This Week in The Journal

Extrasynaptic Kainate Receptors in the Hippocampal Hilus

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(see pages 2872–2884)

Hilar mossy cells (MCs) are part of the hippocampal circuitry that helps organisms detect locations, patterns and novel stimuli, and their dysfunction is implicated in epilepsy and depression. But researchers have much to learn about these enigmatic cells, including how MCs communicate with other hippocampal neurons such as dentate granule cells (GCs), with which they form reciprocal connections. Now Ramos, Lutzu, et al. discover the MCs use an unconventional mode of neurotransmission involving extrasynaptic ionotropic kainate-type glutamate receptors (KARs).

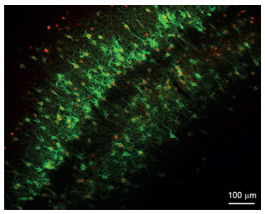
Mossy cells are strongly activated by a KAR agonist, and MC–GC synapses strongly resemble those between mossy fibers of GCs and hippocampal CA3 neurons, where kainate signaling is prominent. Previous work had hinted that kainate receptors were found at synapses between GC mossy fibers and MCs, but that they played only a minor part in excitatory neurotransmission there.

Here, the researchers made electrophysiological measurements from hippocampal slices from rats and mice. Bath applications of even submicromolar concentrations of kainic acid caused large excitatory currents and MC firing. The currents and firing were absent from neurons of mice lacking the KAR subunit GluK2. Surprisingly, they saw no evidence of GC–MC synaptic activation of KARs, in contrast to the robust KAR-mediated excitatory postsynaptic currents they saw at GC synapses onto CA3 neurons.

They next used immunostaining to find where GluK2/3 KAR subunits were located on MCs. Across the hippocampus, they saw intense punctate labeling in CA3 and more moderate, diffuse labeling in the hilus. Concordant with the electrophysiological findings, GluK2/3-positive puncta in the CA3 were colocalized with PSD-95, a postsynaptic protein marker, whereas labeling for KARs on MCs was sparser and nonsynaptic. Immunoelectron microscopy confirmed that GluK2 was absent from GC–MC synapses but present at GC–CA3 synapses.

Blockade of excitatory amino acid transporters (EATTs) halts glutamate reuptake and increases extracellular glutamate; this induced excitatory currents in MCs, indicating activation of extrasynaptic receptors by ambient glutamate. Further experiments suggested that ambient glutamate probably does not activate KARs under physiological conditions thanks to tight regulation by EATTs.

Although its role remains uncertain, this newly discovered kainate signaling may lead to a better understanding of MCs as well as of wider hippocampal circuits. The phenomenon also represents a departure from conventional understanding of extrasynaptic signaling, which has mainly been described for metabotropic receptors.



Pavalbumin-containing neurons (red) enwrapped by perineuronal nets (green) in the somatosensory cortex from a mouse model of chronic pain.

Perineuronal Nets Stabilize Chronic Pain Hypersensitivity

Giada Mascio, Serena Notartomaso, Katiuscia Martinello, Francesca Liberatore, Domenico Bucci, et al.

(see pages 3037–3048)

Chronic pain can persist for years or even decades and involves myriad neuroplastic changes from the peripheral nerve endings all the way to cortical circuits. Researchers hope that by interrogating those changes, they may be able to reverse or prevent hypersensitivity associated with chronic pain. Now, Mascio et al. show that perineuronal nets (PNNs) are formed in cortical brain areas in response to ongoing inflammation in a mouse model of chronic pain. Moreover, pain sensitization abated with enzymatic degradation of the nets.

PNNs are made of extracellular chondroitin sulfate proteoglycans that form a matrix around individual synapses and neurons, structurally stabilizing them in a way thought to form the basis of very long-term memories. Interestingly, PNN deposition in the somatosensory cortex coincides with the end of developmental critical windows, but PNNs remain dynamic into adulthood and may reform, such as during learning or maladaptive processes like addiction. PNNs enwrap parvalbumin-positive (PV^+) GABAergic cortical neurons, which have previously been implicated in chronic pain-related plasticity.

To determine the role of PNNs in chronic pain, the researchers injected complete Freund's adjuvant (CFA; a cocktail of inflammatory mediators) into the mouse hindpaw, causing a substantial reduction in withdrawal threshold from a painful poke or a hotplate 3 and 7 d later. They then fluorescently stained the contralateral somatosensory cortex (SSCtx), prefrontal cortex, and reticular thalamic nucleus with *Wisteria floribunda* agglutinin (WFA), a plant lectin that labels PNNs. About three-quarters of PV^+ SSCtx neurons were stained with WFA in control mice. In all three cortical areas the researchers examined, the overall density of WFA staining and the density of PV^+/WFA^+ cells increased by 7 d after CFA injection, indicating PNN plasticity in multiple chronic pain-associated brain areas. They also observed transcriptional changes in multiple PNN-associated genes in the SSCtx.

The authors next stereotaxically treated the SSCtx with chondroitinase-ABC (ChABC), an enzyme that degrades PNNs, which led to the disappearance of WFA staining in control mice. They then infused ChABC into the SSCtx of CFA-treated mice 4 d after the inflammatory treatment. Remarkably, at day 7, mechanical and thermal withdrawal thresholds were restored toward pre-CFA levels. Importantly, withdrawal thresholds were not changed by ChABC treatment in naive mice.

Mascio et al. report the first findings of PNN dynamics in a model of chronic pain, revealing yet another type of neural plasticity that contributes to this complex disease.

This Week in The Journal was written by Stephani Sutherland, Ph.D.

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