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# At the synapse: Gene may shed light on neurological disorders

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In our brains, where millions of signals move across a network of neurons like runners in a relay race, all the critical baton passes take place at synapses. These small gaps between nerve cell endings have to be just the right size for messages to transmit properly. Synapses that grow too large or too small are associated with motor and cognitive impairment, learning and memory difficulties, and other neurological disorders.

In a finding that sheds light on this system, researchers at the University of Wisconsin-Madison describe a gene that controls the proper development of synapses, which could help explain how the process works and why it sometimes goes wrong.

Reporting today in the journal *Neuron*, a team of geneticists in the College of Agricultural and Life Sciences reveal the role of a gene in fruit flies called "nervous wreck" that prevents synapses from overgrowing by damping the effects of a pro-growth signal. Mutations in a human version of "nervous wreck" have been linked to a severe genetic developmental disability, and these findings may eventually help scientists develop treatments for this and other neurological disorders.

"The precise regulation of synaptic growth — not too much and not too little — is a complex biological process," says Kate O'Connor-Giles, a postdoctoral fellow in the genetics department who led the study. "We really need to have a deep understanding of how all the factors involved are working together to develop rational treatments for neurological

disorders associated with aberrant synaptic growth."

That's no small task. The brain is the most complex organ in the body, containing a hundred billion nerve cells that branch out and make trillions of connections to other neurons, muscle cells and other cell types. Although an estimated 50 million Americans have some kind of neurological disorder, in the majority of cases the underlying cause is unknown. Improper synaptic growth may explain a portion of these unknown cases.

To crack this complex system, O'Connor-Giles studies a particular type of synapse in fruit flies, known as the neuromuscular junction, which is relatively easy to examine and closely resembles the synapses found in the central nervous system of humans. She works with a particular kind of fly that is unable to produce functional Nervous wreck protein, one of a collection of mutant flies engineered more than 20 years ago by UW-Madison geneticist Barry Ganetzky, in whose laboratory the study was completed with the help of researcher Ling Ling Ho. This collection has been the source of many seminal discoveries in brain science over the years.

Using genetic, biochemical and imaging techniques, O'Connor-Giles showed that the "nervous wreck" protein appears to be part of an important protein complex that helps regulate the density of certain receptors on the surface of the nerve cell at the synapse. In particular, the new findings suggest that the protein complex decommissions receptors that respond to pro-growth signals coming from the well-studied BMP signaling pathway. When the protein complex is working properly, it moves the receptors back inside the nerve cell — where they can no longer receive and respond to the pro-growth signal — at the appropriate time.

"'Nervous wreck' and (the other proteins in the complex) work together

to attenuate a positive growth signal," says O'Connor-Giles. "So when it's time for synaptic growth to stop, they are the proteins that ensure the neuron stops listening to the positive growth signal and stops growing. When 'nervous wreck' is absent, you get synapses that are much too large." Problems with other proteins in the complex also lead to synaptic overgrowth in fruit flies and, O'Connor-Giles predicts, may contribute to developmental disabilities in humans as well.

Although her work was done in synapses undergoing initial formation, these findings likely apply to adult brain cells, too. Inside fully formed brains, neural connections grow and change over time in response to experiences, a process called plasticity.

"The presumption is that the same mechanisms that are at play during the initial formation of synapses are then recruited later in life when these synapses need to be modified in response to experience or injury," says O'Connor-Giles. "So by understanding the initial development of synapses, we may also be getting at the molecular mechanisms underlying plasticity."

These findings add to the big picture of how synaptic growth works, a picture that in the long run will help scientists develop treatments for various neurological disorders.

"Being able to manipulate synaptic growth is going to be crucial for treating traumatic spinal chord injuries," says O'Connor-Giles. "It's also going to be important for treating a broad array of other disorders, including epilepsy and developmental disabilities."

Source: University of Wisconsin-Madison