New mechanism links cellular stress and brain damage

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A new study uncovers a mechanism linking a specific type of cellular stress with brain damage similar to that associated with neurodegenerative disease. The research, published by Cell Press in the December 9 issue of the journal *Neuron,* is the first to highlight the significance of the reduction of a specific calcium signal that is directly tied to cell fate.

Body cells are constantly exposed to various environmental stresses. Although cells possess some natural defenses, excessive stress can lead to a type of cell death called apoptosis. "It is thought that excessive stress impacts brain function by inducing neuronal apoptosis and may play a role in neurodegenerative diseases such as Alzheimer's disease and Huntington's disease (HD)," explains senior study author, Dr. Katsuhiko Mikoshiba, from the Laboratory for Developmental Neurobiology at RIKEN Brain Science Institute.

HD is also associated with abnormal calcium signaling and the accumulation of misfolded proteins. Altered function of an intracellular structure called the endoplasmic reticulum (ER) that plays a key role in protein "quality control" and is a critical regulator of intracellular calcium signaling has been implicated in HD pathogenesis, but the specific underlying mechanisms linking ER stress with calcium and apoptosis are poorly understood.

Dr. Mikoshiba and colleagues demonstrated that a neuronal protein called inositol 1,4,5-trisphosphate receptor 1 (IP3R1) which regulates cellular calcium signaling was destroyed by ER stress and subsequently induced neuronal cell death and brain damage. The researchers went on to show that a protective "chaperone" protein called GRP78 positively regulated IP3R1 and that ER stress led to an impaired IP3R1-GRP78 interaction, which has also been observed in an animal model of HD.

"Based on our observation that the functional interaction between IP3R1 and GRP78 is impaired during ER stress and in the HD model, we propose that IP3R1 functions to protect the brain against stress and that the linkage between ER stress, IP3/calcium signaling, and neuronal cell death are associated with neurodegenerative disease." concludes Dr. Mikoshiba.

Provided by Cell Press