

RESEARCH NEWS

SEPTEMBER 23, 1998

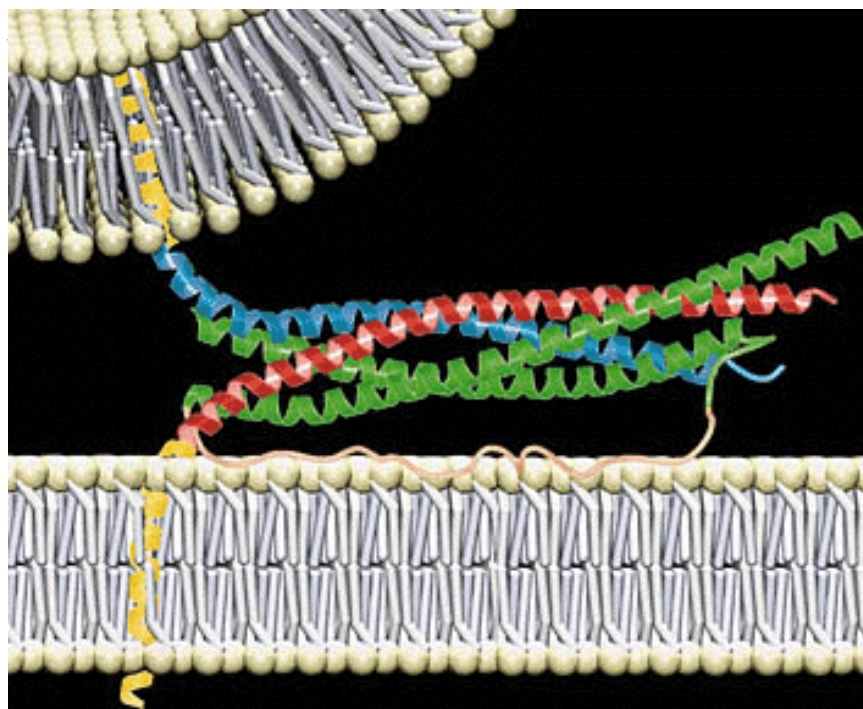


Image Title: A computer-generated model illustrates a possible function of SNARE proteins as they join two membranes. The top (curved) membrane represents part of a vesicle filled with neurotransmitters. The bottom (flat) membrane represents the target membrane of the pre-synaptic neuron. One could imagine that the close juxtaposition of the two membranes leads to membrane fusion, says HHMI investigator Axel T. Brunger. - Bryan Sutton, Kathy Reilly, Axel T. Brunger (HHMI at Yale University), Lothar Esser (HHMI at University of Texas Southwestern Medical Center, Dallas)

The classic image of communication between brain cells shows a neurotransmitter crossing the synapse and binding to receptors on the surface of a neighboring neuron. Yet, scientists have had only a murky picture of the events within the secreting neuron that trigger this neurotransmitter release.

Now, a group of researchers led by Axel T. Brunger, a Howard Hughes Medical Institute (HHMI) investigator at Yale University has deciphered and produced the first glimpses of the molecular machinery that propels neurotransmitters into the synapse. The key players are a family of proteins called SNAREs (S oluble N SF A ttachment protein RE ceptor). These proteins haven't changed much through evolution; SNAREs play a similar

role in the secretions of even primitive life forms like yeast.

In neurons, the merging of these mostly amorphous proteins into a highly structured and charged complex precipitates neurotransmitter release. Formation of the complex fuses vesicles with the cell membrane, spewing the neurotransmitter into the synapse. Such vesicle fusion occurs millions of times daily in each of the human brain's 100 billion neurons. So understanding vesicle fusion promises to shed light on processes like learning and memory, and may lead to improved treatments for brain disorders.

"It's sort of like merging two soap bubbles into one, but hardly that simple," explained R. Bryan Sutton, an HHMI associate in Brunger's laboratory. Sutton, Brunger and their colleagues report the elucidation of the synaptic fusion complex's intricate molecular structure in the September 24, 1998, issue of *Nature*.

The researchers used ultra-bright x-ray radiation from a synchrotron facility funded by the U.S. Department of Energy to illuminate the tiny protein crystals and determine the shape of the complex, atom-by-atom. They then created computer reconstructions that provide clues about how this pivotal protein may accomplish its mission.

Within the neuron, vesicles fill up with neurotransmitters, such as dopamine or serotonin. They then travel out into the neuron's extensions (axons), where they dock at the membrane and await an electrochemical signal to merge. At this moment the SNAREs form a complex.

Like other known fusion mechanisms, such as those used by viruses to infect cells, synaptic fusion employs a protein agent to meld two membranes. But unlike viral mechanisms, in which the fusion protein simply changes its shape, the very assembly of the synaptic fusion protein itself leads to the union of vesicle and cell membrane.

This assembly likely begins when two SNARE proteins in the cell's membrane, SNAP-25 and syntaxin, join together, Brunger says. This two-part complex is then joined by a third protein from the vesicle, synaptobrevin, in a configuration that sets up electrical and chemical forces that could promote membrane fusion. In addition, highly flexible helical structures in the complex, prone to twisting and bending, could cause strains that physically deform fatty layers within the two membranes, allowing them to mix. The complex's highly grooved surface, with distinct electrically and chemically polarized regions, could also be important for fusion and for the binding of regulatory factors affecting neurotransmission, say the researchers.

"The complex may act sort of like a winch to drive the vesicle down into the neuron's membrane," said Brunger. "Diseases such as tetanus and botulism take advantage of the fusion machinery by attacking these ties between neurotransmitter-filled vesicles and the neuron's membrane, effectively cutting the winch cable and causing neurological symptoms."

Advances in knowledge about the protein complex's structure could be of potential use in designing new medications for disorders of brain function, suggests Brunger.