In a flash: dissecting memory with light

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Video Abstract

Keywords: LTP, signaling, hippocampus, amygdala, dendritic spines, structural plasticity, mice, FRET, FLIM

Posted Date: February 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-279923/v1

Abstract

Memories seem to be created in the blink of an eye – we can recall an event as soon as it is over. But is this actually the case? Scientists know the key signals for memory formation but have lacked the tools to figure out the details, such as when and for how long particular molecules need to be active. By developing a more precise way of disrupting signaling, researchers have now defined this window for one of the most important molecules responsible for memory. Memories are recorded through changes in synapses, or the connections, between neurons. Many synapses are located on tiny bumps called spines that are found along the branching dendrites of neurons. When synapses are very active, like they are during learning or a memorable event, molecular signaling cascades turn on. These cascades strengthen synapses and make spines grow. The protein calcium/calmodulin kinase II, or CaMKII, is required for both of these events. But precisely when and how long CaMKII needs to act was unclear. To find out, researchers from the Max Planck Florida Institute for Neuroscience in collaboration with with the National Institute of Physiological Sciences in Japan created a light-activated version of AIP2, a CaMKII inhibitor, by attaching a blue light sensor to it. Turning on the light activated the inhibitor and blocked CaMKII activity almost instantaneously, while turning it off allowed CaMKII activity to resume in less than one minute. With this tool, the researchers could manipulate the timing of memory-related CaMKII activity with second-to-minute resolution. They first investigated the timing of CaMKII activity required for spines to grow and synapses to get stronger. Normally, stimulating a synapse with a particular rhythm strengthens it and makes spines grow. But if the researchers shined the blue light while stimulating – thus turning off CaMKII activity at the same time – those changes didn't happen. When they turned the light on just one minute after stimulation, the synapse grew and the spine got stronger, as expected. These results indicate that memory-related changes in synapse strength and structure only require a short, one-minute burst of CaMKII activity. Next, the researchers looked at the timing of CaMKII activity needed for actual memory formation. They placed mice in the bright side of two rooms connected by a hole and trained the mice to avoid the dark room by giving them a tiny electrical shock whenever they entered it. In some mice, they also shined blue light to inhibit CaMKII in the amygdala, a brain region important for this type of memory formation. Inhibiting CaMKII activity in the amygdala during training, but not after, blocked learning. These results indicate that CaMKII activity during training is necessary for learning, but CaMKII activity after training is not. Using the new light-activated inhibitor, the team was able to define the brief window of CaMKII activity needed for memory and associated synapse changes with an unprecedented level of precision. Because the same strategy can be used to make light-activated inhibitors of proteins in other signaling pathways, the method may also increase understanding of many biological processes and lead to treatments for the many conditions caused by abnormal signaling, such as intellectual disability or addiction.