# Life and Death in the Hippocampus: What Young Neurons Need to Survive

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Whether newborn nerve cells in adult brains live or die depends on whether they can muscle their way into networks occupied by mature neurons. Neuroscientists at the Salk Institute for Biological Studies pinpointed the molecular survival gear required for a young neuron to successfully jump into the fray and hook up with other cells.

In a study published in a forthcoming issue of *Nature*, researchers in the lab of Fred H. Gage, Ph.D., a professor in the Gene Expression Laboratory and the Vi and John Adler Chair for Research on Age-Related Neurodegenerative Diseases, identify a subunit of the NMDA receptor, a protein complex that transduces signals sent by neighboring cells, as the cells' life-saving equipment that allows them to integrate into the existing brain circuitry.

The NMDA receptor is activated by the neurotransmitter glutamate, a chemical released by neurons in order to transmit information to neighboring cells. Whenever the receptor picks up a glutamate signal it is stimulated and relays the signal. But for newborn neurons that signal means something else entirely — survival.

"When we removed the NMDA receptor, that is when cells make connections in response to glutamate in the environment, the newborn neurons withered and died at a specific stage of their maturation," explains Gage. " The NMDA receptor modulates synapse formation and determines what pattern of input activity new neurons receive, which in turn determines survival or death."

Combining mouse genetics and gene transfer techniques, Gage and a team headed by former postdoctoral fellow Ayumu Tashiro, Ph.D., injected a virus carrying a pair of molecular shears capable of deleting a gene encoding part of the NMDA receptor into the hippocampus, a brain region harboring neural stem cells that give rise to new neurons. Newly born neurons infected with virus were marked by a fluorescent dye enabling detection of neurons derived from those cells.

A few weeks later, animals that received the virus showed fewer fluorescent neurons compared to mice injected with a benign virus lacking the shears, meaning fewer new neurons had survived originating from neural stem cells in which the NMDA receptor had been eliminated.

Listening to Gage, one gets the impression that the hippocampus is a dangerous place for a fledgling neuron trying to elbow its way into pre-existing networks. “It’s rough in there!” he concedes. “The NMDA receptor-mediated event is a competition between mature cells vying for connectivity and young guys competing with both the mature cells and their peers to fit in. You are selecting for the cell that performs best in this environment.”

The Gage lab previously showed that the rate at which new neurons emerge from stem cells depends on an animal’s activity. “If you put animals in an enriched environment and give them access to running wheels, you increase survival of new brain cells.” says Gage. “Now we show that stimulation may, in part, mediated through the NMDA receptor.”

Those studies had also shown that young and middle-aged “exercised” rats perform better on learning tasks such as maze swimming, indicating that new neurons are more than just a backup supply but actually enhance learning.

“Remarkably, new neurons are born in the hippocampus, a structure whose function is to acquire new information,” says Gage. “That suggests that new cells are involved in how we learn.”

This ongoing struggle for connections between young and mature neurons is apparently more than just a spectacle designed to keep Mother Nature amused: the fact that enhanced learning is correlated with adult neurogenesis suggests constant rearrangements within neural networks are absolutely necessary for learning to occur.

In fact, data emerging from studies in the Gage lab reinforces the commonly held belief that using one’s brain cells is the best way to optimize brain function throughout one’s lifetime.

“In the natural course of aging there is cognitive decline,” says Gage. “We know we lose the ability to generate new neurons with age. We are currently trying to figure out how generate as many neurons as possible to potentially enhance learning or increase the amount of neurogenesis in adults.”

Also contributing to this study were Gage lab postdoctoral fellows Vladislav Sandler, Ph.D., Nicolas Toni, Ph.D., and Chunmei Zhao, Ph.D. Tashiro now does research at the Norwegian University of Science and Technology in Trondheim.

Source: Salk Institute for Biological Studies