MedicalXpress

Discovery of mechanism that alters neural excitability offers window into neuropsychiatric disease

August 23 2016, by Jeff Hansen

Diseases such as epilepsy, neuropathic pain, anxiety, depression, drug addiction and Alzheimer's are all associated with changes in the excitability of brain neurons. University of Alabama at Birmingham researchers show, for the first time, that the well-known mechanism of gene expression control—dynamic changes in DNA methylation—is also involved in changes to the excitability of neural cells.

This suggests that DNA methylation changes that alter excitability may be a mechanism involved in neuropsychiatric disorders, and that the sites of such changes may offer a potential therapeutic target. The study was published today in *Science Signaling*.

Changes in DNA methylation in brain cells has been an extremely active research area since these epigenetic changes were shown to alter the expression of genes needed to form and maintain long-term memories. Until now, a mechanistic understanding of how DNA methylation might influence the intrinsic membrane excitability of neurons, or IME, was lacking.

IME is the responsiveness of a neuron to stimulation coming from signals received from other neurons. Above a threshold stimulus, the recipient neuron triggers an electrical wave, called an action potential, that speeds down the cell's axon to stimulate a downstream cell in the neural circuit. Such action potentials from the motor cortex of the brain,

for example, are the signals sent to muscles to initiate voluntary movement, such as pointing a finger.

The UAB researchers, led by corresponding author John Hablitz, Ph.D., professor and interim chair of Neurobiology, UAB School of Medicine, found that treatments that inhibit DNA methylation in cultured rat neocortical neurons caused an increase in the IME of those neurons, as shown by an increased frequency of a series of action potentials when the neurons were stimulated.

"This is a very significant change," Hablitz said. "If you compared the change in action potential to a light that is shining in your eyes, it would be like a weak light changing to a very bright light."

Various previous studies had shown that epigenetic remodeling of DNA by methylation or demethylation led to changes located in synapses, where one neuron communicates with another by chemical or electrical signals sent across a small gap. Hablitz and colleagues have now shown that epigenetic remodeling can also alter electrophysiological properties of an individual neuron.

Experimental details

The UAB researchers first showed that inhibition of DNA methyltransferases, or DNMTi, with the drug RG108 for 24 hours increased the IME of cultured rat cortical pyramidal neurons, as shown by current-clamp electrophysiology.

They then showed that the increase in excitability required enzymatic demethylation of the cytosine bases of the DNA and transcription. They also showed that neuronal activity was required for DNMTi-enhanced IME because inhibition of NMDA receptors on the neurons blocked DNMTi-enhanced IME. NMDA receptors are known to be involved in

weakening or strengthening synapses in neural connections, changes that are called synaptic plasticity, and in memory formation.

The UAB group also found that a specific molecular target, the SK family of ion channels, was involved in the enhanced excitability. A drug that specifically inhibits these channels produced a similar increase in IME as seen for DNMTi-enhanced IME.

"We are starting to understand the complexity of neuronal plasticity, and our findings suggest that both synaptic plasticity and the plasticity of intrinsic membrane excitability are involved," Hablitz said.

More information: J. P. Meadows et al, Dynamic DNA methylation regulates neuronal intrinsic membrane excitability, *Science Signaling* (2016). DOI: 10.1126/scisignal.aaf5642

Provided by University of Alabama at Birmingham