Caltech scientists point to link between missing synapse protein and abnormal behaviors

28.11.2011 - Although many mental illnesses are uniquely human, animals sometimes exhibit abnormal behaviors similar to those seen in humans with psychological disorders. Such behaviors are called endophenotypes. Now, researchers at the California Institute of Technology (Caltech) have found that mice lacking a gene that encodes a particular protein found in the synapses of the brain display a number of endophenotypes associated with schizophrenia and autism spectrum disorders.

The new findings appear in a recent issue of the Journal of Neuroscience, with Mary Kennedy, the Allen and Lenabelle Davis Professor of Biology at Caltech, as the senior author.

The team created mutations in mice so that they were missing the gene for a protein called densin-180, which is abundant in the synapses of the brain, those electro-chemical connections between one neuron and another that enable the formation of networks between the brain's neurons. This protein sticks to and binds together several other proteins in a part of the neuron that's at the receiving end of a synapse and is called the postsynapse. "Our work indicates that densin-180 helps to hold together a key piece of regulatory machinery in the postsynaptic part of excitatory brain synapses," says Kennedy.

In mice lacking densin-180, the researchers found decreased amounts of some of the other regulatory proteins normally located in the postsynapse. Kennedy and her colleagues were especially intrigued by a marked decrease in the amount of a protein called DISC1. "A mutation that leads to loss of DISC1 function has been shown to predispose humans to development of schizophrenia and bipolar disorder," Kennedy says.

In the study, the researchers compared the behavior of typical mice with that of mice lacking densin. Those without densin displayed impaired short-term memory, hyperactivity in response to novel or stressful situations, a deficit of normal nest-building activity, and higher levels of anxiety. "Studies of mice with schizophrenia and autism-like features have reported similar behaviors," Kennedy notes.

"We do not know precisely how the molecular defect leads to the behavioral endophenotypes. That will be our work going forward," Kennedy says. "The molecular mechanistic links between a gene defect and defective behavior are complicated and, as yet, mostly unknown. Understanding them goes to the very heart of understanding brain function."

Indeed, she adds, the findings point to the need for a better understanding of the interactions that oc-

cur between proteins at synapses. Studies of these interactions could provide information needed to screen for new and better pharmaceuticals for the treatment of mental illnesses. "This study really reinforces the idea that small changes in the molecular structures at synapses are linked to major problems with behavior," Kennedy says.