Check and balance for neuron activity provides insight into schizophrenia, seizures

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Two genes important for human development and implicated in cancer and schizophrenia also help keep a healthy balance between excitation and inhibition of brain cells, researchers say.

Neuregulin-1 and its receptor, ErbB4, promote inhibition at the site of inhibitory synapses in the brain by increasing release of GABA, a major inhibitory neurotransmitter, Medical College of Georgia researchers led by Dr. Lin Mei report in the May 24 issue of *Neuron*.

In 2000, a research team led by Dr. Mei showed that neuregulin-1 and ErbB4 also are at excitatory synapses, communication points between neurons where the neurotransmitter glutamate excites cells to action. Here, neuregulin-1 and ErbB4 suppress excitation.

"Right beside the place where the excitatory synapse can be activated, there is also something that can suppress it," says Dr. Mei, chief of developmental neurobiology at MCG. "Now we have identified another novel target of neuregulin-1 which is the inhibitory synapse."

Together the findings reveal a check and balance for brain cell activity managed by neuregulin-1 in the brain's prefrontal cortex, where complex reasoning and decisions about appropriate social behavior occur, he says.

They also provide new treatment targets for psychiatric diseases such as schizophrenia and neurological disorders such as epilepsy, researchers say.

The genes are both associated with schizophrenia, a disease that affects about 1 percent of the population, but the exact role of malfunctioning neuregulin-1 signaling was unclear.

"(Dr. Mei's) findings help explain how a gene that is potentially causative in disorders like schizophrenia and bipolar disorder relate to a neurotransmitter that is critical for explaining the cognitive deficits associated with the illness," says Dr. Daniel R. Weinberger, director of the Genes, Cognition and Psychosis Program at the National Institute of Mental Health in Bethesda, Md.

"What we have found is neuregulin-1 can regulate GABA release from these neurons and if the GABA is released here that may play a role in controlling the output of this neuron," Dr. Mei says, pointing to an illustration of pyramid-shaped neurons that looks like a high-tech switchboard with information coming in from all angles.

Pyramidal neurons get information from nearby interneurons, integrate it, then decide what message to move forward. "This pyramidal neuron receives inhibitory input and excitatory input, and neuregulin-1 can regulate both," says Dr. Mei.

They nicely balance input in most people, enabling folks to balance their checking accounts and suppress the urge to run naked down the street.

In 2006, University of Pennsylvania researchers reported in Nature Medicine an altered signaling pathway for neuregulin-1 and ErbB4 genes in the brains of schizophrenics. Dr. Mei's findings show that these factors associated with a schizophrenic brain have at least two places to act.

"There is a ton of evidence that when inhibitory synapses, such as GABA, go wrong, the symptoms of mice and rats look similar to those

of schizophrenia in people," he says.

Mounting evidence suggests that problems with the excitatory and inhibitory synapses regulated by neuregulin-1 result in other problems as well: Excess excitation results in mind-rattling seizures and excess inhibition in depression, as examples.

"If this neuron is too excited, people may get manic or have seizures," says Dr. Mei. "Patients with schizophrenia, for example, show symptoms that implicate alterations in inhibitory neurotransmission in addition to excitatory neurotransmission."

Dr. Mei co-authored a companion paper in Neuron with scientists at Cold Spring Harbor in New York that provides yet another link between neuregulin-1, its receptor ErbB4 and schizophrenia. It shows ErbB4 plays a key role in the maturation and plasticity of excitatory synapses and that normal synapse development is impaired by genetic defects in neuregulin-1 and ErbB4 signaling. The result is impaired function of the excitatory neurotransmitter, glutamate.

Now he wants to study disease processes in a neuregulin-1/ErbB4 knockout mouse and learn more about how neuregulin-1 mediates GABA release. Another key unknown is what regulates neuregulin-1.

Source: Medical College of Georgia

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