This Week in The Journal

Chronic Stress, BNST Hyperexcitability, and Anxiety

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(see pages 2519–2537)

Corticotropin-releasing hormone (CRH) is a key mobilizer of behavioral and physiological responses to threats. One site of CRH action is the bed nucleus of the stria terminalis (BNST). BNST is innervated by CRH-expressing projections from the hypothalamus, but it also contains CRH-producing neurons, particularly in its oval nucleus (ovBNST). Activating ovBNST increases anxiety-like behaviors in mice, and abnormal CRH signaling in the BNST is thought to underlie negative consequences of chronic stress, such as anxiety and depression. Hua et al. suggest that the link between stress and anxiety- and depression-like behaviors involves increased excitability of ovBNST neurons.

As expected, mice exposed to chronic variable mild stress showed reduced sucrose preference (a depression-like behavior) and spent less time in the open arms of an elevated plus maze and in the center of an open field (anxiety-like behaviors) than unstressed mice. In addition, chronic stress increased the number of ovBNST neurons that contained detectable levels of CRH and one of its upstream regulators, and decreased the number of cells expressing a CRH receptor (CRHR) inhibitor.

Chronic stress also altered electrophysiological properties of ovBNST neurons. Specifically, the amplitude of miniature EPSCs (mEPSCs) was greater and the resting membrane potential was more depolarized in CRH-expressing ovBNST neurons from stressed mice than those from controls. Furthermore, potassium-mediated M-currents, which counteract depolarization and limit spiking, were reduced in ovBNST neurons of stressed mice. These electrophysiological effects were mimicked by applying exogenous CRH.

Infusing a CRHR1 antagonist into the ovBNST reversed the behavioral effects of chronic stress, and in brain slices, the antagonist reversed the stress-induced elevation of mEPSC amplitude and suppression of M-currents. Antagonists of protein kinase A (PKA), which is activated

downstream of CRHR1, also reversed the effects of chronic stress on M-currents, mEPSC amplitude, and behavior, whereas a PKA activator blocked the ameliorative effects of the CRHR1 antagonist.

These results suggest chronic stress can increase anxiety- and depression-related behaviors by inducing CRH release in the ovBNST. CRH activates CRHR1, leading to activation of PKA and downstream suppression of M-currents, depolarization of the resting membrane potential, and increased amplitude of mEPSCs. Consequently, ovBNST neurons that drive anxiety- and depression-like behaviors are more easily activated in mildly stressful situations.

EP3 receptors (red) are expressed in MnPO neurons that also express the peptide PACAP (cyan). These neurons are proposed to excite interneurons that inhibit neurons that promote heat production and retention, and inhibiting them is thought to produce fever. See Machado et al. for details.

Redefining the Neural Bases of Fever

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(see pages 2573–2588)

Peripheral infections induce fever by acting on brain circuits that regulate body temperature. Specifically, peripheral cytokines induce endothelial cells in the hypothalamic preoptic area to release prostaglandin E_2 , which binds to EP3 receptors (EP3Rs) on thermoregulatory neurons in the median preoptic nucleus (MnPO). These MnPO neurons express the GABA-synthesizing enzyme GAD67 and are thought to inhibit neurons in dorsal hypothalamic areas and in the raphe pallidus nucleus (RPa) that promote heat generation and retention. Because EP3Rs couple with inhibitory

G-proteins, prostaglandin is thought to inhibit GABAergic MnPO neurons, thus disinhibiting their targets.

A problem with this model is that activating MnPO neurons that express the vesicular GABA transporter Vgat has little effect on body temperature, suggesting GABAergic MnPO neurons do not inhibit thermogenic neurons. Instead, activating MnPO neurons that express the glutamate transporter Vglut2 reduces body temperature, suggesting glutamatergic neurons promote heat loss. How, then, does activation of EP3Rs on GAD67-expressing MnPO neurons produce fever? Machado et al. provide an answer: GAD67-expressing MnPO neurons are in fact glutamatergic.

Nearly all EP3R-expressing and most RPa-projecting MnPO neurons expressed Vglut2, whereas few expressed Vgat. Furthermore, ablating Vglut2⁺ MnPO neurons prevented the fever response normally induced by systemic injection of lipopolysaccharide (LPS), whereas ablating vGat⁺ MnPO neurons did not. In addition, knocking out EP3Rs selectively in Vglut2⁺ neurons prevented LPS-induced fever, but knocking out EP3Rs in vGat⁺ neurons had no effect. Nevertheless, mice in which either Vglut2⁺ or vGat⁺ MnPO neurons were ablated showed greater-than-normal increases in body temperature in response to mild stress and had higher-than-normal body temperatures in warm environments.

These results suggest that both Vglut2⁺ and vGat⁺ MnPO contribute to heat loss under warm conditions, but only Vglut2⁺ neurons are involved in the fever response. These neurons likely synthesize GABA for uses other than as a neurotransmitter; this has been suggested for some other types of neurons previously. Machado et al. still suggest that the fever response results from disinhibition of thermogenic neurons, but they propose that rather than directly inhibiting these neurons, EP3R-expressing neurons excite inhibitory interneurons in the RPa and other thermogenic regions. Future work should test this hypothesis.

This Week in The Journal was written by Teresa Esch, Ph.D.
<https://doi.org/10.1523/JNEUROSCI.twij.40.12.2020>