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Molecular body guards for neurons

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In the brain, patterns of neural activity are perfectly balanced. The interplay between activating and inhibitory neurotransmitters ensures that the level of activity stays within the physiological range. During an epileptic attack excitation gains the upper hand resulting in the death of neurons. Researchers of the Bonn University Medical School have now discovered a key player in a signal transduction cascade, which protects neurons from hyperexcitation-induced cell death. These results open a new direction for the development of novel therapy options. The results are now published in the *Journal of Neuroscience*.

Pathophysiological activity often triggers neuronal cell death. This can for example be observed after an epileptic insult. The cause for this hyperexcitation is excessive release of the signaling molecule glutamate. "This neurotransmitter can switch on signaling cascades that act neurotoxic", says Prof. Dr. Schoch McGovern of the Institute of Neuropathology and the Department of Epileptology at the University Clinic Bonn. However, neurons try to protect themselves and prevent the damaging hyperexcitation.

The molecular nature of these "body guards" is so far unresolved. Accumulating evidence shows transcription factors to play an essential role in the processes by which neurons protect themselves. These factors switch on certain genes, which then via signal transduction cascades result in the production of neuroprotective substances. These in turn counteract the damaging glutamate-induced hyperexcitability.

Increased neuronal cell death in the absence of Syt10

The team of Prof. Dr. Schoch McGovern could now show that the protein Synaptotagmin 10 (Syt10) is an integral part of this protective shield. If rats for example experience an epileptic seizure, the amount of Syt10 in the hippocampal formation of the brain strongly increases. The researchers used neurons from mice, in which the Syt10 gene had been ablated, and stimulated them with a glutamate like substance. This treatment resulted in substantial neuronal death.

NPAS4 modulates the production of protective factors

The research team discovered, which transcription factor activates the gene for Syt10 in response to pathophysiological neuronal activity. This essential member of the neuronal body guard is called NPAS4. The researchers cultured rodent neurons and added several transcription factors. NPAS4 activated the Syt10 gene and required Syt10 to exert its neuroprotective function. "NPAS4 triggers a signaling cascade that results in the production of neuroprotective factors", says Prof. Dr. Schoch McGovern.

Search for novel therapy approaches

The molecular identity of the neuroprotective substances is still unknown. "A potential candidate, the insulin-like growth factor IGF-1, was not able to reverse the increased neuronal cell death in the absence of Syt10", reports the neurobiologist. The next step therefore is to test other substances. Once the identity of the neuroprotective body guards is revealed, novel avenues for therapy development open up, for example for stroke and epilepsy patients. "The goal would be to administer these protective substances from the outside in order to prevent neuronal cell death in the brain", says Prof. Dr. Albert Becker, a medical doctor, who was part of the study. However, there is still a long road ahead.

More information: Identification of Synaptotagmin 10 as Effector of NPAS4-Mediated Protection from Excitotoxic Neurodegeneration, The *Journal of Neuroscience*, DOI: 10.1523/JNEUROSCI.2027-15.2016