How Do Neurons Communicate?

The answer is surprisingly elusive—and the subject of intense debate

BY KAREN A. FRENKEL

WE SAY something is "rocket science" when it is stunningly complex. But perhaps "neuroscience" would be a more apt metaphor—the more we learn about the brain, the more new questions arise. Case in point is a seemingly simple question: How do brain cells communicate? We know they use chemicals to send messages to one another. But exactly how do neurons release these neurotransmitters and then ready themselves to send out another rapid-fire message?

This operation takes place on a vanishingly small scale—scientists cannot actually watch the process, so they have to rely on less direct measures to determine what is going on. And because such data can often be interpreted in multiple ways, a controversy about neurotransmitter release has persisted for decades. Recent advances in laboratory techniques have escalated the debate, and the promise of finally understanding this basic cellular mechanism has set the stakes high. The answer is vital because the chemicals in our brain are implicated in everything from thought and emotion to mental illness, addiction and disease.

We already know much about the journey of a neurotransmitter. Take, for example, dopamine: Within each neuron, the chemical is contained in vesicles, small balloonlike sacs that transport material throughout the cell. When a vesicle gets an electrical signal, it carries the dopamine to the cell wall and releases it into the synapse, the space between neurons. In dopamine's case, the signal could be an electrical impulse generated by your taste buds after they receive a morsel of chocolate cake. The signal causes the vesicle to release its dopamine load, which floats in the synapse until it is detected by other neurons that receive the message, "This is pleasurable!"

Do neurons release their chemical messengers with a brief kiss?

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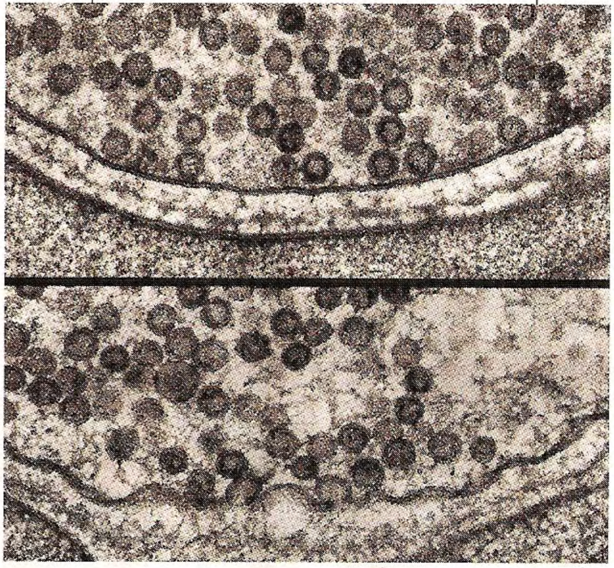
But what happens to a vesicle after it dumps its dopamine? This is where the debate comes in. With a finite number of vesicles, how do cells rapidly respond to subsequent impulses? Scientists have proposed two main opposing mechanisms for vesicle recycling, much like the two primary options available for recycling glass bottles. The fast way is to leave the bottles intact and simply refill them. The slower method involves completely melting down the bottles and making new ones. In cells, the big question is, Are vesicles ever recycled the fast way? That is, can they briefly touch the cell wall, release their contents and then disengage while retaining

> (“Opponents have **moved the goalposts** from whether ‘kiss and run’ exists or not to how prevalent it is,” one expert says.)

their shape? Or are vesicles always completely absorbed into the cell wall and then reformed later?



In cells, neurotransmitters are contained within vesicles, which appear as small black circles in this electron micrograph. The bottom panel shows vesicles fully collapsing into the cell wall as they release their contents into the surrounding space.

JOHN E. HEUSER *Washington University in St. Louis*

Kiss and Run

When scientists first began isolating vesicles and studying them, it was thought that these storage containers always completely fused with the cell wall, were broken down, and then reassembled later at a kind of cellular bottle factory. In 1961 researchers found that vesicles were coated with a protein. In 1973 biophysicists John E. Heuser, now at Washington University School of Medicine, and Thomas S. Reese of the National Institutes of Health found this protein to be an essential player in vesicle reconstitution. Two years later the protein was purified and named clathrin. Clathrin-aided assembly is now considered the classical model of vesicle fusion, but it turns out to be rather slow. Researchers can measure how long vesicle recycling takes by monitoring the cell wall’s ability to store electrical charge, or its capacitance. When a vesicle collapses into the cell wall, the cell’s capacitance increases, and when the vesicle is reconstituted and breaks away again the capacitance returns to normal—and the entire process takes about 30 seconds.

Half a minute seems an eternity in the context of the nervous system, which must react and respond to dozens of stimuli every second. In 1973 biologist Bruno Ceccarelli first proposed a quick recycling method, dubbed “kiss and run,” to account for fast transmitter release and rapid firing of synapses in frogs. Kiss and run also seemed to explain static images captured by electron microscopy that showed a vesicle at a cell wall with only a narrow passage opening into the synapse—it did not appear that the vesicle was in the process of completely collapsing. Over the years, more sophisticated experiments have suggested that kiss and run accounts for at least some, if not all, vesicle recycling events. Many neuroscientists, including Richard W. Tsien of Stanford University, use fluorescent dye to track the movement of vesicles in single neurons. If a vesicle fully collapsed after unloading its contents, the dye would be expected to dissipate into the synapse. Tsien showed that only some fluorescent markers dispersed, suggesting that the vesicle remained intact after releasing its cargo—consistent with the kiss-and-run scenario.

But others have found exceptions using this and similar dye techniques, and they doubt kiss and run’s existence. Timothy A. Ryan of Weill Cornell Medical College thinks the evidence is ambiguous at best: “The data can be interpreted in other ways that don’t necessarily imply kiss and run.” He cautions against inventing a mechanism to explain observations of a very rapid neuronal response.

Most researchers, however, are starting to accept that both mechanisms probably exist. “It may be that vesicles undergo kiss and run on their way to an eventual full-collapse event,” Tsien says. Ling-Gang Wu of the NIH recently measured electrical activity in a brain center for auditory processing in rats and found that kiss and run happened in 3 to 17 percent of recycling events. Kiss-and-run doubter Ryan points out that Wu is the first kiss-and-run proponent who admits that it occurs in a minority of events—an interpretation, Tsien says, that indicates the debate is no longer about kiss and run’s existence. “Opponents have moved the goalposts from whether it exists or not to how prevalent it is. We happily accept their implicit concession and are willing to debate how important it is,” Tsien says.

Although most experts do not feel that this debate will be over soon, they agree on one thing—in the process of trying to sort out the details of vesicle recycling, we are sure to learn a great deal about the way neurons work. Pinpointing exactly how neurotransmitters are created and how vesicles transport and release them could lead the way to new treatments for depression, Parkinson’s disease, autism and epilepsy, to name just a few neurotransmission-related disorders. And that kind of knowledge is the real goal. M

(Further Reading)

◆ **Curbside Recycling at the Synapse.** Kendall Powell in *Journal of Cell Biology*, Vol. 170, No. 2, page 166; 2005.