This Week in The Journal

Fentanyl Primes Neurons for More Pain

Dioneia Araldi, Eugen V. Khomula, Luiz F. Ferrari, and Jon D. Levine

(see pages 2226–2245)

The United States is currently in the grip of an epidemic of misuse of opioids, powerful pain-relieving drugs that cause a range of side effects including addiction and death. A lesser-known side effect of opioids is hyperalgesia, or an exaggerated pain response to a stimulus. Opioid-induced hyperalgesia (OIH) can develop with extended use, and opioids predispose animals and humans to future hyperalgesia, in a phenomenon called priming.

Priming is a form of neuroplasticity at primary sensory afferent neurons that detect painful stimuli in the periphery and synapse onto spinal cord neurons. There are two types of priming: type I, which involves changes in protein translation, and type II, which relies on signaling by a pair of protein kinases. Fentanyl is a potent, fast-acting synthetic opioid drug increasingly contributing to overdose; even a single administration of the drug can cause priming in humans. Araldi et al. set out to understand how the analgesic drug rapidly sensitizes pain.

To determine the mechanisms activated by fentanyl, the researchers treated male rats with intrathecal, intradermal, or systemic fentanyl and used inhibitors of priming at central and peripheral terminals. Thirty minutes after intrathecal treatment, mechanical pain threshold was reduced by approximately one-third, indicative of OIH. To measure fentanyl-induced priming, the authors treated rats with prostaglandin E2 (PGE2), an inflammatory mediator that causes transient mechanical hyperalgesia. The sensitivity was prolonged in rats that had received fentanyl treatment at least 8 h beforehand to initiate priming. Regardless of delivery site, fentanyl led to type II priming at central nociceptor terminals and type I priming at peripheral terminals. When fentanyl was delivered intradermally, priming developed at the injection site. Priming could be blocked by μ-opioid receptor (MOR) antisense oligodeoxynucleotides, confirming that it depended on activation of the MOR.

Ablation of specific types of nociceptors showed that both peptidergic and nonpeptidergic nociceptors were required to establish central priming after intrathecal fentanyl administration. But surprisingly, priming at peripheral terminals arose even when both cell types were absent. Although the cell type involved in this peripheral priming is still unclear, the rapid signaling depended on signaling by calcium released from the endoplasmic reticulum. The findings further demonstrate the drawbacks of fentanyl, but a better understanding of MOR signaling and the mechanisms contributing to priming could lead to better, safer pain treatments.

Derivatives of the opium poppy have been used to ease pain and produce euphoria for millennia. Efforts to produce more potent agonists of endogenous opiate receptors continue. One of the strongest synthetic opiates is fentanyl. Paradoxically, fentanyl and other opiates prime nociceptors to generate exaggerated pain responses to future insults. See Araldi et al. for details. Photo by Kora27, CC BY-SA 4.0, https://commons.wikimedia.org/w/index.php?curid=59048260.

Synaptic Changes in Hyperandrogenized Neuroendocrine System

Tova Berg, Marina A. Silveira, and Suzanne M. Moenter (see pages 2283–2293)

Polycystic ovary syndrome (PCOS) is a leading cause of infertility that affects an estimated 8% of women. PCOS arises from overactivity in the neuroendocrine signaling between the hypothalamus, pituitary, and gonads that controls the reproductive cycle; clinical studies suggest the disruption begins in advance of puberty. Now, Berg et al. have described in detail electrophysiological activity in the circuit from pre-puberty through adulthood in normal male and female mice and those prenatally treated with androgen (PNA), a rodent model of PCOS.

Hypothalamic neurons release gonadotropin-releasing hormone (GnRH) onto pituitary cells that in turn release leutinizing hormone (LH) and follicle-stimulating hormone (FSH) into the bloodstream. In response, the ovaries release steroids that feed back to the hypothalamus, fine-tuning the circuit. In women with PCOS, the cyclic release of GnRH—and thereby other hormones—is disrupted. GnRH neurons receive hypothalamic GABAergic inputs that are excitatory due to GnRH neurons' unusual chloride reversal potential. The researchers made whole-cell voltage-clamp recordings of GABAergic postsynaptic currents (PSCs) from GnRH neurons in brain slices from 1-, 2-, 3-, and 4-week-old and adult mice. Spontaneous GABAergic PSCs were detectable by 1 week in neurons from all mice. Transmission increased between 2 and 3 weeks in females, and by 4 weeks in males. PNA caused a more robust developmental increase in signaling in female mice than in controls, and this persisted through adulthood. In contrast, a boost in male signaling was transient.

In females, the frequency of miniature PSCs was higher in PNA-treated females than in controls, indicating increased presynaptic contacts onto GnRH neurons. GnRH neurons from both control and PNA-treated adult females fired in response to acute GABA application, but during development, neurons from PNA mice were significantly less responsive to GABA than controls. And whereas resting membrane potential was unaffected by PNA, at 3 weeks of age, GABA's depolarizing effect was blunted in PNA female mice compared with controls. The chloride reversal potential, however, was not affected by PMA treatment. Together, the results suggest that altered synaptic development underlies the lasting neuroendocrine changes seen in PNA-treated adult mice, perhaps providing clues to the mechanisms behind PCOS.

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