Location, location, location

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Neuroscientists at Georgetown University Medical Center have solved a mystery that lies at the heart of human learning, and they say the solution may help explain some forms of mental retardation as well as provide clues to overall brain functioning.

Researchers have long puzzled over why a gene known as brain-derived neurotrophic factor (BDNF), which is crucial to the ability of neurons in the hippocampus to grow and connect to each other – forming the basis of memory and learning – produces two different transcripts, which then each fabricate identical proteins.

In the July 11 issue of *Cell*, the scientists report the answer, and it has to do with transportation. They found that the longer of the two transcripts (messenger RNAs, or mRNAs) include extra sequences that "motor" molecules attach to, in order to move the information far away from the nucleus of the cell and toward the long, tree-like branches of the nerve cell known as dendrites. There, protein-synthesizing machines use that mRNA to produce protein that helps small protrusions (called dendritic spines) on these dendrites grow.

The shorter of the mRNAs are also moved from the nucleus into the cytoplasm of the neuron, but they do not need to be transported to dendrites. These transcripts produce an identical protein, but in this case, investigators believe they help the axon, the long cable-like body of a neuron, grow.

Learning occurs when both axons and dendritic spines grow and touch

each other, forming connections, and existing connections are strengthened. The scientists' findings provide a critical understanding of how dendritic spines grow and mature, but this understanding may be more broadly applied.

That's because as exciting as the findings are for understanding the function – and dysfunction - of BDNF as it relates to human learning, they also are relevant for other genes and proteins, says the study's lead investigator, Baoji Xu, Ph.D., an assistant professor in the Department of Pharmacology at Georgetown.

"The fascinating thing is that many genes produce multiple transcripts for the same protein – and no one has known why," he says. "So what we found here is likely very applicable to other genes. It reveals a mechanism for differential regulation of subcellular functions of proteins."

In this study, Xu and his research team, which included investigators from the National Institute of Child Health and Human Development (NICHHD), Emory University, and the University of Colorado, looked at why a neuron needs two "species" of BDNF mRNAs.

The gene produces a growth factor that makes neurons grow, and is vital to initial development of the brain; mice born without BDNF have developmental deficits and soon die. BDNF is also secreted by neurons in adult brains when needed, and that is usually when synaptic junctions between neurons require strengthening, a condition known as "synaptic plasticity" that underlies memory and learning. "If BDNF is deleted in an adult animal's brain, the animal will struggle to learn new tasks," Xu says.

Scientists had found that protein translation occurs in dendrites, and they believed that this protein production was important for synaptic

plasticity, "but it has been difficult to study local protein synthesis only in dendrites," Xu says. "When you change protein synthesis in dendrites, you also affect protein production in other parts of the neuron."

To solve that problem, Xu and the scientists managed to create mouse mutants in which the long BDNF mRNA variant is converted to the shorter mRNA form. They found that in these mice, dendritic spines form normally, but do not mature properly and aren't "pruned" as they need to be. "This process is important for the normal function of the brain. Without it, the mice can't refine neuronal connections in response to learning," he says.

Some people diagnosed with mental retardation suffer from the same problem, Xu adds. "At a certain stage of development, maturation of dendritic spines is frozen. For example, in Fragile X Syndrome, there are too many immature dendritic spines.

"What we see in our mutant mouse and in Fragile X is similar," he says. "If we could find a way to increase BDNF synthesis in dendrites, it may be helpful to people with mental retardation.

"That, of course, is just a theory, but now that we understand the function of these two different mRNAs, we can begin to explore what issues their dysfunction causes in humans," Xu says.

Source: Georgetown University