This Week in The Journal

Estrus-Cycle-Dependent Role of mGluR1 in Opioid Analgesia

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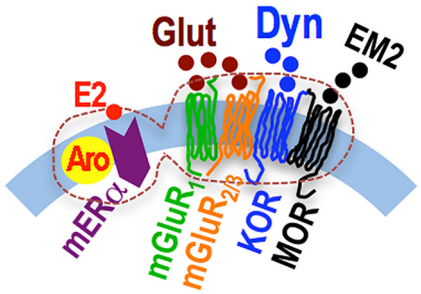
(see pages 11181–11191)

Chronic pain conditions are more common in women than in men, and in laboratory studies, women have lower pain thresholds than men. These differences are paralleled by sex differences in both neural activation patterns induced by nociceptive stimuli and the levels or activity of proteins involved in pain processing, including μ-opioid receptors (MORs). Rodent studies have revealed numerous additional sex differences in the cellular mechanisms underlying pain processing.

Differences in pain processing exist not only between the sexes, but also over the course of the reproductive cycle in females. For example, endomorphin 2, an endogenous MOR ligand, increases pain thresholds similarly in male and proestrus female rats, but this antinociceptive effect requires activation of κ-opioid receptors (KORs) only in females. Moreover, endomorphin-induced antinociception is minimal in diestrus females. This change stems not from reduction in circulating estrogens, as one might predict, but from activation of membrane estrogen receptor α (mERα) on spinal neurons by locally synthesized estrogen. Activated mERα then activates type 1 metabotropic glutamate receptors ($mGluR_1$), which form a complex with mERα in MOR-expressing spinal neurons (Liu et al. 2017 Pain 158:1903).

Blocking either mERα or $mGluR_1$ reinstates endomorphin-mediated antinociception in diestrus female rats. Liu et al. asked whether suppression of this signaling pathway also underlies the emergence of endomorphin antinociception during proestrus. Surprisingly, blocking $mGluR_1$ eliminated antinociception during proestrus, indicating that activation of $mGluR_1$ either promoted or suppressed antinociception, depending on the estrus phase. But blocking glutamate release eliminated antinociception during proestrus, without unmasking antinociception during diestrus. In addition, $mGluR_1$ formed a complex with $mGluR_{2/3}$ selectively during proestrus, and blocking $mGluR_{2/3}$ eliminated endomorphin antinociception during this phase. Additional experiments suggested that $mGluR_1$/$mGluR_{2/3}$ signaling during proestrus led to greater release of the KOR ligand dynorphin, and that inhibition of this release blocks endomorphin-induced antinociception during diestrus.

Together, the results suggest that during proestrus, activation of a $mGluR_1$–$mGluR_{2/3}$ complex by glutamate removes endomorphin-induced inhibition of dynorphin release, allowing activation of KORs, which is required for endomorphin-mediated antinociception. During diestrus, activated mERα associates with $mGluR_1$, preventing the disinhibition of dynorphin release and thus blocking antinociception. If similar mechanisms exist in humans, they might affect pain processing throughout the menstrual cycle.



During proestrus, activation of a mGluR1–mGluR2/3 complex disinhibits dynorphin (Dyn) release, allowing activation of MORs by endomorphin (EM2) to produce antinociception. During diestrus, estrogen (E2), produced by aromatase (Aro) binds to mERα and prevents signaling through the mGluR1–mGluR2/3 complex. See Liu et al. for details.

Comparing fMRI, LFP, and Spiking after Spinal Lesion

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(see pages 11192–11203)

While we lie quietly with eyes closed, our brains are highly active. Functional magnetic resonance imaging (fMRI) performed under such conditions reveals spontaneous waves of activity that are correlated across brain areas. This correlated activity is said to reflect functional connectivity, and it is used extensively to investigate normal and pathological brain function. Functional connectivity doesn't necessarily indicate anatomical connectivity, however: activity in two areas might be correlated because each receives similar inputs, for example. Furthermore, the blood oxygen level-dependent (BOLD) signal used in fMRI measures deoxyhemoglobin levels, an indirect measure of neural activity that depends on how activity affects cerebral blood flow. Although cortical BOLD signals are strongly correlated with local field potentials (LFPs) in healthy animals performing tasks, questions remain about the neural correlates of resting-state BOLD signals, particularly in pathological conditions in which neurovascular coupling might be disrupted. Moreover, how changes in resting-state activity relate to altered brain function is not entirely clear.

Simultaneously recording BOLD signals, LFPs, and spiking in monkeys in healthy and pathological conditions can help address these questions. Wu et al. obtained such recordings from primary (area 3b) and secondary (S2) somatosensory cortex before and after severing dorsal columns, which convey afferent information to these areas via the thalamus. They first examined responses to tactile stimulation, and found that dorsal column lesion reduced responses in 3b and S2 measured by fMRI, LFP, and spiking activity. Activity in these areas during rest was also reduced after lesion, as was resting-state functional connectivity between the areas, as measured by all three signals. Reductions in stimulus responses were much greater than reductions in resting-state correlations, however. Moreover, the magnitude of the reductions—as well as the relationship between reductions in evoked versus resting responses—differed depending on which measure was used.

The fact that lesions reduced stimulus responses more than resting-state correlations in 3b and S2 suggests that these correlations arise only partially from common sensory input. The results also show that resting-state fMRI can detect changes in functional connectivity induced by elimination of afferent input to cortical regions. Nonetheless, the study indicates that changes in the magnitude of BOLD signals might not provide an accurate measure of changes in neural activity.

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