Autism-related Proteins Control Nerve Excitability, Researchers Find

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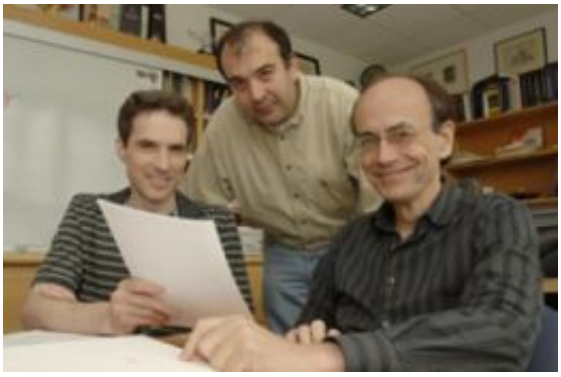

A research team that included (from left) Drs. Jay Gibson, associate professor of neuroscience, Ege Kavalali, associate professor of neuroscience and physiology, and Thomas Südhof, chairman of neuroscience, has discovered that two proteins implicated in autism control the strength and balance of nerve-cell connections. Credit: UT Southwestern Medical Center

Two proteins that are implicated in autism have been found to control the strength and balance of nerve-cell connections, researchers at UT Southwestern Medical Center have found.

The proteins, which serve to physically link nerve cells together, were discovered more than a decade ago by UT Southwestern scientists, but their function has been unclear.

In the new study, which appears in the June 21 edition of the journal

Neuron, the researchers found that one protein increases the excitability of nerve cells, while the other inhibits cell activity. Most importantly, these effects depended on how often the cells fired.

The activity levels of neurons play a vital role during normal brain development in children. Active connections become stronger and survive to adulthood, while inactive ones disappear.

Autism is believed to involve an imbalance of excitatory and inhibitory nerve connections, a theory supported by this study, said Dr. Ege Kavalali, associate professor of neuroscience and physiology at UT Southwestern and an author of the paper.

“Mutations in these proteins have recently been linked to certain varieties of autism,” Dr. Kavalali said. “This work provides clear insight into how the proteins function. We can never design a therapeutic strategy without knowing what these mutations do.”

The proteins are called neuroligin-1 and neuroligin-2. At the junction of two nerve cells, called a synapse, the proteins stick out from the surface of the cell that receives a signal from the first cell. The neuroligins bind to other molecules on the first cell, thus creating a physical bridge across the synapse.

In some cases, a signal from the first cell excites the second cell, while at other synapses, the signal inhibits the second cell.

Infants are born with far more synapses, both excitatory and inhibitory, than adults end up with. In a process called pruning, synapses that are inactive during development disappear while active ones proliferate.

In the current study, the researchers genetically manipulated rat neurons in culture so that the cells created too much neuroligin-1. The cells

developed twice the usual number of synapses, raising the question of whether neuroligin-1 contributed to the formation of additional synapses or contributed to the failure of existing ones to be pruned. Similar tests showed that excess neuroligin-2 also led to more synapses, but in this case, the synapses were inhibitory.

When the cells that overexpressed either neuroligin-1 or neuroligin-2 were chemically prevented from firing, they did not develop excess synapses, despite the presence of the respective proteins.

Together, the tests indicate that nerve cells with excess neuroligins developed extra synapses only when those cells are allowed to fire.

“The two neuroligins have complementary roles under normal conditions, with neuroligin-1 increasing the excitatory links between nerve cells, and neuroligin-2 increasing the number of inhibitory links, creating a balance,” Dr. Kavalali said. “In both cases, the neuroligins are not necessary for creating the synapses, but they have a role in determining which synapses make it in the long run, and thus setting up how responsive the nerve cells are.”

Because mutations in neuroligins occur in some people with autism spectrum disorders, the researchers also engineered a mutation in neuroligin-1 comparable to one observed in humans and introduced the mutant neuroligins into rat neurons.

“The nerve cells carrying the mutant neuroligin showed a dramatic decrease in the number of synapses and a more than twofold decrease in excitability, showing that the mutation interferes with the stability of the synapses,” Dr. Kavalali said.

Source: UT Southwestern Medical Center