

# A mechanism that alters the regulation of calcium in cells could be involved in neurodegenerative disease

November 14 2014

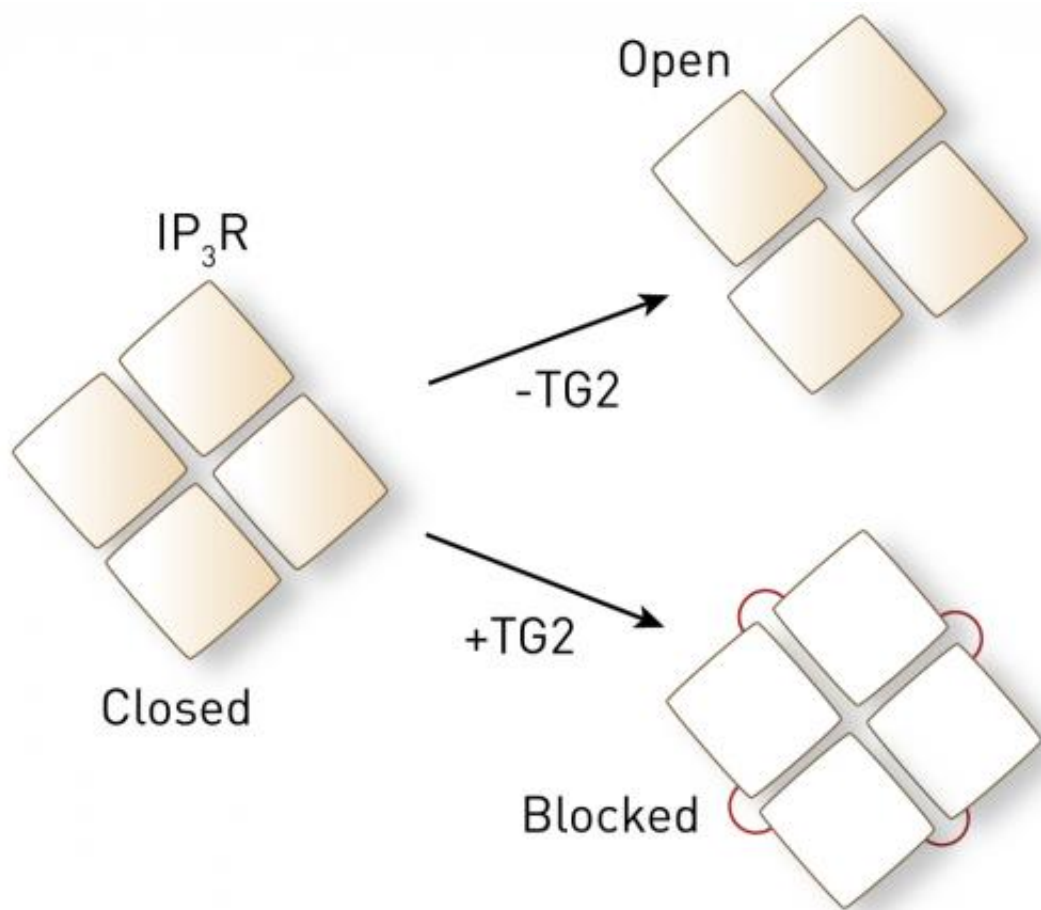


Figure 1: Without the enzyme transglutaminase type 2 (TG2), the four 1,4,5-trisphosphate receptor (IP<sub>3</sub>R) proteins move to open the cell-membrane channel (top). TG2 links the IP<sub>3</sub>R proteins together (red lines, bottom) so that they cannot move, blocking IP<sub>3</sub>R function. Credit: Katsuhiko Mikoshiba, RIKEN Brain Science Institute

The calcium ion  $\text{Ca}^{2+}$  regulates an enormous number of cellular processes. Control of  $\text{Ca}^{2+}$  is therefore crucial and is achieved by precise regulation of proteins that allow the ion to move between different parts of the cell. Research led by Katsuhiko Mikoshiba and Kozo Hamada from the Laboratory for Developmental Neurobiology at the RIKEN Brain Science Institute has now revealed a previously unknown mechanism that regulates the release of  $\text{Ca}^{2+}$  from stores inside cells and which could be involved in several brain disorders.

The research team investigated the role of an enzyme called transglutaminase type 2 (TG2) in the regulation of the inositol 1,4,5-trisphosphate receptor (IP3R) protein, which forms a channel in the membranes of cellular compartments. The IP3R channel opens and closes in response to regulatory signals to control the release of  $\text{Ca}^{2+}$  from cellular stores.

"IP3R is required for vital processes that involve [calcium signaling](#), but excessive IP3R function promotes cell death processes, so regulation is important," says Mikoshiba. "TG2 levels are higher than normal in various neurodegenerative diseases, including Alzheimer's, Huntington's and Parkinson's diseases, so we were interested in the effect of TG2 on IP3R."

The researchers measured the amount of  $\text{Ca}^{2+}$  that passed through IP<sub>3</sub>Rs in a simplified system of [cellular compartments](#) that were isolated from mouse cells and loaded with calcium. Adding TG2 to this system reduced the amount of  $\text{Ca}^{2+}$  that could pass through IP<sub>3</sub>Rs. In living cells, blocking the function of TG2 had the reverse effect: it increased  $\text{Ca}^{2+}$  release from the cellular stores. Both findings show that TG2 blocks the function of IP<sub>3</sub>Rs.

The team then went further and looked at exactly how TG2 affects IP<sub>3</sub>Rs on a molecular level (Fig. 1). "Four IP<sub>3</sub>R proteins assemble to form a calcium channel, which normally opens by changing the spatial relationship between the four proteins," explains Mikoshiba. "TG2 links the four proteins together and chronically locks the spatial relationship between IP<sub>3</sub>R proteins to block their function."

Because TG2 levels are abnormal in many neurodegenerative disorders, the researchers also investigated how TG2 affects IP<sub>3</sub>Rs in a mouse model of Huntington's disease. They found that reduced IP<sub>3</sub>R function in mice with Huntington's disease occurred only in association with elevated TG2, suggesting that increased TG2 levels contribute to the disease.

"This mechanism of TG2 might serve as a general principle for many other diseases of the brain and other tissues in which TG2 is upregulated by disease-inducing agents," says Mikoshiba.

**More information:** Hamada, K., Terauchi, A., Nakamura, K., Higo, T., Nukina, N., Matsumoto, N., Hisatsune, C., Nakamura, T. & Mikoshiba, K. "Aberrant calcium signaling by transglutaminase-mediated posttranslational modification of inositol 1,4,5-trisphosphate receptors." *Proceedings of the National Academy of Sciences* 111, E3966–E3975 (2014). [DOI: 10.1073/pnas.1409730111](https://doi.org/10.1073/pnas.1409730111)

Provided by RIKEN

Citation: A mechanism that alters the regulation of calcium in cells could be involved in neurodegenerative disease (2014, November 14) retrieved 24 June 2024 from <https://medicalxpress.com/news/2014-11-mechanism-calcium-cells-involved-neurodegenerative.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.