First animal model for studying schizophrenia

Scientists have created what appears to be a schizophrenic mouse by reducing the inhibition of brain cells involved in complex reasoning and decisions about appropriate social behaviour.

Findings by Medical College of Georgia scientists, published Dec. 28 in *PNAS*, elucidate the critical balan between excitation and inhibition of these cells that appears to go awry in schizophrenia. They also provide the first animal model for studying the disabling psychiatric disorder that affects about 1% of the populatio

"We believe the mouse, which exhibits some of the same aberrant behaviour as patients with this disorde will help identify better therapies," said Dr. Lin Mei, a developmental neurobiologist who directs MCG's Institute of Molecular Medicine and Genetics. "We are doing testing to see if antipsychotic drugs already o the market are effective in treating the mouse."

ErbB4 deleted

MCG scientists made the mouse by deleting a candidate gene for schizophrenia, ErbB4, from interneuron which are brain cells that help shower larger decision-making neurons, called pyramidal cells, with inhibitio

In their earlier work, they identified how ErbB4 and another candidate gene, neuregulin-1, work together to balance the activity of these pyramidal cells. They reported in Neuron in May 2007 that the two help keep a healthy balance between excitation and inhibition by increasing release of GABA, a major inhibitory neurotransmitter in the inhibitory synapses of the brain's prefrontal cortex. Seven years earlier, they showe the two also put a damper on excitatory synapses, communication points between neurons where the neurotransmitter glutamate excites cells to action.

To further test these findings, this time they altered the natural check and balance in cells directly involved with supplying pyramidal neurons with the inhibitor GABA. They did this by knocking out the ErbB4 gene in nearby chandelier and basket interneurons that supply GABA to pyramidal cells. "If we take out ErbB4 in these two interneurons, the neuregulin should have no effect because it can't promote GABA," Dr. Mei, Georgia Research Alliance Eminent Scholar in Neuroscience, said.

His postulation played out in the behaviour of the mouse, who exhibited schizophrenia-like behaviour including increased movement and impaired short-term memory. The scientists are still gathering data on the manic aspect of schizophrenia in their mice.

Knockouts take longer to learn

For example, both the normal and knockout mice learned they would find a food pellet in each arm of an eight-armed chamber but that if they went to the same arm for seconds, there were none. However, the knockouts took longer to learn and finish the task. Knockouts also spent a lot more time sniffing and snooping around and revisiting empty arms.

In another test, knockouts couldn't - or wouldn't - make the connection that a relatively low noise would be followed by a slightly louder one. When they treated the knockouts with diazepam, an anti-anxiety medication, they responded similarly to the normal mice: the first sound prepared them for the second.

Dr. Mei suspects that if he could look at the chandelier and basket interneurons in the prefrontal cortex of schizophrenics, he would also find something wrong with their usual role of sensing the need for the inhibit GABA and supplying it to the pyramidal cells. "In schizophrenia, the baseline of the excitatory neurotransmitter is probably high," he said.

Source: Medical College of Georgia