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Researchers find zinc's crucial pathway to the brain

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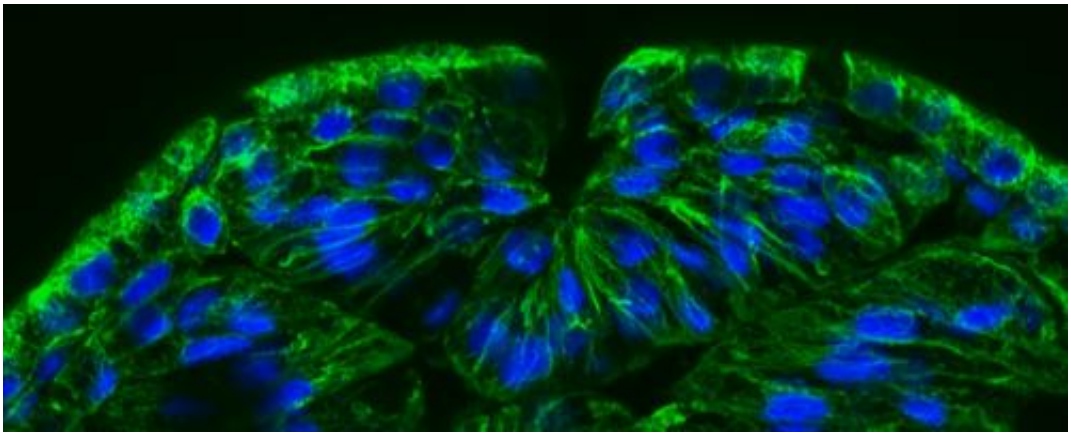

ZIP12 RNA is marked with blue dye in a frog brain. Credit: Mark Messerli, MBL

A new study helps explain how parts of the brain maintain their delicate balance of zinc, an element required in minute but crucial doses, particularly during embryonic development.

The study, led at the MBL by Dr. Mark Messerli in collaboration with scientists from the University of California, Davis, shows that neural cells require zinc uptake through a membrane transporter referred to as ZIP12. If that route is closed, neuronal sprouting and growth are significantly impaired and is fatal for a developing embryo. Their discovery was published in the *Proceedings of the National Academy of Sciences*.

"This particular transporter is an essential doorway for many neurons in the central nervous system," explains Messerli. "You knock out this one gene, this one particular pathway for the uptake of zinc into these cells, and you essentially prevent neuronal outgrowth. That's lethal to the embryo."

Previously, scientists thought that zinc could use more than one pathway to enter the cell during early brain development. Some other elements, like calcium, enjoy such luxury of multiple options.

Knocking out ZIP12, affected several critical processes in the brain, the scientists found. For example, frog embryos were unable to develop their neural systems properly. Additionally, neurons had trouble reaching out to connect to other neurons; their extensions were both shorter and fewer in number than normal.

"We were surprised that ZIP12 was required at such an early and critical stage of development," said Winyoo Chowanadisai, a researcher in nutrition at the University of California at Davis and visiting scientist in the Cellular Dynamics Program at the MBL. Dr. Chowanadisai was the first on the team to realize that ZIP12 is expressed in such abundance in the brain."This study also reinforces the importance of periconceptional and prenatal nutrition and counseling to promote health during the earliest stages of life."

ZIP12 is part of a larger family of transporters involved in the movement of metal ions from outside the cell. Other reports showed that simultaneously blocking 3 other transporters in the family – including ZIP1, 2, and 3 – had no major effects on embryonic development.

Zinc is needed for healthy neural development, helping the brain to learn and remember new information. However, too much zinc can also be problematic.

The research team is investigating the implications of their results on processes like embryonic brain development and wound healing.

"[The result] was not expected," said Messerli, a physiologist in the MBL's Bell Center for Regenerative Biology and Tissue Enginering and Cellular Dynamics Program. ""We found that zinc uptake through ZIP12 is a regulatory point for neuronal growth, required for development and possibly required for learning and memory throughout life. We want to elucidate the downstream targets that zinc is affecting. That's the next exploration."

More information: Chowanadisai W, Graham DM, Keen CL, Rucker RB and Messerli MA (2013) Neurulation and neurite extension require the zinc transporter ZIP12 (slc39a12). *PNAS* 110: 9903-9908. www.ncbi.nlm.nih.gov/pubmed/23716681

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