aggregates are responsible,” Edwards says. “It now appears that the degenerative process involving synuclein may begin long before the protein forms clumps in the brain.”

“This finding shifts the focus in Parkinson’s from cell loss to the much earlier phenomenon of synaptic dysfunction — something that will be much more amenable to treatment,” Edwards says.

Parkinson’s Disease – More than a Loss of Nerve Cells and Dopamine

The most familiar symptoms of Parkinson’s disease – tremors, rigidity and a general lack of movement – are considered to result from the gradual loss of brain cells that make the neurotransmitter dopamine. Currently, the mainstay of treatment is dopamine replacement with L-dopa or other drugs that mimic dopamine.

Treatment can for a time compensate for the loss of naturally produced dopamine and alleviate symptoms. However, these drugs eventually fail to work, due to progression of the disease.

“We have no treatment for the underlying degeneration, because it

remains poorly understood," Edwards says.

Because increases in synuclein have been shown to cause Parkinson's, synuclein provides a crucial entry point for understanding the degenerative process, according to Edwards, including the loss of neurons.

The loss of function n Parkinson's disease that is attributed to loss of neurons in the brain may in part be due to impaired signaling, Edwards suggests.

"Even people with advanced Parkinson's still have a substantial number of dopamine-producing neurons that remain. Our prediction is that even the neurons that survive don't work very well, due to functional impairment at synapses."

Less well-recognized symptoms of Parkinson's disease do not involve the loss of dopamine-producing neurons, but almost certainly reflect an increase in synuclein within other cells, according to Edwards.

Late in the disease, these symptoms include dementia, low blood pressure and incontinence, which do not respond to dopamine replacement. However, symptoms that can precede the typical motor problems by two decades or more include depression, constipation, and an unusual sleep problem called REM (rapid eye movement) behavior disorder. These symptoms most likely reflect the increased production of synuclein by neurons that do not make dopamine, and impaired neurotransmitter release from these neurons, Edwards says.

Parkinson's Disease – Synuclein in Humans and Mice

Another UCSF Parkinson's disease researcher, Robert Nussbaum, MD, earlier directed research teams that identified mutations or extra copies

of the synuclein gene as the cause of rare, inherited forms of the disease.

In Edwards' recent studies of synuclein, published this year in a leading neuroscience journal, Neuron, his group used both laboratory-grown neurons and a mouse model for the disease. The neurons and mice have both of their two normal synuclein genes, plus additional copies of the normal human gene. This results in the production of abnormally large amounts of the protein.

Synuclein inhibits the transmission of signals within nerve pathways, Edwards found. But there was not yet any evidence of typical Parkinson's symptoms in the young mice. "In addition, there was no obvious pathology in their brains – basically they look okay," Edwards says.

On a molecular level there is still more to learn about how synuclein inhibits neurotransmitter release. Edwards' lab group also found that the increase in synuclein triggers a reduction in the amount of other proteins normally found at the synapse, especially a class of proteins called synapsins, which also remain poorly understood.

"We're trying to look at the earliest steps in Parkinson's disease," Edwards says. "The earliest event is that synuclein goes up. We think that this leads directly to the inhibition of neurotransmitter release, before aggregation of the protein or cell death. Once we understand more about how synuclein inhibits neurotransmitter release, we should be able to develop a simple assay to screen potential drugs.

"My hypothesis is that the activity of this gene is normally going up and down in all of our neurons in response to signals we don't understand. I think that this fluctuation is a normal process, and what triggers Parkinson's disease is when synuclein goes up too much, for too long.

“Others are trying to make synuclein levels go down using drugs. I would like to understand when and how the protein goes up under normal circumstances, and then avoid these conditions – that might be a lot easier.”

Possible Link to Constipation, an Early Symptom of Parkinson’s

In another recent UCSF study, Nussbaum found that increased levels of synuclein cause constipation in a mouse model, due to accumulation of the protein in nerves of the gut. Importantly, no other signs of Parkinson’s — such as the loss of dopamine-making cells or the deposition of synuclein – were apparent in these animals, suggesting that they represent an early stage of Parkinson’s.

Constipation may develop a decade or more before other Parkinson’s symptoms, many clinicians have found. Edwards suggests that the effects of excess synuclein on nerve pathways in the gut may play a role.

“We found that synuclein inhibits the release of neurotransmitter, before there is any actual injury to the cell,” Edwards says. “This probably explains the early symptoms in Parkinson’s, such as constipation, which Bob also reported in mice.”

More information: Increased Expression of α-Synuclein Reduces Neurotransmitter Release by Inhibiting Synaptic Vesicle Reclustering after Endocytosis, Venu M. Nemani et al., *Neuron* (January 14 2010).

Provided by University of California, San Francisco

Citation: Parkinson's disease protein impedes nerve signaling long before brain cells die (2010, October 5) retrieved 17 April 2024 from https://medicalxpress.com/news/2010-10-parkinsons-disease-protein-impedes-nerve.html

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