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A toxic byproduct of hemoglobin could provide treatments for Creutzfeldt-Jakob Disease

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Scientists at Case Western Reserve University School of Medicine have identified a novel mechanism that could be used to protect the brain from damage due to stroke and a variety of neurodegenerative conditions, including sporadic Creutzfeldt-Jakob disease, Alzheimer's disease, and Parkinson's disease.

Neena Singh, MD, PhD, a professor of pathology at the school, has spent much of her career studying the role of metals such as iron, copper, and zinc in the pathology of neurodegenerative diseases. She has previously reported that some of these metals are regulated by the brain's normal prion protein, called PrPC. Her goal is to identify common pathogenic processes in neurodegenerative diseases that could lead to the development of a new generation of treatments.

In her latest study, published in *The Journal of Alzheimer's Disease*, Singh and post-doctoral research fellow Ajai K. Tripathi, PhD, studied a byproduct of hemoglobin called hemin that is released from red blood cells during stroke and is toxic to neurons. Other scientists have reported that PrPC is upregulated in damaged tissue following stroke, and protects the tissue from further damage.

It was this finding that got Singh and her group interested in how PrPC protects neurons from hemin-induced toxicity. In a series of elegant experiments, Singh said they found that hemin binds to PrPC on many

diverse cell lines. What was surprising was that the interaction between hemin and PrPC actually up-regulated hemoglobin synthesis in hematopoietic and neuronal cells. "Neuronal hemoglobin may be endowed with similar biological functions that are found in red cells, and is likely to improve neuronal survival by supporting their metabolism," explained Singh.

In addition, hemin and PrPC form a complex, resulting in the removal of hemin and reducing the amount of PrPC available for conversion to the PrP-scrapie form. The latter is responsible for scrapie in sheep and goats and Creutzfeldt-Jakob disease in humans. Treatment with hemin has been shown to delay the onset of scrapie in experimental models. This study suggests that in addition to reducing the generation of PrP-scrapie, hemin protects neurons by inducing hemoglobin synthesis. "The hemin-PrPC interaction therefore reveals a unique function of PrPC that is likely to impact the therapeutic management of cerebral hemorrhage and CJD."

This synergy may play a role in other brain diseases as well. Dr. Singh said that altered levels of neuronal hemoglobin have been reported in multiple sclerosis, Alzheimer's disease, Parkinson's disease, and dementia with Lewy bodies. "We think that manipulation of neuronal hemoglobin may provide an effective method of improving neuronal survival," said Dr. Singh. "Further studies are necessary to explore viable options that take advantage of PrPC and hemin in this process."

Provided by Case Western Reserve University