This Week in The Journal

Synaptic Determinants of Tonal Receptive Fields in Colliculus

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(see pages 6905–6921)

Auditory information travels from the cochlea to brainstem nuclei, which send converging projections to the central nucleus of the inferior colliculus (CNIC). Responses of CNIC neurons depend on sound frequency and intensity: at threshold intensity, neurons respond to a narrow frequency band, called the characteristic frequency; as intensity increases, the range of frequencies that elicit a response broadens, creating a V-shaped frequency-intensity tonal receptive field.

The precise shape of tonal receptive fields varies across CNIC neurons. In some cells (selective cells) the V is narrow with steep slopes, indicating the neuron responds to a narrow range of frequencies regardless of intensity. In other cells (sensitive-asymmetrical cells), the V has a shallow slope on one side and a steep slope on the other, indicating the cell responds to more frequencies on one side of the characteristic frequency than the other. And in sensitive-symmetrical cells, the V has two shallow slopes. These shapes are thought to arise from the pattern of excitatory and inhibitory inputs to cells.

To examine the relative contribution of excitatory and inhibitory inputs, Lee et al. used *in vivo* cell-attached recordings to map tonal receptive fields of mouse CNIC neurons, then obtained whole-cell voltage-clamp recordings of the same cells to measure synaptic inputs evoked by the same range of sounds. The relative shape and timing of excitatory and inhibitory inputs differed across cell types. Sensitive-symmetrical cells received excitatory and inhibitory input across a broad frequency range; the ranges overlapped, but inhibition lagged excitation at all frequencies. Sensitive-asymmetrical cells received excitatory and inhibitory input over a similarly broad range of frequencies, but the frequency tuning was sharper and the range was shifted toward higher frequencies for inhibition; inhibition lagged excitation at frequencies below the characteristic

frequency, but it was concurrent with excitation at higher frequencies. Finally, selective cells received excitatory inputs over a narrower frequency range than sensitive cells and received inhibition over a broader range; and excitation and inhibition arrived concurrently at all frequencies.

These results show that inhibition has a prominent role in shaping the response patterns of CNIC neurons. The source of this inhibition and whether it differs for sensitive and selective cells remains to be determined.

Schematic illustration of excitatory (blue) and inhibitory (yellow) frequency tuning curves for sensitive-symmetrical (top), sensitive-asymmetrical (middle), and selective (bottom) CNIC neurons. See Lee et al. for details.

Role of APP Extracellular Domain in Vesicle Release

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(see pages 6992–7005)

Amyloid precursor protein (APP) is a transmembrane protein that is cleaved by secretases and caspases to generate a variety of peptides. The most studied peptide fragment is β -amyloid ($A\beta$), which is generated by cleavage of APP in its extracellular domain by β -secretase, then in its transmembrane domain by γ -secretase. When produced at low levels, $A\beta$ enhances synaptic plasticity, but when overproduced, it forms oligomers that impair synaptic function and likely contribute to

Alzheimer's disease. Full-length APP also influences synaptic function, and this role can be disrupted by cleavage. For example, the intracellular domain of APP interacts with synaptic vesicle proteins to enhance vesicle release, and this function is inhibited by cleavage of the intracellular domain by caspase. Yao, Tambini, et al. suggest that a portion of the extracellular domain—which is present inside vesicles and endosomes after endocytosis—also interacts with vesicle proteins, but these interactions inhibit synaptic vesicle release and are disrupted by cleavage by α - or β -secretase.

Pull-down assays revealed that the extracellular/intravesicular domain of APP interacted with several synaptic vesicle proteins, including some proteins found exclusively in glutamate-containing vesicles, but few found exclusively in GABA-containing vesicles. These interactions were reduced by β -secretase-mediated cleavage and were eliminated by α -secretase cleavage. When an exogenous peptide representing a portion of the extracellular domain that included the α - and β -secretase cleavage sites was applied to hippocampal cultures, it reduced paired-pulse facilitation and increased the frequency of miniature EPSPs without affecting miniature IPSP frequency, presumably because the peptide interfered with interactions between vesicle proteins and endogenous full-length APP. A peptide that extended from the α -secretase cleavage site to beyond the β -secretase cleavage site similarly reduced paired-pulse facilitation and increased miniature EPSP frequency, but a peptide spanning from the membrane to the β -secretase cleavage site had no effect on synaptic transmission.

These results suggest that a portion of the APP extracellular/intravesicular domain spanning the β -secretase cleavage site contains a sequence that interacts with synaptic vesicle proteins and inhibits release at glutamatergic synapses. This site is disrupted by β -secretase cleavage and is eliminated by α -secretase cleavage. Thus, the results add to accumulating evidence that APP regulates synaptic transmission and that this regulation is tuned by cleavage.

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