Study uses Botox to find new wrinkle in brain communication

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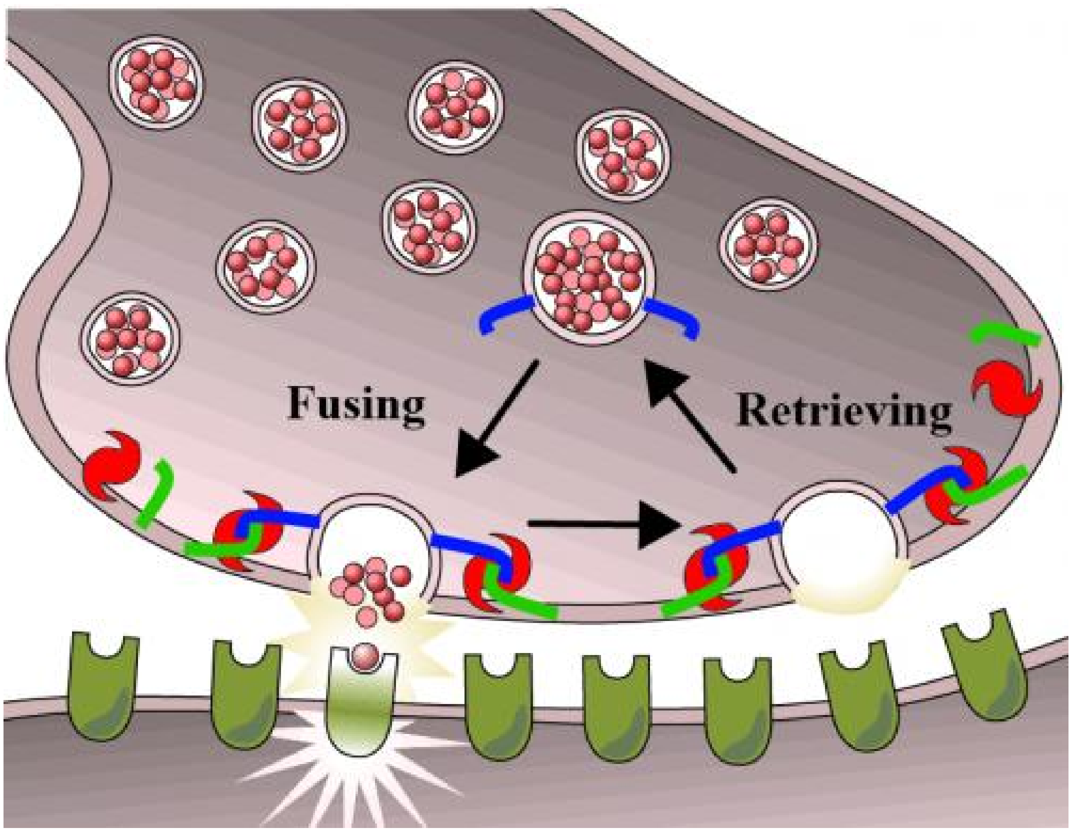

SNARE proteins (red, green and blue objects) are molecules found at most synapses throughout the body. They are known for their role in helping nerve cells send messages by releasing neurotransmitters. Dr. Wu and his colleagues used Botox and similar toxins to show that SNARES may also be important for retrieving synaptic message carriers. Credit: NINDS

National Institutes of Health researchers used the popular anti-wrinkle agent Botox to discover a new and important role for a group of molecules that nerve cells use to quickly send messages. This novel role for the molecules, called SNARES, may be a missing piece that scientists have been searching for to fully understand how brain cells communicate under normal and disease conditions.

"The results were very surprising," said Ling-Gang Wu, Ph.D., a scientist at NIH's National Institute of Neurological Disorders and Stroke. "Like many scientists we thought SNAREs were only involved in fusion."

Every day almost 100 billion nerve cells throughout the body send thousands of messages through nearly 100 trillion communication points called synapses. Cell-to-cell communication at synapses controls thoughts, movements, and senses and could provide therapeutic targets for a number of neurological disorders, including epilepsy.

Nerve cells use chemicals, called neurotransmitters, to rapidly send messages at synapses. Like pellets inside shotgun shells, neurotransmitters are stored inside spherical membranes, called synaptic vesicles. Messages are sent when a carrier shell fuses with the nerve cell's own shell, called the plasma membrane, and releases the neurotransmitter "pellets" into the synapse.

SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) are three proteins known to be critical for fusion between carrier shells and nerve cell membranes during neurotransmitter release.

"Without SNAREs there is no synaptic transmission," said Dr. Wu.

Botulinum toxin, or Botox, disrupts SNAREs. In a study published in *Cell Reports*, Dr. Wu and his colleagues describe how they used Botox and similar toxins as tools to show that SNAREs may also be involved in retrieving message carrier shells from nerve cell membranes immediately after release.

To study this, the researchers used advanced electrical recording techniques to directly monitor in real time carrier shells being fused with and retrieved from nerve cell membranes while the cells sent messages at synapses. The experiments were performed on a unique synapse involved with hearing called the calyx of Held. As expected, treating the synapses with toxins reduced fusion. However Dr. Wu and his colleagues also noticed that the toxins reduced retrieval.

For at least a decade scientists have known that carrier shells have to be retrieved before more messages can be sent. Retrieval occurs in two modes: fast and slow. A different group of molecules are known to control the slow mode.

"Until now most scientists thought fusion and retrieval were two separate processes controlled by different sets of molecules", said Dr. Wu.

Nevertheless several studies suggested that one of the SNARE molecules could be involved with both modes.

In this study, Dr. Wu and his colleagues systematically tested this idea to fully understand retrieval. The results showed that all three SNARE proteins may be involved in both fast and slow retrieval.

"Our results suggest that SNAREs link fusion and retrieval," said Dr. Wu.

The results may have broad implications. SNAREs are commonly used by other cells throughout the body to release chemicals. For example, SNAREs help control the release of insulin from pancreas cells, making them a potential target for diabetes treatments. Recent studies suggest that SNAREs may be involved in neurological and psychiatric disorders, such as schizophrenia and spastic ataxia.

"We think SNARES work like this in most nerve cell synapses. This new role could change the way scientists think about how SNAREs are involved in neuronal communication and diseases," said Dr. Wu.

More information: Xu J et al. "SNARE proteins synaptobrevin, SNAP-25 and syntaxin are involved in rapid and slow endocytosis at synapses." *Cell Reports*, May 2, 2013. DOI: 10.1016/j.cellrep.2013.03.010

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