This Week in The Journal

Interferon Produces Pain during Viral Infection

Paulino Barragán-Iglesias, Úrsula Franco-Enzága, Vivekanand Jeevakumar, Stephanie Shiers, Andi Wangzhou, et al.

(see pages 3517–3532)

A general feeling of achiness often accompanies viral infections. What causes this achiness is unclear, but sensitization of nociceptors is likely involved. Although some infectious bacteria and fungi produce agents that directly stimulate nociceptors, elements of the immune system are responsible for persistent pain after tissue injury. Therefore, Barragán-Iglesias et al. hypothesized that immune molecules, specifically interferons, enhance nociceptor responses during viral infection.

The production and secretion of type I interferons is one of the earliest cellular responses to viral attack. These cytokines bind to interferon receptors (IFNRs) on healthy cells and initiate signaling cascades that alter gene transcription and translation to inhibit viral infection and replication. Barragán-Iglesias et al. found that IFNRs are expressed broadly in dorsal root ganglia (DRGs) neurons, including in nociceptors. In addition, interplantar injection of interferons produced mechanical hypersensitivity that lasted for several days, and interferons increased the excitability of presumptive nociceptors in cultured DRGs.

How might interferons increase nociceptor sensitivity? Treating DRGs with interferons led to phosphorylation of several kinases that are involved in IFNR-dependent signaling in other tissues. These included JNK and STAT, which are involved in transcriptional regulation, and ERK and its downstream effector MNK1, which enhances translation by phosphorylating eukaryotic initiation factor 4E (eIF4E). Notably, eIF4E phosphorylation was also increased in DRGs after interferon treatment. Furthermore, mechanical hypersensitivity produced by interplantar injection of interferon was significantly reduced in mice lacking MNK1 or expressing a mutant form of eIF4E that lacked the MNK1 phosphorylation site. Finally, mimicking viral infection

by injecting a synthetic analog of double-stranded RNA into mouse paws led to increases in mechanical sensitivity and phosphorylation of eIF4E, and these effects were attenuated in mice lacking MNK1 or expressing mutant eIF4E.

These results suggest that viral infection produces achiness by stimulating production of interferons, which increase nociceptor sensitivity by enhancing eIF4E-dependent translation. Whether JAK/STAT-dependent changes in gene transcription also contribute to nociceptor sensitization remains unclear. Which genes are subject to increased translation and/or transcription in response to interferons also remains to be determined, but genes encoding voltage-dependent ion channels or their regulators are likely candidates.

IFNRs (red) are expressed in peptidergic (green) and nonpeptidergic nociceptors (blue), as well as in non-nociceptive neurons (cyan) in DRGs. Activation of IFNRs increases nociceptor sensitivity during viral infection. See Barragán-Iglesias et al. for details

Reward Increases Arm Stiffness to Improve Motor Performance

Olivier Codol, Peter J. Holland, Sanjay G. Manohar, and Joseph M. Gal

(see pages 3604–3620)

Choosing an appropriate action and performing it skillfully in a timely fashion are often essential for survival. Unfortunately, acting quickly increases the risk of choosing or performing poorly. Notably,

however, the relationship between speed and accuracy is altered by the presence of reward. Specifically, the opportunity for reward can speed action selection and performance without reducing accuracy. This effect is mediated at least partly by increased feedback control and error correction during task performance. Codol et al. now provide evidence that reward also increases accuracy by increasing muscle stiffness.

Volunteers used a robotic arm to move a cursor to a target as quickly as possible. In some trials, a distractor was present, necessitating correct action selection. As expected, the availability of reward reduced responses to distractors (i.e., increased selection accuracy) without slowing reaction time, and it sped movement without increasing errors.

To investigate how reward improved motor performance, the authors analyzed the between-trial variability in the paths taken to reach the target when reward was present or absent. Trajectories were less similar on rewarded trials than on unrewarded trials, but the trajectories became more similar as the hand reached the target. Computational modeling showed that this pattern could be explained by increased error correction throughout trials, with a reduction in motor noise at the end of trials. Such reductions in motor noise can occur through an increase in arm stiffness. Displacing the robotic arm at different points of the reach trajectory confirmed that arm stiffness increased at the end, but not at the start of reaches on rewarded trials.

These results confirm that reward simultaneously enhances action selection and execution speed in reach tasks without affecting accuracy, thus shifting the speed–accuracy function. In addition, the results show that the effect of reward stems not only from an increase in error correction (feedback control), but also from an increase in arm stiffness. Increases in arm stiffness might result from an increase in cocontraction of antagonist muscles. Whether reward increases such cocontraction should be tested in future work.

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