Protein 'Tweek' rare but critical in synaptic process

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(July 29, 2009) - Recycling is a critical component in the process of transmitting information from one neuron to the next, and a large protein called Tweek plays a critical role, said an international consortium of researchers led by Baylor College of Medicine in a report in the current issue of the journal *Neuron*.

Fruit flies that lack the protein, named for the over-caffeinated character in the cartoon South Park, shake in a hyperactive manner, said Dr. Hugo Bellen, professor of molecular and human genetics at BCM, and senior author of the report. "Loss of this protein causes endocytic defects," he said.

As part of the process of transmission of information from one neuron to another, tiny bubbles called vesicles transport chemicals called neurotransmitters to the neuron's tip called the synapse. Once there, they fuse to the cell's membrane in a process called exocytosis. The extra membrane is then captured in a process called endocytosis and recycled to form a new vesicle to enable the next cycle of release.

Electron microscopy, which allowed the researchers to see the terminals of the synapse in great detail, showed flies that lacked the tweek gene were largely devoid of vesicles. This showed that the protein was important for endocytosis, but its role in the process was still unclear, said Bellen, also director of BCM program in developmental biology and a Howard Hughes Medical Institute investigator.

Cloning the gene was difficult because it had been misannotated or mislabeled in almost all species. Eventually, Bellen and his colleagues found that it was more than three times as big as previously thought. When they initially tried to do a form of gene therapy to cure the flies of the endocytotic defect by supplying tweek-deficient neurons with Tweek protein, the procedure failed.

Eventually, they continued to look in other spots and found that the gene was interrupted by other genes but it was actually made up of more than 5,000 amino acids. When Bellen and colleagues supplied the full, newly labeled Tweek protein to tweek mutant neurons, the endocytic defects observed were reversed. The gene is found in almost all species, indicating that it is important in many organisms.

Bellen and his colleagues knew that phosphoinositide lipids and in particular one known as PI(4,5)P2 play important roles in regulating cellular processes. PI(4,5)P2 is concentrated in the plasma membrane of most cells, including neurons. They found that cells lacking tweek also had low levels of PI(4,5)P2.

When they manipulated the cell's activity to increase the levels of PI(4,5)P2, they also suppressed the defect in endocytosis of the vesicles, said Bellen.

"We concluded that the protein Tweek plays a role in making sure the right amounts of PI(4,5)P2 are there so that other proteins can be recruited to the endocytic zone," said Bellen.

The finding is only the beginning of the Tweek puzzle, he said. The protein occurs in minute quantities in the cell and is difficult to locate, he said.

Source: Baylor College of Medicine (news : web)