This Week in The Journal

Retinoic Acid and Presynaptic Homeostatic Plasticity in V1

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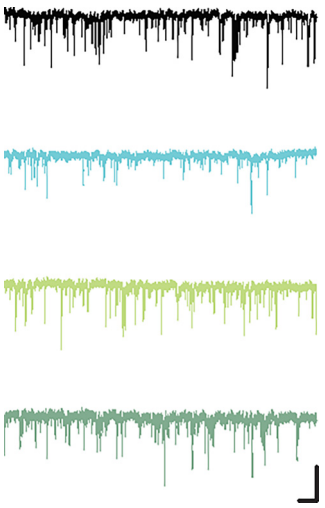
(see pages 10454–10466)

Chronic disruption of neuronal activity engages countervailing mechanisms that alter the ability of excitatory input to elicit spiking in postsynaptic neurons. These homeostatic mechanisms include changes in presynaptic vesicle release, postsynaptic receptor expression, and intrinsic excitability. Several signaling pathways involved in triggering this type of plasticity have been identified. In cultured hippocampal neurons, for example, dendritic translation of AMPA receptor subunits is normally repressed by retinoic acid receptor α (RARα), but chronic inhibition of spiking and NMDA receptors induces synthesis of retinoic acid, which binds to RARα and relieves translational repression, and thus increases AMPA receptor levels and mEPSC amplitude. In parallel, binding of retinoic acid to RARα leads to increased endocytosis of $GABA_A$ receptors, thus reducing mIPSC amplitude. Together, these changes in excitation and inhibition increase spike probability.

To determine whether retinoic acid contributes to homeostatic plasticity under more physiological conditions, Zhong et al. examined its role in primary visual cortex (V1). Exogenous retinoic acid reduced the amplitude and frequency of mIPSCs in V1 layer 2/3 pyramidal neurons in slices, but it did not affect mEPSCs. Surprisingly, knocking out RARα selectively in pyramidal neurons did not prevent retinoic-acid-induced reductions in mIPSCs, indicating the changes did not result from internalization of GABA receptors. Instead, the effects required expression of RARα in parvalbumin-expressing GABAergic interneurons. Importantly, knocking out RARα in parvalbumin-expressing interneurons also prevented the decreases in mIPSC frequency and amplitude that occurred in wild-type neurons 3 d after binocular enucleation *in vivo*. A similar failure of enucleation to reduce mIPSC frequency and amplitude occurred after fragile X mental retardation protein (FMRP), which regulates retinoic-acid signaling at synapses, was knocked out in parvalbumin-expressing interneurons.

These results suggest that after loss of visual input, retinoic acid reduces inhibitory transmission in V1 by acting on RARα in inhibitory interneurons. Thus, retinoic acid can trigger homeostatic plasticity in either presynaptic (V1) neurons or postsynaptic (hippocampal) neurons to compensate for chronic reductions in synaptic activity. Future work should determine whether the source of retinoic acid in deprived V1 is presynaptic or postsynaptic, identify the presynaptic targets of RARα, and determine how these targets regulate GABA release.



The frequency and amplitude of mIPSCs are lower in V1 layer 2/3 of wild-type mice after 3 d binocular enucleation (light blue trace) than after normal rearing (black). This effect is absent in mice lacking RARα in parvalbumin-expressing neurons (light green, normally reared; dark green, after enucleation). See Zhong et al. for details.

Reliving Past Experiences with the Angular Gyrus

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(see pages 10438–10443)

The angular gyrus in the ventral lateral parietal lobule is a major hub in the default mode network, which is active when people are not engaged in explicit tasks and their minds may be wandering. The angular gyrus is also active during tasks involving semantic processing, episodic memory retrieval, and imagining the future. Its precise role in these cognitive processes has been debated, however. In particular, its role in episodic memory has been questioned, because people with angular gyrus lesions perform normally on many memory tests. Curiously, however, these patients are less confident about their answers than people whose angular gyrus is healthy. Moreover, free recall of autobiographical memories is impaired in people with angular gyrus lesions. These findings led to the proposal that the angular gyrus is important for focusing attention on internally generated memories. Alternatively, the deficits might arise from an inability to place oneself in the remembered event to produce a subjective experience of remembering.

To test these hypotheses, Bonnici et al. asked people to recall previously learned word pairs and personally chosen past experiences, both with and without prompts and with and without continuous theta burst stimulation (cTBS) of the angular gyrus. The authors reasoned that if the role of the angular gyrus is to direct attention to internally generated memories, cTBS should disrupt free recall of word pairs as well as autobiographical memories. This was not the case. Whereas cTBS significantly reduced the number of autobiographical details recounted during free recall, it had no effect on free recall of word pairs. In addition, autobiographical memories were less likely to have a first-person perspective during cTBS of angular gyrus than during the control condition. Consistent with lesion studies, cTBS did not affect cue-triggered recall of either autobiographical memories or word pairs.

These results argue against the hypothesis that the angular gyrus is required to focus attention on internally generated memories, but they are consistent with the hypothesis that the angular gyrus is involved in remembering subjective experiences. This hypothesis fits into a broader view of the angular gyrus that suggests the area integrates emotional and sensory information into a rich, unified representation that allows people to relive events as they are recalled.

This Week in The Journal was written by Teresa Esch, Ph.D.