This Week in The Journal

New Genetic Insight into Neurodevelopmental Disease

Marta Vieira, Shixiao Peng, Sehoon Won, Eunhye Hong, Sara Inati et al.

(see article e0557232023)

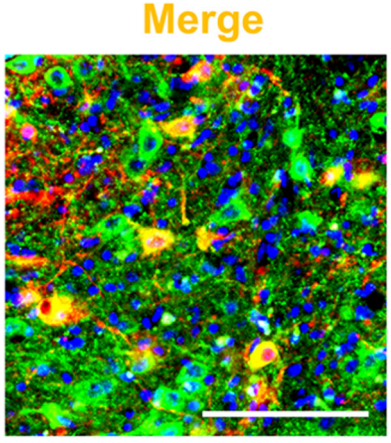
The glutamate *N*-methyl-D-aspartate (NMDA) receptor plays an important role in neuron development. When these receptors are dysfunctional, neurodevelopmental disorders can occur. To better understand the mechanisms that cause irregular NMDA receptor functionality, researchers study how receptor subunit mutations of different kinds affect synapses and behavior. In a male epileptic patient with severe language comprehension and communication deficits and behavioral changes, Vieira et al. identified a genetic variant that truncates, or shortens, the C-terminal domain of NMDA receptors. They followed up on this observation by exploring the effects of the missense variant on receptor function and trafficking in rat neuronal cultures. They found that, while it did not significantly alter the biophysical or pharmacological properties of the NMDA receptor, it impaired the ability of interacting proteins to bind the receptor, altered the localization of the receptor to synapses, diminished the number of dendritic spines on neurons, and reduced neuron activity. These findings suggest that this variant perturbs the contribution of the NMDA receptor to normal cell function through a change in localization and trafficking, providing new insight into the mechanistic underpinnings of neurodevelopmental disease.

A Novel Mechanism for Modulating Pain

Di Liu, Su-Wan Hu, Di Wang, Qi Zhang, Xiao Zhang, Hai-Lei Ding, and Jun-Li Cao

(see article e0869232023)

Chronic pain, or pain hypersensitivity, is a leading cause of disability worldwide. The dorsal raphe nucleus (DRN) contributes to the modulation of pain, but much is unknown about the discrete roles of the subsets of neurons residing in the DRN in pain sensation. Liu et al. identified a novel pain-regulating projection from the DRN to the ventral tegmental area (VTA). They found that chronic pain increased the activity of glutamatergic, but not serotonergic, DRN neurons innervating the VTA. Artificially activating this neuron population induced a pain-like response in mice, and artificially inhibiting it produced analgesic effects in mice experiencing chronic pain. The authors probed the circuitry further to discover that this group of DRN neurons regulated pain by innervating VTA neurons that target a region of the nucleus accumbens shell. They were able to manipulate this three-node pathway to bilaterally regulate pain behaviors. This work uncovers a novel circuit mechanism for pain sensation, thus pointing to potential novel treatment strategies.



For experiments demonstrating that serotonergic dorsal raphe nucleus (DRN) neurons innervating the VTA do not modulate pain, a cre-dependent channelrhodopsin (red) targeting serotonergic neurons (green) was injected into the DRN to artificially activate these neurons. In blue are cell bodies, stained with DAPI.

This Week in The Journal was written by Paige McKeon

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