This Week in The Journal

EAAT4 Levels Shape Interneuron Responses in Cerebellum

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(see pages 8126–8133)

The cells of the cerebellar cortex are arranged in a series of sagittal strips, called microzones, that each serve a specific motor, cognitive, or autonomic function. Microzones can be divided roughly into two groups based on a number of factors, including the proteins expressed, baseline firing rate of simple spikes in Purkinje cells, how simple spiking is modified by input from climbing fibers, and the types of synaptic plasticity that occur in the circuit during the early stages of learning. For example, microzones with high expression of aldolase C (also called zebrin II because it is expressed in a striped pattern), the simple-spike rate of Purkinje cells is low at baseline, but increases during training; in contrast, low expression of aldolase C is associated with a high rate of simple spikes that decreases during learning (De Zeeuw, 2021, *Nat Rev Neurosci* 22:92). Purkinje cells with high expression of aldolase C also express high levels of the excitatory amino acid transporter EAAT4, which contributes to glutamate uptake at synapses. Glutamate uptake is slower in microzones with low EAAT4 expression, resulting in greater activation of metabotropic glutamate receptors and thus greater long-term depression at parallel-fiber synapses.

Because glutamate spillover from synapses between climbing fibers and Purkinje cells activates nearby molecular layer interneurons (MLIs), Malhotra et al. asked whether climbing-fiber recruitment of MLIs also differs between microzones. Indeed, activation of climbing fibers evoked larger EPSCs in microzones with low EAAT4 expression than in microzones with high expression. Furthermore, kynurenic acid—a low-affinity AMPA receptor antagonist that is most effective when glutamate concentration is low—had a larger effect in microzones with high EAAT4 levels than those with low levels. Finally, although inhibiting EAAT4 increased

EPSC amplitude in all microzones, it eliminated differences between microzones.

These results indicate that the extent to which climbing fibers excite MLIs depends on the expression level of EAAT4, which differs across microzones. Consequently, the extent to which climbing fiber-induced complex spikes in Purkinje cells are followed by MLI-induced inhibition may differ across microzones. How this contributes to the function of specific microzones remains to be determined.

After peripheral injection of formalin (right panels), spinal neuron responses to paw warming increase (top), while responses to paw cooling decrease (bottom) compared to baseline responses (left). See Ran et al. for details.

Inflammation Alters Temperature Encoding in Spinal Cord

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(see pages 8210–8219)

Ambient temperature is sensed by two largely distinct populations of peripheral sensory neurons in mammals. Neurons that express the transient receptor potential channel TRPM8 are activated when temperatures fall below normal skin temperature (32°C in mice), whereas neurons that express TRPV1 respond when the ambient temperature is above 32°C. Within these populations, neurons have different temperature activation thresholds, with some neurons responding only to noxious

temperatures. Tissue injury and some drugs can sensitize temperature-sensitive sensory afferents, causing normally innocuous temperatures to evoke pain responses. Changes in the activity of spinal cord neurons also contribute to hypersensitivity, but considerably less is known about these changes than those in the periphery. To address this issue, Ran et al. performed *in vivo* calcium imaging in mice to measure responses of dorsal horn neurons to changes in paw temperature, and they investigated how these responses were altered by peripheral administration of formalin, an inflammatory agent that causes behavioral heat hypersensitivity, and oxaliplatin, a chemotherapy drug that causes behavioral cold hypersensitivity.

Formalin greatly increased the responses of dorsal horn neurons to warming the paw (i.e., raising the temperature to 37°C). This heightened responsiveness was mediated partly by the recruitment of neurons that had previously responded only to noxious heat (45°C) and partly by recruitment of neurons that had previously been unresponsive to thermal stimuli. Conversely, formalin suppressed neuronal responses to innocuous (29°C) and noxious (16°C) cold. Notably, selectively ablating peripheral sensory neurons that express TRPV1 attenuated the effect of formalin on cold sensitivity, suggesting the suppressive effect resulted from increased activity in heat-sensitive afferents that inhibit cold-sensitive spinal neurons. In contrast to formalin, oxaliplatin increased the responses of spinal neurons when the paw was cooled to 16°C, but slightly reduced the responses to 29°C and greatly reduced the responses to 37°C and 45°C stimuli.

These results demonstrate that molecules that induce thermal hypersensitivity do so in part by changing the responsiveness of neurons in the spinal cord. They further suggest that heat- and cold-sensing afferents exert inhibitory effects on dorsal horn neurons that respond to cold and warm temperatures, respectively. Future work should elaborate the circuits responsible for this crossover inhibition.

This Week in The Journal was written by Teresa Esch, Ph.D.
<https://doi.org/10.1523/JNEUROSCI.41.39.2021>