This Week in The Journal

Input and Intrinsic Properties Shape GnRH Neuron Output

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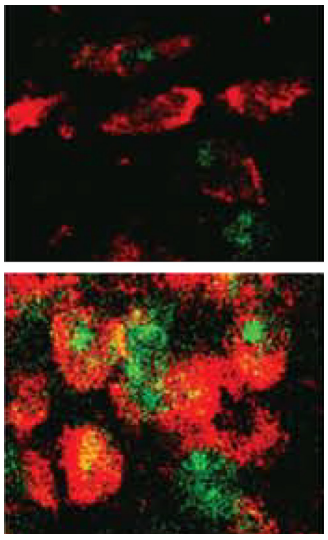
(see pages 2091–2101)

Hypothalamic neurons that secrete gonadotropin-releasing hormone (GnRH) have a central role in the estrous/menstrual cycle. Early in the cycle, low-frequency release of GnRH stimulates release of follicle-stimulating hormone from gonadotropic cells in the pituitary. GnRH release during this period is limited by low levels of circulating estrogens. As ovarian follicles mature, circulating estrogen levels rise, but rather than further suppressing GnRH release, high levels of estrogen indirectly trigger a surge of GnRH secretion, and thus induce ovulation. This positive regulation of GnRH secretion by estrogens can depend on the time of day: in nocturnal rodents, for example, the GnRH surge occurs only in the afternoon, even in ovariectomized (OVX) animals receiving a continually high dose of exogenous estradiol (OVX+E).

The mechanisms through which the effects of estradiol on GnRH secretion switch from negative to positive are incompletely understood; but GABAergic input to GnRH neurons (which can be excitatory), as well as the excitability of GnRH neurons, increases around the time of the switch. To determine whether both of these changes contribute to the increase in spiking that occurs in the afternoon of proestrus in mice, Adams et al. used dynamic clamp to introduce artificial postsynaptic conductance trains to GnRH neurons in brain slices. The conductance trains were designed to mimic GABAergic input received by GnRH neurons when estradiol promoted firing (positive feedback), suppressed firing (negative feedback), or was absent (as in OVX-only mice). Slices were taken from OVX+E mice in AM and PM and from OVX-only mice.

Regardless of brain slice condition, conductance trains mimicking positive feedback evoked more spikes than conductance trains mimicking negative or no feedback. But the greatest number of spikes was evoked when positive-feedback conductance trains were delivered to OVX+E PM slices. Mathematical models of GnRH neurons replicated these results. In addition, the models showed that all conductance trains evoked more spikes in neurons with intrinsic properties characteristic of the positive feedback condition than in neurons with properties mimicking the negative feedback condition. These results suggest that time-of-day-dependent effects of estradiol on the intrinsic properties of GnRH neurons and on the pattern of GABAergic conductance trains both contribute to the elevated spiking of GnRH neurons that leads to ovulation.



Expression of circRNA-Filip1l (green) is higher in spinal cord neurons (red) after peripheral injection of an inflammatory agent (bottom) than in controls (top). See Pan et al. for details.

Circular RNA Contributes to Inflammatory Pain

Zhiqiang Pan, Guo-Fang Li, Meng-Lan Sun, Ling Xie, Di Liu, et al.

(see pages 2125–2143)

Nearly all genes contain introns that are removed to generate mature mRNAs. After intron excision, the 3′ end of the upstream exon is spliced to the 5′ end of the next downstream exon to generate a linear protein-coding sequence. Sometimes, however, the 3′ end of an exon is spliced to the 5′ end of an upstream exon, forming circular RNA (circRNA). Although circRNAs were long thought to be aberrations, evidence is accumulating that at least some of them have functional roles. For example, several circRNAs have been shown to regulate protein expression by binding to and blocking the regulatory effects of miRNAs. Other circRNAs regulate gene transcription (Li et al., 2018 Mol Cell 71:428).

Pan et al. have now discovered a role for circRNAs in inflammatory pain. Injecting an inflammatory agent into mouse paws altered the levels of ~50 circRNAs in the dorsal spinal cord; circRNA-Filip1l was the most strongly affected, increasing by 2.8-fold. Blocking circRNA-Filip1l function with antisense RNA reduced thermal and mechanical nociceptive responses after induction of inflammation, whereas overexpressing circRNA-Filip1l lowered the threshold for nociceptive responses in naïve mice.

To determine how circRNA-Filip1l might influence nociception, the authors searched databases for miRNAs and genes that might bind to circRNA-Filip1l or its precursor RNA. One such partner was miRNA-1224, which suppressed circRNA-Filip1l expression. miRNA-1224 was downregulated in spinal cord during inflammation, and its overexpression suppressed inflammation-induced increases in circRNA-Filip1l levels and nociceptive responses. Conversely, blocking miRNA-1224 increased circRNA-Filip1l levels and reduced nociceptive thresholds in naïve mice.

A likely downstream target of circRNA-Filip1l is the E3 ubiquitin protein ligase Ubr5. Binding of circRNA-Filip1l near the transcription start site of the Ubr5 gene increased Ubr5 transcription. Ubr5 expression also increased in spinal cord neurons after induction of inflammatory pain, and this was suppressed by blocking circRNA-Filip1l. Finally, knocking down Ubr5 suppressed increases in nociceptive responses induced by inflammation or circRNA-Filip1l overexpression.

These results suggest that circRNA-Filip1l promotes transcription of Ubr5, but is inhibited by miRNA-1224. Inflammation reduces expression of miRNA-1224 in spinal neurons, and consequently, circRNA-Filip1l and Ubr5 levels increase. Ubr5 may then enhance neuronal responses to nociceptive stimuli by ubiquitinating targets.

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