MedicalXpress

Protein linked to Alzheimer's disease doesn't act alone

June 10 2009

A team of U.S. investigators led by neuroscientists at Georgetown University Medical Center (GUMC) are steadily uncovering the role that amyloid precursor protein (APP) - the protein implicated in development of Alzheimer's disease - plays in normal brain function. In the June 10 issue of the *Journal of Neuroscience*, they discovered that APP interacts with another protein known as Reelin to promote development of abundant connections between brain neurons.

Reelin, named for mice that "reel" around when they don't have the protein, has been thought to be involved in stimulating growth of neuronal dendrites - the branching projections that transmit signals to other neurons. It also has been implicated in some brain disorders, but up until now, little was known about how Reelin interacts with APP.

Researchers say that showing that APP and Reelin work together doesn't have immediate implications for therapeutic treatment of Alzheimer's disease in humans, but they say the work helps provide the background necessary to understand finally why a brain veers toward the progressive memory loss seen in this devastating disease, which impacts 5.3 million people yearly in the U.S..

"In the last 20 years we have made tremendous progress in understanding how APP can become toxic. But I think the flip side is equally interesting: Why does APP even exist in the brain? We are only now just beginning to figure that out," says the study's senior author, G. William Rebeck, PhD, associate professor in the Department of Neuroscience at

GUMC.

What has long been known is that mutations in the gene that produces APP causes an inherited form of Alzheimer's disease, and that APP is cut by enzymes into shorter pieces of protein known as amyloid beta (A-beta) when it is presumably no longer needed in neurons. But certain forms of A-beta - those that are cut to one particular length - stick to one another to form the plaque found in the disease. A-beta cut into other sizes don't bind to one another.

"We understand how the protein is cut to make A-beta and we are even testing drugs to counteract this errant slicing," Rebeck says. "But it might be more efficient to know what APP is doing in the brain, and approach therapy from that standpoint."

Rebeck and his GUMC collaborator, Hyang-Sook Hoe, PhD, the first author of this study, have performed experiments in which they over-expressed APP in neurons in laboratory culture or reduced their levels. They then measured changes in the normal functioning of the neurons.

Those results suggested that APP actually acts like a structural bridge to stabilize the synaptic space between two dendrites in neurons. Neurons, aligned in circuits, send chemical signals to each other via axons and dendrites to control systems in the body. The presynaptic neuron releases neurotransmitters to the postsynaptic neuron, and APP appears to promote the structure of these synapses, Rebeck says. "APP is important to keep synapses stable and to have the receptors in the right place and working. When communication between these dendrites isn't necessary anymore, APP is cut into fragments to sever the connection."

In this study, Rebeck, Hoe and their collaborators looked at Reelin and APP, because Reelin had previously been shown to be important in growth of the dendrites.

In laboratory neurons, they found that adding Reelin increased the number of neurite connections (dendrites and axons) that these cells send out from the cell body in order to communicate with each other, but they also discovered that these branches did not grow if APP was not available. And in mice experiments, they found that animals born without APP had increased levels of Reelin, and mice that overproduced APP had less Reelin. "This suggests that two molecules are necessary for a single function, and if you get rid of one of them, the other increases in order to drive that function," Rebeck says.

Along with his other findings, Rebeck says this study now suggests that APP is not only important in stability of dendrites but also in their formation and maintenance.

Source: Georgetown University Medical Center (news : web)