This Week in The Journal

DNA Methylation Changes in Chronic Pain

Judit Garriga, Geoffroy Laumet, Shao-Rui Chen, Yuhao Zhang, Jozef Madzo, et al.

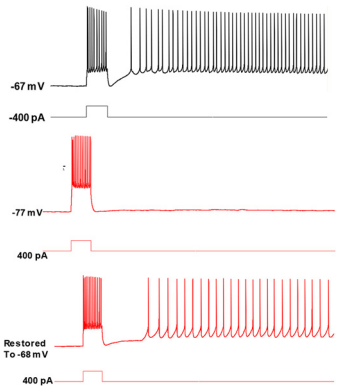
(see pages 6090 – 6101)

Injury, inflammation, and chemical agents activate nociceptors, producing acute pain. Like other neural pathways, those transmitting pain exhibit activity-dependent plasticity. Thus, acute pain can lead to long-lasting changes in neural sensitivity, resulting in chronic pain that persists after the precipitating insult resolves. Neural plasticity underlying chronic pain occurs at all levels of the pain pathway, from primary nociceptor neurons to the cerebral cortex, and it involves numerous cellular and molecular changes that increase excitability and reduce inhibition. Some of these changes likely stem from epigenetic modifications, which underlie long-term changes in gene expression. Indeed, Garriga, Laumet, et al. show that numerous changes in DNA methylation occur in rat dorsal root ganglia (DRGs) after spinal nerve ligation, a model of chronic neuropathic pain.

Comparison of DNA extracted from DRGs of ligated nerves and contralateral DRGs 3 d after nerve ligation revealed ligation-induced increases in methylation at 4.6% of CpG sites (where methyl groups attach to DNA) and decreased methylation at 3% of sites. But 3 weeks later, during the chronic pain state, ligation was associated with methylation loss at 6.5% of sites, and methylation gains at only 1.4% of sites. Nonetheless, there was significant overlap in the sites with methylation changes at 3 d and 3 weeks after injury. These sites tended to be in introns and intergenic regions.

To determine whether such methylation changes occur across chronic pain-like states, the authors treated rats with paclitaxel to model chemotherapy-associated pain. Surprisingly, relatively few sites (<2%) showed methylation changes, and these did not significantly overlap with sites affected by nerve ligation. Methylation changes induced by nerve ligation were more similar to those occurring during development. Given this, the authors asked whether the methylation changes were linked to chronic pain, rather than just regeneration. To test this, they treated rats with a methyltransferase inhibitor to reduce overall methylation. This produced long-lasting decreases in mechanical withdrawal thresholds, suggesting increased pain sensitivity.

These data suggest that long-lasting decreases in methylation contribute to pain hypersensitivity following some types of injury. What triggers these changes in methylation remains unknown. Future work should investigate this and determine which genes regulated by methylation contribute most strongly to the development of chronic pain.



Injecting current into pyramidal cells in layer 5 of PrL-PFC in the presence of a muscarinic agonist evokes spiking that persists beyond the current pulse (top traces). This persistent activity was absent in neurons of adolescent mice that consumed alcohol (middle), but it was restored when those neurons were held at normal resting membrane potential. See Salling et al. for details.

Effects of Adolescent Binge Drinking on Prefrontal Neurons

Michael C. Salling, Mary Jane Skelly, Elizabeth Avegno, Samantha Regan, Tamara Zeric, et al.

(see pages 6207– 6222)

During adolescence, mammals transition from dependence on parents to autonomy. This transition is facilitated by increased risk-seeking, which motivates adolescents to explore on their own. In humans, such exploration often includes the use of alcohol. This can be problematic, because the brain continues to develop during adolescence: white matter integrity increases, enabling more efficient communication between brain areas, and prefrontal cortical circuits develop, improving decision-making and self-control. Alcohol use during this period can lead to persistent impairments in cognitive function. For example, adolescents who engage in binge drinking show subsequent deficits in short-delay memory. Similar effects occur in rodents, which, like humans, voluntarily engage in binge-like drinking when given intermittent access to alcohol. And rodent studies link alcohol-induced cognitive impairments to slowed brain development (Spear, 2018 Nat Rev Neurosci 19:197).

Salling et al. provide additional evidence that alcohol slows neural development, showing that binge-like drinking in adolescent mice is associated with immature intrinsic properties in layer 5 pyramidal neurons in the prelimbic region of medial prefrontal cortex (PrL-PFC). In control mice, resting membrane potential became less depolarized with age; it remained hyperpolarized in mice that were given intermittent access to alcohol, however. Furthermore, during normal development, some PrL-PFC neurons gained a strong hyperpolarization-activated cation current that produced gradual depolarization (called a sag) during hyperpolarizing current steps. The average sag ratio was lower in alcohol-exposed mice than in controls. Finally, ethanol exposure reduced the number of neurons that displayed intrinsic persistent activity when depolarized in the presence of a muscarinic acetylcholine receptor agonist. Although the effects of alcohol were attributable to a reduction in current mediated by HCN1 channels, the expression of these channels was unaffected by alcohol exposure. Instead, reduced expression of Trip8b, an accessory subunit that enhances membrane insertion of HCN1 channels, appeared to be involved.

These results indicate that intermittent consumption of alcohol in amounts characteristic of binge drinking produces long-term changes in the intrinsic properties of layer 5 PrL-PFC neurons in mice, and this alters firing patterns evoked by current injection. Loss of persistent activity in these neurons might contribute to working memory deficits, which were also present in alcohol-exposed mice.

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