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NIH-funded study points to a common cause for many effects of the disease

By studying cells from individuals with Parkinson's disease (PD), a study published in *Science* suggests that a toxic form of the brain chemical dopamine may contribute to all forms of PD. This work was partially funded by the National Institute of Neurological Disorders and Stroke (NINDS), a part of the National Institutes of Health (NIH).

"We found that the oxidation of dopamine links three of the major pathological features of PD," said Dimitri Krainc, M.D., Ph.D., professor and chair of the Department of Neurology at Northwestern University, and senior author of the study. "The improper metabolism of dopamine appears to be a mechanism where the multiple pathways converge."

Parkinson's disease kills nerve cells that use dopamine to communicate with other cells in the brain. In this study, researchers grew dopamine neurons from induced pluripotent stem cells (iPSCs) derived from skin cells from Parkinson's patients carrying one of four different mutations liked to PD. Their results showed that neurons with PD-causing mutations had higher levels of an oxidized form of dopamine compared to cells from control subjects. This accumulation of oxidized dopamine puts stress on mitochondria, the cells' power generators, which produce less energy and release additional toxic products into the cells. Similar problems developed more slowly in neurons grown from the skin cells of PD patients who have no known genetic cause for the disorder.

The build-up of a protein called synuclein in neurons is a signature of PD, and the investigators found that blocking the production of dopamine prevented the build-up of synuclein in the neurons derived from patients with PD mutations. In addition, oxidized dopamine accumulated in lysosomes, effectively the garbage recyclers within cells. This accumulation led to a decrease in the activity of a lysosomal enzyme, glucocerebrosidase. Mutations in that enzyme are known to increase the risk of PD.

Importantly, treatment with antioxidants, which reduce the levels of oxidized dopamine and mitochondrial stress, slowed or prevented the accumulation of α-synuclein and the loss of lysosome enzyme activity. Similarly, the treatment of the cells with the calcium channel blocker isradipine, which decreased the mitochondrial stress in neurons, was also beneficial. NINDS currently funds clinical trials testing isradipine, as well as an antioxidant strategy (inosine), to determine whether either of these drugs can slow progression of PD.

"Human iPSCs allow researchers to rapidly discover more pieces to the Parkinson's disease puzzle and identify new pathways for potentially treating all forms of the disease," said NINDS program director Margaret Sutherland, Ph.D. "These tools complement research on animal models for Parkinson's disease, which do not typically demonstrate the dopamine neuron cell death we see in humans."

For years, scientists have been able to only partially recreate the problems associated with Parkinson's by genetically engineering mice to have mutations linked to the disease. For instance, dopamine neurons from mice that have the DJ-1 mutation did not have high levels of oxidized dopamine or clusters of synuclein. In this study, it was found that human neurons contained more dopamine compared to mouse neurons. When additional dopamine was provided, the dopamine-containing cells from mice behaved more like human cells in that they showed increased oxidation and eventual cell death.

Further experiments suggested that the reason human neurons were more susceptible to damage is that the human cells are more likely to convert dopamine into its toxic form and contain higher levels of a protein called calcineurin, which is regulated by calcium levels in the cell.

"We wondered how these genes, which all have different functions, could lead to the development of Parkinson's disease and specifically the degeneration of dopamine-containing neurons in the brain," said Dr. Krainc. "If we can treat neurons early enough in the process, it might be possible to interrupt this vicious cycle of neurotoxicity."

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For more information:
http://www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page

http://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Hope-Through-Research/Parkinsons-Disease-Hope-Through-Research

http://www.ninds.nih.gov

References:
Burbulla et al. Dopamine oxidation mediates a human-specific cascade of mitochondrial and lysosomal dysfunction in Parkinson's disease. Science. September 7, 2017. DOI:10.1126/science.aam9080

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The NINDS (**http://www.ninds.nih.gov**) is the nation's leading funder of research on the brain and nervous system. The mission of NINDS is to seek fundamental knowledge about the brain and nervous system and to use that knowledge to reduce the burden of neurological disease.

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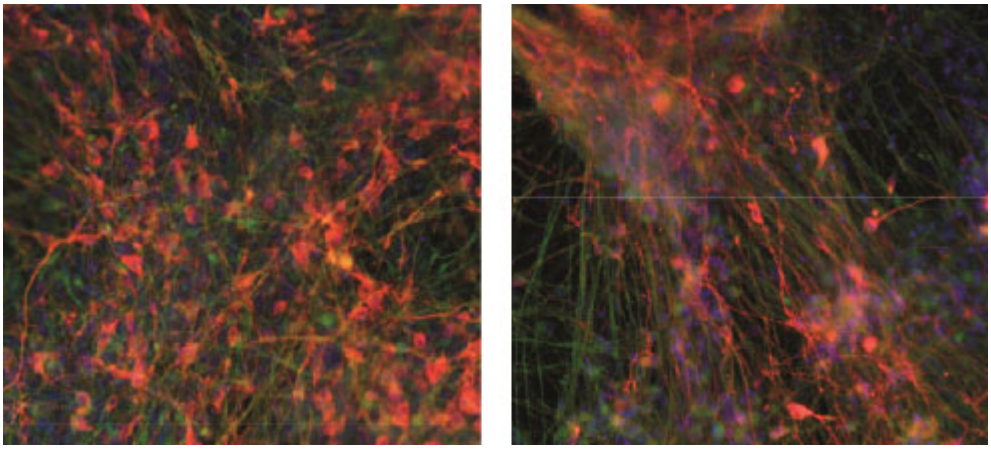

Creating dopamine neurons from skin samples
Using iPSC technology, dopamine neurons can be created from both healthy individuals (left) and individuals with PD (right). Fewer neurons survived when made from PD cells. *Image courtesy of Krainc lab*

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