This Week in The Journal

● Cellular/Molecular

Different PSD-95 Domains Regulate Synaptic Stability and Plasticity

James F. Sturgill, Pascal Steiner, Brian L. Czervionke, and Bernardo L. Sabatini

(see pages 12845–12854)

Neurotransmitter receptors, ion channels, second messengers, and cytoskeletal proteins are organized in the postsynaptic density (PSD) by scaffolding proteins such as PSD-95. Although the PSD is fairly stable, its makeup can be altered by neuronal activity to produce long-term potentiation (LTP) or depression (LTD). To study the dynamics of the PSD, Sturgill et al. tagged proteins with photoactivatable GFP and followed their turnover after two-photon laser photoactivation in dendritic spines in rat hippocampal slices. Turnover of PSD-95 was slower than that of other PSD proteins, suggesting it is a highly stable component. Brief application of NMDA to chemically induce LTD led to a rapid decrease in PSD-95 in the spine. Expressing various modified forms of PSD-95 in place of or in addition to endogenous PSD-95 revealed that only the two N-terminal protein-interaction domains were required for stable retention of PSD-95 in the spine and for the loss of stability after NMDA treatment.

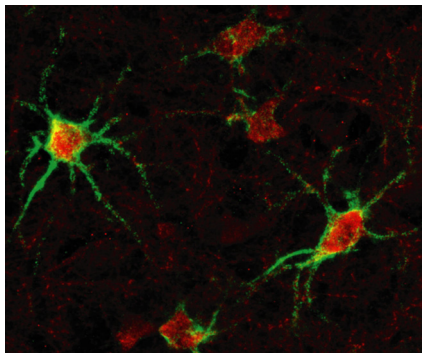
▲ Development/Plasticity/Repair

Development of Perineuronal Nets Parallels Song Maturation

Timothy S. Balmer, Vanessa M. Carels, Jillian L. Frisch, and Teresa A. Nick

(see pages 12878 –12885)

Much evidence suggests that ocular dominance plasticity is driven by a subset of fast-spiking, parvalbumin-expressing inhibitory interneurons that emerge as the critical period opens. As development proceeds, the somata and proximal dendrites of these interneurons become encapsulated by perineuronal nets composed of extracellular matrix proteins, and this might close the critical period. Similar mechanisms are thought to regulate critical periods in other sensory systems, and according to Balmer et al., also in the sensorimotor song system of zebra finches. In songbirds, sensory experience shapes the development of neuronal circuits required for producing normal song, and the premotor area HVC, which responds to auditory input and is essential for song production, is thought to be important in learning. The number of parvalbumin-expressing interneurons and the percentage of those with perineuronal nets increased during the critical period. Delaying the critical period decreased the percentage of neurons expressing parvalbumin and decreased intensity of labeling of perineuronal nets.



The percentage of parvalbumin-expressing neurons (red) that have perineuronal nets (green) increases during development in the zebra finch HVC. See the article by Balmer et al. for details.

■ Behavioral/Systems/Cognitive

FM Directional Selectivity Is Amplified in Bat Inferior Colliculus

Joshua X Gittelman, Na Li, and George D. Pollak

(see pages 13030 –13041)

Most sounds bats produce for communication and echolocation exhibit frequency modulation (FM); the sound sweeps upward or downward through a range of frequencies. Some neurons in the inferior colliculus (IC) are selective for upward or downward sweeps, and this selectivity is thought to be generated within the IC based on the relative timing of nonselective excitatory and inhibitory inputs. But Gittelman et al. now show that the inputs to IC have some directional selectivity, producing EPSPs of different magnitudes. IC neurons received excitatory input regardless of the FM sweep direction, but the sweeps in the preferred direction produced larger EPSPs that were more likely to elicit spikes. Although the timing of inputs was sometimes appropriate for producing directional selectivity, this was not always true, and modeling indicated that the magnitude of inputs was a stronger determinant of directionality in the recorded neurons. The authors note, however, that other IC cells might use timing asymmetries to construct FM directionality.

♦ Neurobiology of Disease

γ-Secretase Cleaves APP Terminal Fragment Multiple Times

Mako Takami, Yu Nagashima, Yoshihisa Sano, Seiko Ishihara, Maho Morishima-Kawashima, et al.

(see pages 13042–13052)

Amyloid precursor protein (APP) is cleaved by α-, β-, and γ-secretases, yielding various intracellular and extracellular fragments. Alzheimer's disease (AD) is associated with an increase in the levels of 42-amino-acid amyloid-β ($A\beta_{42}$) relative to $A\beta_{40}$, which results from a specific cleavage sequence by β-secretase then γ-secretase. Many mutations linked to AD are thought to increase processing of APP along this pathway. Whether AD pathology stems mainly from changes in the relative levels of Aβ or from the loss of products of alternative cleavage sequences is not clear, but regardless, driving APP toward nonpathological processing might be an effective treatment. Takami et al. have therefore studied how γ-secretase produces Aβ. They determined that the C-terminal fragment generated by β-secretase is first cleaved by γ-secretase at the membrane–cytoplasm border, producing $A\beta_{48}$ and $A\beta_{49}$. Subsequently, γ-secretase removes 2–3 tripeptides to produce $A\beta_{42}$ or $A\beta_{40}$, respectively. Conditions that favor cleavage to produce $A\beta_{49}$ might therefore reduce AD pathology.