This Week in The Journal

Role for Intracellular FGF in Itch

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(see pages 9589–9601)

The fibroblast growth factor (FGF) family of proteins has numerous roles in the nervous system. Although most FGFs are secreted proteins that act by binding to cell-surface receptors, some act intracellularly, usually by interacting with voltage-gated sodium channels. One of these molecules, FGF13, is expressed in somatosensory neurons, including nociceptors, in the dorsal root ganglion (DRG). Previous work showed that knocking out FGF13 in small DRG neurons eliminated behavioral responses to noxious heat. This effect was attributed to a heat-dependent interaction between FGF13 and Na_v1.7 sodium channels; the interaction was required to maintain spiking in DRG neurons as temperatures rose to noxious levels. Notably, although Na_v1.7 channels contribute to mechanical, as well as thermal, nociception, mechanical nociception was not affected by FGF13 depletion. Therefore, the authors hypothesized that FGF13 is only required to stabilize Na_v1.7 channels in the plasma membrane when the temperature is high (Yang et al., 2017, *Neuron* 93:806). But Dong et al. now suggest FGF13–Na_v1.7 interactions are also required for responses to itch.

Depleting FGF13 in mouse DRG neurons reduced scratching induced by histamine, serotonin, and (to a lesser extent) chloroquine. It also reduced the number of cultured DRG neurons that exhibited calcium responses to histamine or serotonin, and it eliminated histamine-induced spiking in small DRG neurons. The number of chloroquine-responsive DRG neurons was not affected by FGF13 depletion, however.

H1-type histamine receptors were found to be the major mediators of histamine-induced scratching, but FGF13 did not interact directly with or alter the function of these receptors. Instead, as in previous studies, FGF13 interacted with Na_v1.7. This interaction was increased by treating DRG cultures with histamine, and blocking the interaction reduced the number of cultured

neurons that responded to histamine, as well as reducing histamine-induced scratching *in vivo*.

These results show that interaction between FGF13 and Na_v1.7 is required for itch-inducing substances to activate subpopulations of DRG neurons. This suggests that the interaction does more than prevent heat-induced destabilization of Na_v1.7. Future work should determine how FGF13–Na_v1.7 interaction supports neuronal activation by some stimuli, and why the interaction is dispensable for neuronal activation by other stimuli.

Compared with sham-injured control mice (top), control mice subjected to ischemia (middle) exhibited robust activation of astrocytes, including hypertrophy and upregulation of GFAP (magenta), S100A10 (red), and aromatase (green). These changes were attenuated in mice lacking astrocytic aromatase (bottom). See Wang et al. for details.

The Benefits of Astrocyte-Derived Estrogen

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(see pages 9751–9771)

Estradiol produced in the brains of male and female animals promotes synaptic plasticity, cognition, and neuron survival after injury. Under normal conditions, the estradiol-synthesizing enzyme aromatase is expressed predominantly by neurons; but after injury, astrocytes begin to produce the enzyme as well, leading to increases in brain

estrogen levels. Previous work investigating the relative importance of neuron- and astrocyte-derived estradiol in neuroprotection found that knocking out aromatase selectively in neurons increased neuronal loss and memory impairment after ischemic brain injury. But loss of neuronal aromatase also blunted the upregulation of aromatase in astrocytes. Consequently, whether increases in neuron death resulted from the loss of neuron-derived estradiol or instead stemmed from impaired upregulation of aromatase in astrocytes remained unclear (Lu et al., 2020, *J Neurosci* 40:7355). To address this question, Wang et al. knocked out aromatase selectively in astrocytes of male and female mice.

As in previous studies, control mice that experienced global cerebral ischemia subsequently exhibited impairment on memory tests. This was accompanied by the loss of neurons and the activation of astrocytes and microglia. Astrocytic activation involved hypertrophy and increased expression of glial fibrillary acidic protein (GFAP), S100A10, and leukemia inhibitory factor (LIF), a cytokine that activates the STAT3 signaling pathway. Notably, previous work has shown that STAT3 signaling is required for astrocytes to acquire a neuroprotective phenotype.

Knocking out astrocytic aromatase exacerbated memory impairment, neuron loss, and microglial activation. In contrast, ischemia-induced upregulation of astrocytic GFAP, S100A10s, and LIF, as well as activation of astrocytic STAT3 signaling, were lower in knock-out mice than in controls. Importantly, all the effects of aromatase knockout were rescued in ovariectomized female mice by peripheral administration of estrogen.

These results indicate that upregulation of aromatase in astrocytes after ischemia increases neuron survival by increasing brain estrogen levels. Previous work has shown that one effect of estrogen is to promote the production of neuroprotective factors by astrocytes. Whether estrogen also acts directly on neurons to promote survival, and whether the increase in microglial activation after aromatase knockout occurs upstream or downstream of increased neuronal death remain to be tested.

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