This Week in The Journal

Pain Suppresses Dopamine Release Via Hypothalamus and Habenula

Soo Min Lee, Han Byeol Jang, Yu Fan, Bong Hyo Lee, Sang Chan Kim, et al.

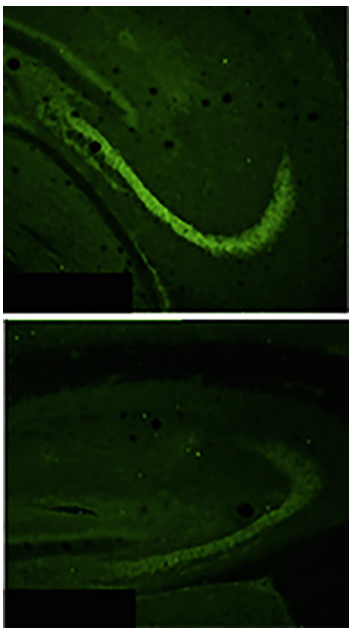
(see pages 9180–9192)

When one is injured, it is best to avoid unnecessary activity and instead devote all available energy to the healing process. Therefore, the nervous system is wired to discourage activity when one is sick or injured. One way it does this is by suppressing activity in dopaminergic neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAc). Several brain areas are involved in linking nociception to reduced dopamine release. One key player is the lateral habenula (LHb), which sends glutamatergic projection to the rostromedial tegmental nucleus (RMTg), which contains GABAergic neurons that inhibit dopaminergic neurons in the VTA. The lateral habenula receives excitatory input from the lateral hypothalamus (LH), and activation of this pathway is aversive. Therefore, it is likely that projections from the LH to the LHb lead to suppression of dopamine release in the NAc, and thus decreased motivation to seek rewards. Lee, Jang, Fan, et al. provide support for this hypothesis.

As expected, pinching the tail of male rats activated neurons first in LH and shortly thereafter in LHb and RMTg. After LH was ablated, tail pinch no longer activated LHb or RMTg neurons. Moreover, tail pinch reduced dopamine release in the ventrolateral shell of the NAc that was evoked by stimulating the medial forebrain bundle, and this effect was reduced after LH was ablated.

Cocaine administration induces dopamine release in the NAc, but this too was prevented by tail pinch, as were cocaine-induced increases in locomotion and ultrasonic vocalizations. But after an inhibitory designer receptor was expressed in LH neurons that project to LHb, and these neurons were silenced with a designer drug, tail-pinch no longer suppressed cocaine-induced increases in locomotion and vocalizations. Finally, although tail-pinch did not deter rats from self-administering cocaine, it reduced cocaine-induced reinstatement of drug seeking after the behavior had been extinguished, and this effect was blocked by silencing projections from LH to LHb.

Altogether, these results support the hypothesis that nociceptive information is transmitted to the LH, which then activates LHb neurons that drive inhibition of dopaminergic neurons that project to the ventrolateral shell of the NAc. The resulting reduction in dopamine release in NAc dampens motivation to seek drug rewards.



Expression of GluK2 (green) is lower in the hippocampus of APP/PS1 mutant mice (bottom) than in controls (top). See Barthet, Moreira-de-Sá, et al. for details.

APP and Presenilin Enhance Kainate Receptor Expression

Gaël Barthet, Ana Moreira-de-Sá, Pei Zhang, Séverine Deforges, Jorge Castanheira, et al.

(see pages 9253–9262)

Cleavage of amyloid precursor protein (APP), first by β-secretase and then by γ-secretase, results in production of β-amyloid peptides (Aβ). These cleavage events are promoted by synaptic activity, and both APP and Aβ are thought to have roles in synaptic plasticity and homeostasis. Yet excessive production or inadequate degradation of Aβ species, which are prone to oligomerization and aggregation, is thought to underlie synaptic loss, neurodegeneration, and cognitive decline in Alzheimer's disease (AD). This is supported by the fact that mutations in APP and presenilin-1 (PS1), the catalytic subunit of γ-secretase, result in overproduction of Aβ and cause inherited forms of early-onset AD. Nevertheless, the cellular and molecular events linking APP and PS1 mutations to AD continue to be investigated and debated.

Barthet, Moreira-de-Sá, et al. have discovered a previously unrecognized synaptic effect of AD-linked mutations in APP and PS1. Specifically, they found that mice expressing mutant forms of both proteins had reduced levels of the GluK2 subunit of kainate receptors (KARs) at synapses between dentate granule cell mossy fibers and hippocampal area CA3 pyramidal cell dendrites. KARs expressed on the presynaptic terminals of mossy fibers mediate presynaptic facilitation during spike trains, while KARs at postsynaptic sites on CA3 neurons contribute to sustained depolarization during such trains; the postsynaptic KARs mediate only ~10% of the glutamate-induced current at these synapses, however. In APP/PS1 mutant mice, the amplitude of mossy fiber-evoked EPSCs in CA3 neurons and the facilitation of EPSCs during trains were comparable to those in wild-type mice; but the amplitude and duration of the KAR-mediated portion of EPSCs were significantly reduced. Importantly, similar effects were obtained by deleting either PS1 or APP selectively in CA3 pyramidal cells and by treating organotypic hippocampal slice cultures with a γ-secretase inhibitor. Finally, coimmunoprecipitation assays indicated that KARs interact with full-length APP.

These results suggest that interaction between APP and KARs and cleavage events mediated by γ-secretase are required to sustain expression of KARs at postsynaptic sites in CA3 pyramidal cells. The loss of KARs at these synapses may therefore contribute to cognitive impairment resulting from mutation of APP and/or PS1. Future work should determine whether APP and PS1 also regulate KAR expression and function at other sites.

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