The Mechanisms of Memory

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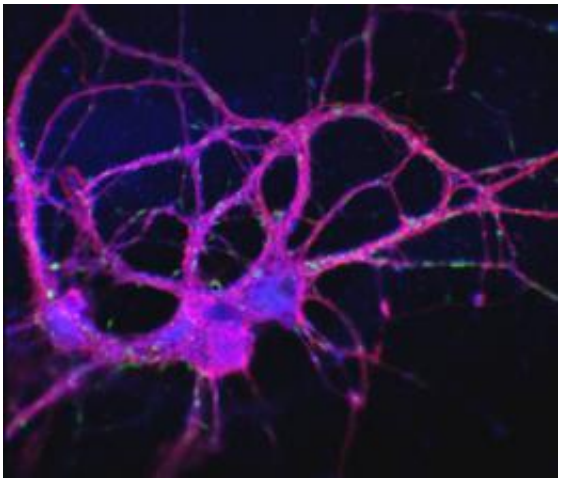

An image of neurons treated with estrogen that shows calpain activation in green. The red color shows the structural elements of the cells, called actin filaments, which are important for cell growth and movement. Image courtesy Michel Baudry.

(PhysOrg.com) -- USC College's Michel Baudry and graduate student Sohila Zadran brought forty years of research to a pinnacle with their breakthroughs in the science of learning and memory.

It's not a unique situation in scientific research to have a hypothesis disputed. But finally having visual evidence that basically closes the books on decades of scientific debate is a unique and sweet success.

For USC College's Michel Baudry, professor of biological sciences and biomedical engineering, and neuroscience graduate student Sohila

Zadran, the success was even sweeter because their breakthrough was instantaneous and somewhat unexpected.

By mid-2008, when Zadran came to the College, Baudry had already spent 30 years researching the cellular mechanisms behind the learning and memory process, exposing the connections between the various proteins, enzymes and synapses. But there were still connections to make, steps to break down.
Zadran had only been at the College for a few months, “and by Summer 2008, she’d practically solved it,” Baudry said.

Zadran attempted a new imaging technique that, on the first try, showed visual proof of the activation of calpain, a proteolytic enzyme vital to the memory-making process.

The role of calpain in learning and memory has been disputed since Baudry was a postdoctoral fellow, and in an instant, his hypothesis had finally been supported.

The Beginning

In 1973, University of Oslo researchers Timothy Bliss and Terje Lømo discovered that when neurons are stimulated a certain way, the strength of neuronal synaptic connections changes, a process they called long term potentiation (LTP).

After graduating from the University of Paris with his Ph.D. in biochemistry, Baudry started working for his postdoctoral advisor Gary Lynch at UC Irvine in 1978. Lynch was one of the few scientists who thought LTP would make for interesting research. The team focused on the neurochemistry of LTP, and they soon realized that the features of LTP were similar to the features of the learning and memory process.

When a memory is made, the brain is changed permanently because the process changes the neuronal synapses — the bridge between neurons that allows them to communicate with one another. Likewise, LTP also changes the connections between neurons. Because the two processes had the same outcome, Lynch and Baudry believed that LTP could possibly be the cellular mechanism behind learning and memory.

In 1984, Lynch and Baudry published a paper in Science in which they theorized that the activation of the enzyme calpain was critical to the formation of LTP, and therefore to learning and memory.

Because the hypothesis was so novel, “the scientific community didn’t buy it,” Baudry said. “Ever since, we’ve been struggling and fighting to get the hypothesis confirmed and accepted.”

Connecting the Dots

In 1989, Baudry came to the College to continue his research. For the next two decades, he and his team encountered setbacks and made great breakthroughs, but yet the question still remained: Could someone actually prove that calpain was a link in the memory-making process?

This brings us to 2008, when Zadran arrived at the College. After graduating with her bachelor’s degree from UC Berkeley, Zadran started working in the lab before the school year began.

Baudry and his research team had been trying to come up with a way to visualize the activation of calpain and find out what is activating it. One of Zadran’s first forays into the research was to apply a technique called fluorescence resonance energy transfer (FRET), which uses two fluorescent probes that interact differently depending on their distance. When calpain is activated in a neuron, a fluorescent signal is produced.

The results were immediate.

“It was like lightning in a dish,” Zadran said. “Everything worked, literally, the first time.”

Baudry and Zadran discovered that calpain is activated by a protein called MAP kinase, which regulates several types of cellular activities. MAP kinase itself, they also found, is activated by estrogen.

So the team set up the beginning of the chain of events: estrogen activates MAP kinase, which activates calpain. The next step was proving that calpain is linked to LTP.

The factor that connects the two, they revealed, is a process called actin polymerization, which is the growth of actin filaments in the dendritic spine, where the synaptic contact takes place in the brain.

“All this work fits well into the framework and provides a molecular explanation for how estrogen facilitates learning and memory,” Baudry said. “We now know the cascade of events that takes place: estrogen to MAP kinase to calpain to actin polymerization to glutamate receptors.”

Zadran, Baudry and their research team released two articles on their findings. The first, published in *Proceedings of the National Academy of Sciences* (PNAS) in December 2009, described how estrogen’s effect on learning and memory occurs through calpain. Their second paper, published in *The Journal of Neuroscience* in January 2010, reports that brain-derived neurotrophic factor (BDNF) activates calpain in the brain.

The Team’s Future

The research done by Baudry, Zadran and their predecessors is applicable to a wide range of medical conditions, including cancer and

Alzheimer's disease.

Researchers have hypothesized that the onset of Alzheimer's, especially in post-menopausal women, results from lack of estrogen. Clinical trials focusing on estrogen replacement therapy were largely unsuccessful because the therapy involved a combination of estrogen and the hormone progesterone, which actually cancels out estrogen benefits.

Current research is focusing on other ways to initiate estrogen-mediated benefits without using estrogen itself, as use of estrogen alone can increase the risk of breast cancer. The research done by Baudry and Zadran suggests that it might be possible to bypass the receptor level entirely and activate the MAP kinase, or find other ways to facilitate calpain activation, and therefore enhance the learning and memory process without the use of estrogen.

Zadran is currently studying the impact that calpain activation could have on cancer metastasis. She is also hard at work on her third paper, which will focus on what happens between two steps in LTP — on which protein calpain is activating, and how it results in actin polymerization. Zadran will graduate in Spring 2010, and she was recently accepted as a postdoctoral student at CalTech.

Baudry will continue examining the series of events that lead up to LTP and learning and memory. His next step is to find the exact point in the process that calpain is activating.

"After that, we're going to say this is it, learning and memory is solved!" Baudry said, half-joking. "Then we can move on to something else."

Baudry knows that research is never finished, even when a piece of the puzzle is put into place. There will always be more discoveries to make, new methods to try, more dots to connect in our understanding of human

memory.

Provided by University of Southern California