Parkinson's-linked mutation makes neurons vulnerable to calcium-induced death

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A new study reveals the mechanism by which a genetic mutation linked with Parkinson's disease (PD) renders dopamine neurons particularly vulnerable to cell injury and death. The research is published by Cell Press in the March 13th issue of the journal *Molecular Cell*.

PD is a neurodegenerative disease characterized by a specific loss of dopamine neurons. Several genes have been linked with inherited forms of PD. Many of these genes encode proteins that are targeted to mitochondria, tiny intracellular "power plants" that metabolize oxygen and generate energy. Mitochondria also play a major role in maintaining appropriate calcium levels inside of cells. Abnormal calcium levels can be toxic to neurons and are associated with a range of neurodegenerative diseases.

Mutations in the PINK1 gene cause an inherited form of PD and research has shown that PINK1 is localized to mitochondria. "We previously demonstrated that PINK1 deficiency results in an age related loss of neuronal viability, and an increased sensitivity to mitochondrial dysfunction. However, the mechanisms underlying this mitochondrial pathophysiology remained unknown," explains senior study author Dr. Andrey Y. Abramov from the Institute of Neurology in London.

Dr. Abramov and colleagues used a sophisticated and dynamic imaging technique to explore the mitochondrial pathophysiology of PINK1-dependent PD. They found that loss of PINK1 resulted in an aberrant calcium overload inside the mitochondria. This overload stimulated production of dangerous reactive oxygen species that interfered with the ability of the mitochondria to transport sugar needed for energy production. This phenomenon could be reversed by providing substrates for energy production. "These data strongly suggest that the respiratory complexes in PINK1 deficiency are still intact and that their functional inhibition is in fact secondary to reduced substrate supply," offers Dr. Abramov.

Importantly, adult dopamine-producing neurons are frequently exposed to large influxes of calcium that must be buffered by the mitochondria. Mitochondria dysfunction and an inability to process these calcium loads are likely to make the dopamine neurons quite vulnerable to injury "Our findings define a mechanism whereby PINK1 dysfunction may cause the death of dopamine neurons," concludes Dr. Abramov.

Source: Cell Press (news : web)