This Week in The Journal

Inhibition Varies Tonotopically in Avian Cochlear Nucleus

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(see pages 8904–8916)

Animals can localize sounds by comparing the time at which sounds reach each ear. In birds, this comparison relies on precise spike timing in the nucleus magnocellularis (NM), which receives direct input from auditory nerve fibers. How NM neurons achieve temporal precision varies with their characteristic frequency (CF), the sound frequency (pitch) that elicits the largest response. High-frequency sounds produce precisely timed spikes in auditory nerve fibers, and these provide powerful input that drives spikes with similar temporal precision in high-CF NM neurons. In contrast, auditory-nerve spikes evoked by low-frequency sounds have more temporal jitter. Because low-CF NM neurons receive relatively weak input from auditory fibers, however, they must integrate input from several fibers to reach spike threshold, and this increases temporal precision.

Differences in excitatory input are accompanied by differences in inhibition across NM. Notably, GABAergic input depolarizes NM neurons because the chloride reversal potential (E_{Cl}) is above resting membrane potential. Nevertheless, GABAergic input weakens the effects of excitatory input by producing shunting inhibition. This inhibitory effect is enhanced by the activation of K_{V1} potassium channels selectively in high-CF NM neurons. In addition, whereas both excitation and feedforward inhibition of low-CF NM neurons scale with the intensity of auditory nerve stimulation, only strong nerve stimulation produces inhibition in high-CF neurons.

Al-Yaari et al. further explored differences in inhibitory input across the tonotopic axis of NM. Compared with high-CF neurons, low-CF neurons received more GABAergic inputs and double the frequency of miniature IPSCs (mIPSCs). In contrast, the mean amplitude of mIPSCs, as well as evoked unitary IPSCs, was twofold smaller in low-CF than in high-CF neurons.

In addition, E_{Cl} was less depolarized in low-CF than high-CF neurons, and, consequently, exogenous GABA evoked less chloride efflux in low-CF neurons. Computational modeling suggested that the less depolarized E_{Cl} in low-CF neurons provided a compromise between increased temporal jitter, which occurred when E_{Cl} was below resting membrane potential, and loss of GABAergic inhibition, which occurred when a more depolarized E_{Cl} was paired with low expression of K_{V1} .

These results demonstrate that neurons' intrinsic properties, excitatory input, and inhibitory input must be coregulated to optimize neuronal output, and that this regulation may differ across neurons tuned to different values of the same class of stimuli.

Neurons in the low-CF region of NM (top) receive more inputs containing the vesicular GABA transporter (green) than neurons in the high-CF region (bottom). See Al-Yaari, Onogi, Yamada, et al. for details.

Cdkl5 Deficiency Boosts Inhibition and Blunts LTP in Dentate

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(see pages 9031–9046)

Mutation of the X-linked gene *CDKL5* causes CDKL5 deficiency disorder (CDD), characterized by intellectual disability, motor impairment, and seizures beginning in infancy. CDKL5 is a cyclin-dependent kinase-like protein that has roles in cell differentiation, neuron migration, dendrite growth, and spine dynamics. Although CDD is considered a neurodevelopmental

disorder, cognitive impairment in *Cdkl5*-deficient mice can be rescued by expressing the wild-type protein in adult animals. Therefore, a fuller understanding of how CDKL5 deficiency alters brain function may lead to the development of effective treatments for CDD. Hao, Wang, et al. have made progress on both of these fronts.

Because X chromosome inactivation leads to large phenotypic variation in females with heterozygous deletion of X-linked genes, most studies of CDKL5 deficiency have used male mice. Yet CDD affects more girls than boys. Therefore, Hao, Wang, et al. studied *Cdkl5*-deficient mice of both sexes. Consistent with previous work, male *Cdkl5*-deficient mice showed impairment on hippocampus-dependent learning tasks; females had similar impairments, but the deficits emerged later. At ages when learning deficits were present, *in vivo* stimulation of perforant pathway inputs to the dentate gyrus induced weaker long-term potentiation (LTP) of synapses with granule cells and produced greater feedforward inhibition of granule cells in *Cdkl5*-deficient mice than in controls. These effects were associated with suppression of AMPA-evoked currents in granule cells, reduced release probability at perforant-path inputs to these cells, and increases in AMPA currents in molecular-layer perforant-pathway (MOPP) interneurons—a major source of feedforward inhibition to granule cells. Notably, perforant pathway stimulation in hippocampal slices evoked larger-amplitude EPSCs in MOPP cells than in granule cells in wild-type mice, and *Cdkl5* deficiency increased this difference. Importantly, hippocampal infusion of a GABA antagonist reduced learning deficits in male *Cdkl5*-deficient mice, and deep brain stimulation in the fornix—a treatment previously shown to improve cognitive function in a mouse model of Rett syndrome—rescued learning deficits, LTP, and feedforward inhibition in female *Cdkl5*-deficient mice.

These results suggest that excessive feedforward inhibition and impaired LTP in the dentate gyrus contribute to cognitive deficits resulting from *Cdkl5* deficiency and that these effects can be reversed by stimulating the fornix. Future work should examine how fornix stimulation exerts its beneficial effects.

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