Memory's master switch

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Neuroscientists have long wondered how individual connections between brain cells remain diverse and "fit" enough for storing new memories. Reported in the prestigious science journal *Neuron*, a new study led by Dr. Inna Slutsky of the Sackler School of Medicine at Tel Aviv University describes what makes some memories stick.

The key is GABA (γ-Aminobutyric acid), a natural molecule that occurs in the brain, which could be the main factor in regulating how many new memories we can generate, the new study has found. The understanding of these mechanisms might lead to the development of new memory enhancers and new treatments for neurodegenerative diseases such as Alzheimer's.

Memories, Dr. Slutsky says, are stored in synaptic connections between neurons in our brain. In the past, other teams, including her own, have demonstrated that the strength of individual synapses is highly variable, even at the single neuron level. This variability ultimately determines if and how new memories are stored, and the key to this variability is GABA, a naturally-occurring chemical found in the brain.

Tight connections and lone rangers

Dr. Slutsky's graduate student Tal Laviv and postdoctoral fellow Inbal Riven, the lead authors in the study, applied advanced nanotechnology methods in optical imaging to track how proteins engineered by Prof. Paul Slesinger and his team at The Salk Institute interact with GABA at the single-synapse level.

In the hippocampus, one of the main areas of the brain involved in learning and memory, the strength of neuronal connections is known to be highly variable. Some neurons are tightly connected to others, while some appear to be "lone rangers."

The new paper, which examines individual synapses in the hippocampus, demonstrates that this process is regulated by GABA, the main inhibitory neurotransmitter in our brain. "We determined that variations in the local level of GABA in the vicinity of individual synapses are responsible for the differences or 'heterogeneity' of synaptic strength. And this heterogeneity may facilitate the formation of new memories," Dr. Slutsky explains.

Looking at the brain at rest

While looking at the brain in its basal state -- when the activity was "at rest" before attempting to memorize a list of items or after a memory had been stored -- Dr. Slutsky's team could actually "see" where synapses differ at different dendritic branches in the neuronal network. Those branches of neurons close to a cell body displayed a larger number of weak synapses, while the most distant branches were composed of a smaller number of strong synapses.

"Why the difference?" they asked. GABA was the answer. Higher concentrations of GABA near a synapse induced a stronger activation of its receptors, weakening basal synapse strength. As a result, GABA makes this synapse more liable to the formation of new memories, the researchers propose.

Dr. Slutsky, who previously discovered a basal-state regulator molecule, says that the research may also have implications for treating diseases of the mind. "We found that amyloid-beta, a well-known hallmark of Alzheimer's disease, regulates basal synapse strength in an opposite way

to GABA," she notes, suggesting that an increase in the basal activity of synapses may initiate memory decline in Alzheimer's and other neurodegenerative disorders.

Experiments in the study were done using neuronal cultures and brain slices of rats subjected to molecular biology, optical imaging and electrophysiological techniques. The study also constituted a technical achievement, since it used advanced imaging techniques such as fluorescence resonance energy transfer (FRET) spectroscopy that looked at protein-to-protein interactions in the brain at the 10 nanometer scale. In the past, such fine resolution was impossible — brain scientists could only investigate interactions at the level of entire tissues, not between molecules at individual synapses.

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