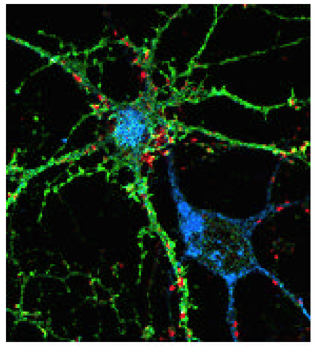
HHMI news
HOWARD HUGHES MEDICAL INSTITUTE

Researchers continue to learn more about the location and function of specific proteins (in green) that anchor signalling molecules in place in neurons.



Protein Studies Reveal Sophisticated Control of Nerve Communication

July 2, 1999 —With their discovery of a curious brain protein, named for a Chinese breakfast noodle, a team of HHMI investigators have provided a new understanding of just how exquisitely nerve cells control the electrical impulses they use to communicate with one another.

The protein yotiao (pronounced "YOH-tee-ow") anchors itself on the inner membrane of neurons in the hippocampus, a small brain region associated with learning and memory. Like other anchoring proteins, yotiao is an organizer whose purpose is to corral particular enzymes or other molecules that govern cell functions into specific "compartments" or pools within a cell. Yotiao itself is somewhat unusual in that it binds not one but two kinds of enzymes, both of which help regulate electrical signals that pass from neuron to neuron.

But "the really cool thing about yotiao," explained HHMI investigator John D. Scott, is that it holds the enzymes right next to their site of action — a crucial type of receptor known as N-methyl-D-aspartate (NMDA) receptors. NMDA receptors nestle in the specific part of the nerve cell membrane where neurons communicate chemically with each other across a tiny gap known as a synapse. They are the principal channels through which positively charged calcium ions stream into the nerve cell. The rapid inflow of calcium and outflow of another ion, potassium, generates an electrical nerve signal.

"This is one of the first times, if not the first, that we've seen an anchor protein that physically attaches not only to signaling enzymes but also to their receptor," said Scott, whose laboratory is at the Vollum Institute of Portland's Oregon Health Sciences University. "That means the receptor has everything it needs absolutely at the right place, ready for action whenever it needs it.

"We've known that the cell is not just a bag of enzymes floating around," he continued. "But yotiao tells us that its signaling control is much, much more sophisticated and precise than we thought."

Scott and other members of his team, including Lorene Langeberg and Iain Fraser, collaborated with members of HHMI investigator Morgan Sheng's laboratory at the Massachusetts General Hospital, describe their findings in the July 2, 1999 issue of the journal *Science* .

The story of yotiao's discovery began in the early 1990s, when

Fraser isolated a small piece of DNA. "We had very little idea what it was," said Scott. But a better picture began to emerge as postdoctoral researcher Ryan Westphal with help from graduate student Neal Alto gradually isolated overlapping pieces of DNA, and regions of the sequence began to look familiar. That recognition led Scott and his team to their eventual identification of yotiao.

Since the early 1990s, Scott has focused his research on the process by which chemical signals from outside a cell are transported through the nerve cell membrane to particular locations within the cell, where they exert their biological effect. He is particularly interested in one such signaling pathway that activates an enzyme called cAMP-dependent protein kinase (PKA), and how nerve cells organize specialized pools of PKA so that these pools will be ready for instant use.

As it turns out, PKA is one of the two enzymes that yotiao holds near the NMDA receptors. Whenever the anchor protein releases it, PKA stimulates the channels to allow in more calcium ions.

Yotiao's other closely held enzyme, called type 1 protein phosphatase (PP1), has the opposite effect: it downregulates NMDA receptors, or slows the flow of ions. Steven Tavalin, an HHMI associate in Scott's laboratory, has shown that PP1 is also at work even while it is still bound to yotiao. The net effect, then, of yotiao and its two enzymes is that calcium is prevented from entering neurons at rest.

That constant blockade may sound curious at first, Scott said, but he believes it's an important feature of signaling control. "Think of an electrical signal traveling along a nerve, how rapidly the neuron needs to fire and then get back to the resting state," he pointed out. "PP1 helps the neuron reach that resting state quickly so that it is ready to help you do or think something else almost instantly."

In learning a new skill, for example, nerve cells in the brain's hippocampus begin to fire off electrical impulses, storing one step of the instructions after another for later recall. One stimulated neuron tells the next in line to fire by releasing chemical messengers called neurotransmitters across the synaptic gap, which serves as a sort of firewall against short-circuits.

The neurotransmitters — in this case, glutamate and cyclic AMP — act as on-off switches for the electrical impulses. They bind to and activate their targets on the receiving neuron, which are none other than NMDA receptors. Calcium ions flood the cell, and the corresponding change in electrical state causes that neuron in turn to fire.

And if neurotransmitters are the switches, said Scott, yotiao's enzymes PKA and PP1 are the volume controls. Because of their proximity to the channel, they can instantly enhance or dampen the level of ion flow to ensure proper firing and rapid recovery.

photo: Lorene Langeberg

Top of Page...