New insight into neuronal survival after brain injury

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A new study identifies a molecule that is a critical regulator of neuron survival after ischemic brain injury. The research, published by Cell Press in the January 13 issue of the journal *Neuron*, may lead to new therapies that reduce damage after a stroke or other injuries that involve an interruption in blood supply to the brain.

Ischemic brain injury is damage caused by a restriction in blood supply. Neuronal death after an interruption in the supply of oxygen and glucose involves a complex cascade of pathological events and, although previous research has identified key signaling pathways involved in neuronal death, factors contributing to neuronal survival after ischemia are not well understood. "Although a number of molecules and compounds conferring resistance to ischemic stresses have been identified, they have failed to be protective in clinical trials despite promising preclinical data," explains senior study author, Dr. Kazuo Kitagawa from the Osaka University Graduate School of Medicine in Japan.

Earlier research implicated a molecule called cAMP responsive elements binding protein (CREB) in the protection of neurons after ischemia. CREB is known to regulate many different genes and plays a role in diverse physiological processes. In the current study, Dr. Kitagawa, coauthor Dr. Hiroshi Takemori, and their colleagues found that salt-inducible kinase 2 (SIK2) was expressed in neurons at high levels but was reduced after ischemic injury. They went on to show that SIK2 suppressed CREB-mediated gene expression after oxygen and glucose deprivation and that neuronal survival after ischemia was significantly increased in mice that were lacking SIK2.

"We found that oxygen and glucose deprivation induced SIK2 degradation concurrently with regulation of the CREB-specific coactivator transducer of regulated CREB activity 1 (TORC1), resulting in activation of CREB and its downstream targets," says Dr. Takemori. These findings suggest that SIK2 plays a critical role in neuronal survival and may have clinical applications. "Our results suggest that the SIK2-TORC1-CREB signaling pathway may serve as a potential therapeutic target for promoting the survival of neurons," concludes Dr. Kitagawa. "These findings also raise new opportunities for the development of novel therapeutics."

Provided by Cell Press

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