New study associates oxidative stress with the spreading of aberrant proteins

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Oxidative stress could be a driving force in the spreading of aberrant proteins involved in Parkinson's disease. This is the result of lab studies by researchers of the German Center for Neurodegenerative Diseases (DZNE). The findings are published in the "*Journal of Clinical Investigation*".

Parkinson's is a neurodegenerative disease with clinical manifestations that include motor (e.g., tremor and slowness in movements) as well as non-motor (e.g., sleep disorders and depression) symptoms. At the microscopic and pathological levels, the disease is characterized by accumulation of abnormal intraneuronal inclusions. They are formed as a result of aggregation of a protein called "alpha-synuclein." In the course of the disease, these inclusions progressively appear in various brain regions, contributing to the gradual exacerbation of disease severity. The mechanisms behind this advancing pathology are poorly understood. Research by DZNE scientists now indicates that "oxidative stress," i.e. an excessive and uncontrolled production of reactive oxygen species, could play an important role in the pathological spreading of alpha-synuclein. The findings are based on in-vivo studies with mice and in-vitro experiments in cultured cells.

"Oxidative stress has long been considered to be involved in the pathogenesis of Parkinson's disease. Our work, however, reveals a new intriguing mechanism that may link oxidative stress to disease development. We show that under oxidative stress the propensity of alpha-synuclein to 'travel' from one neuron to the other is significantly

enhanced, thus facilitating the exchange of harmful protein species, occurrence of pathology and the spreading of this pathology throughout the brain," said Professor Donato Di Monte, a senior DZNE scientist, who headed the current research.

He adds, "Although in our study we induced oxidative stress artificially in laboratory models, we know that increased production of deleterious oxygen species could occur in Parkinson's brain. It might be caused by a variety of conditions, such as genetic mutations and environmental exposures and might be related to the aging process itself, as some of the cellular mechanisms counteracting oxidative stress decline with age. Parkinson's is an age-related disease, making it quite likely that aging brain cells would become more vulnerable to pathological processes involving oxidative stress."

Experimental setting

In a series of experiments, Di Monte and colleagues studied mice that overproduced alpha-synuclein in a specific brain region, namely the dorsal medulla oblongata, known to be a primary target of alpha-synuclein pathology in Parkinson's disease. Under this condition, the researchers were able to show oxidative stress, formation of small alpha-synuclein aggregates (so called oligomers) and neuronal damage. Increased production of alpha-synuclein also led to its "jump" from donor neurons in the medulla oblongata into recipient neurons in neighboring brain regions that became affected by progressive alpha-synuclein accumulation and aggregation. Interestingly, treatment of mice with paraquat, a chemical agent that generates substantial amounts of reactive oxygen species and thus triggers oxidative stress, exacerbated alpha-synuclein pathology and resulted in its more pronounced spreading throughout the brain.

"Our findings support the hypothesis that a vicious cycle may be

triggered by increased alpha-synuclein burden and oxidative stress," Di Monte said. "Oxidative stress could promote the formation of alpha-synuclein aggregates which, in turn, may exacerbate oxidative stress. Jumping from neuron to neuron, this toxic process could affect more and more brain regions and contribute to progressive pathology and neuronal demise."

Abnormal proteins

The precise mechanisms underlying enhanced neuron-to-neuron transfer of alpha-synuclein under oxidative stress are not fully understood. However, more detailed analyses by Di Monte and colleagues, including in-vitro experiments, revealed formation and accumulation of abnormal forms of alpha-synuclein that were oxidized and nitrated as a result of oxidative stress. These abnormal protein species were found to be particularly mobile and more prone to travel from donor to recipient cells.

"Identification of toxic alpha-synuclein species with high propensity to aggregation and spreading bears significant implications," Di Monte said. "They could be targeted for therapeutic intervention that may prevent early disease development and/or counteract the progression of pathology at later disease stages."

More information: Ruth E. Musgrove et al, Oxidative stress in vagal neurons promotes parkinsonian pathology and intercellular α-synuclein transfer, *Journal of Clinical Investigation* (2019). DOI: 10.1172/JCI127330

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