This Week in The Journal

Role for HDAC2 in Suppressing Pain

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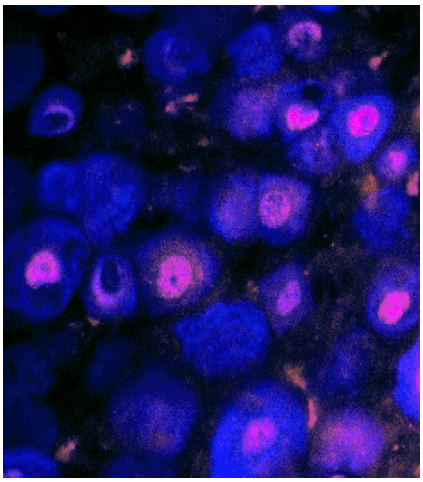
(see pages 8918–8935)

Gabapentin is commonly prescribed for treating pain. Although it was originally designed to mimic the effect of GABA, gabapentin does not actually act on GABA receptors. Instead its primary target is $\alpha2\delta$-1, a protein persistently upregulated in dorsal root ganglion (DRG) neurons after peripheral nerve injury in rodent models of pain. $\alpha2\delta$-1 interacts with several proteins, including NMDA receptors (NMDARs), which it helps traffic to the plasma membrane. Injury-induced upregulation of $\alpha2\delta$-1 leads to increased expression of NMDARs in the presynaptic terminals of DRG nociceptor afferents in the spinal cord. The resulting potentiation of glutamate release is thought to cause chronic activation of pain pathways, which is blunted by blocking $\alpha2\delta$-1 with gabapentin.

How $\alpha2\delta$-1 expression increases after nerve injury has been unclear, but the persistence of the effect suggests epigenetic regulation is involved. Therefore, Zhang et al. asked whether histone acetylation, a common epigenetic modification, was altered in mouse DRG neurons after nerve injury. Indeed, spinal nerve ligation led to increased acetylation of histones surrounding the promoter of *Cacna2d1*, the gene that encodes $\alpha2\delta$-1. This hyperacetylation was attributable to reduced association of histone deacetylase 2 (HDAC2) with the *Cacna2d1* promoter. Notably, knocking out HDAC2 selectively in DRG neurons lowered thresholds for paw withdrawal from mechanical stimuli. In addition, HDAC2 knockout increased histone acetylation at the *Cacna2d1* promoter and increased DRG $\alpha2\delta$-1 levels. HDAC2 knockout also increased the frequency of miniature EPSCs, increased the amplitude of evoked EPSCs, and reduced the paired-pulse ratio recorded in spinal targets of DRG neurons. The effects on synaptic transmission were reversed by treating spinal cord slices with gabapentin, an NMDAR antagonist, or a peptide that blocks interaction between $\alpha2\delta$-1 and NMDARs. These same treatments reversed mechanical hypersensitivity in mice. Finally, HDAC2 knockout caused minimal mechanical hypersensitivity if *Cacna2d1* was also knocked out.

These results suggest that nerve injury causes HDAC2 to disassociate from the *Cacna2d1* promoter, resulting in increased histone acetylation and thus increased transcription of *Cacna2d1* in DRG nociceptor neurons. This promotes insertion of NMDARs at the presynaptic terminals of DRG neurons, potentiating synaptic transmission. Now researchers need to determine how nerve injury causes HDAC2 to dissociate from the *Cacna2d1* promoter.



HDAC2 (purple) is expressed in neurons (blue) in the DRG, where it affects synaptic transmission by regulating expression of *Cacna2d1*. See Zhang et al. for details.

CRF Expression in Primate Central Extended Amygdala

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(see pages 8997–9010)

The central extended amygdala (CEA) in higher primates stretches from the central nucleus of the amygdala to the lateral bed nucleus of the stria terminalis (BSTL), encompassing a region of basal forebrain without clear subdivisions, called the central sublenticular extended amygdala (SLEAc). The CEA works with the ventral pallidum (VP) to drive motivated behaviors, and it expresses many neuropeptides, including the stress-associated peptide corticotropin releasing factor (CRF). CRF is typically co-released with either GABA (the predominant neurotransmitter in the CEA and VP) or glutamate, and it enhances the effects of these neurotransmitters. The pattern of CRF expression in primates is more diffuse than that in rodents, consistent with the lack of discrete subdivisions in much of primate CEA. Because knowing where CRF is expressed is essential for learning how stress influences motivated behaviors, Fudge et al. detailed the pattern of CRF expression and its coexpression with vesicular glutamate and GABA transporters (VGlut2 and VGAT, respectively) in the CEA and VP of male macaques.

CRF mRNA was present in ~11% of CEA and VP neurons that expressed VGAT and/or VGlut2. CRF-expressing neurons were located diffusely along the full extent of the CEA, but dense clusters were found in the BSTL. CRF-expressing neurons were also found throughout the VP. As expected, ~90% of CEA and VP neurons expressed VGAT, and a small percentage of these (~11%) also expressed VGlut2. Intriguingly, VGAT/VGlut2 coexpressing neurons were more common among CRF-expressing neurons than in the general population: of the CRF-expressing neurons that expressed VGAT (~87% of CRF-expressing neurons), ~40% also expressed VGlut2. CRF/VGAT/VGlut2 neurons were rare in the caudal CEA, but they comprised about a third of CRF-expressing neurons in the BSTLP and SLEAc and a whopping two-thirds of CRF-expressing neurons in the VP.

These results indicate that CRF is expressed more broadly in primates than in rodents, where CRF appears to be confined to the caudal and rostral poles of the CEA. They also suggest that many BSTL and VP neurons that express CRF have opposing excitatory and inhibitory effects. Future work should identify the targets of these CRF/VGAT/VGlut2 neurons and determine whether release of CRF alters the ratio of inhibitory and excitatory transmission at these synapses.

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