This Week in The Journal

Cellular/Molecular

Zn^{2+}-Induced Cannabinoid Synthesis Reduces Vesicle Release

Tamara Perez-Rosello, Charles T. Anderson, Francisco J. Schopfer, Yanjun Zhao, David Gilad, et al.

(see pages 9259–9272)

Zinc is present in synaptic vesicles at glutamatergic terminals throughout the brain. After activity-induced release into the synaptic cleft, zinc modulates the activity of various receptors and ion channels—for example, inhibiting NMDA receptors and potentiating glycine receptors—and it activates metabotropic zinc-sensing receptors (mZnRs). Although zinc appears to affect synaptic plasticity, its roles have not been fully elucidated. Perez-Rosello et al. have discovered a new and unexpected action of zinc in the dorsal cochlear nucleus (DCN). In mouse brain stem slices, bath application of zinc reduced evoked release probability at parallel fiber terminals, reducing EPSC amplitudes in fusiform neurons of the DCN. Surprisingly, zinc also increased synthesis of the endocannabinoid 2-arachidonoylglycerol (2-AG) in DCN, and the effects of zinc on synaptic transmission were blocked by inhibiting 2-AG synthesis or antagonizing cannabinoid CB1 receptors on parallel fiber terminals. Altogether, the results suggest that zinc activates postsynaptic mZnRs, triggering synthesis of endocannabinoids that reduce release probability by acting on presynaptic CB1 receptors.

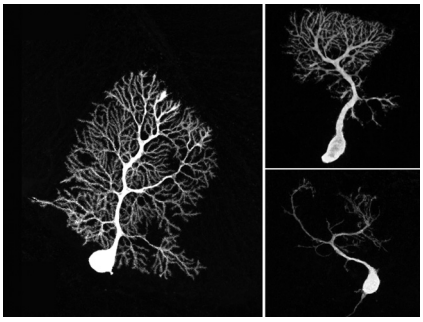
Development/Plasticity/Repair

RORα Is Required to Maintain Mature Purkinje Cell Dendrites

Xiao Ru Chen, Nicolas Heck, Ann M. Lohof, Christelle Rochefort, Marie-Pierre Morel, et al.

(see pages 9546–9562)

The acquisition of specific neuronal phenotypes is achieved through sequential expression of transcription factors, some of which continue to be expressed and define neuronal phenotype throughout life. One such factor is retinoic acid-related orphan receptor α (RORα), which is required during development of cerebellar Purkinje cells (PCs), particularly for elaboration of the dendritic arbor. To investigate the role of RORα in mature neurons, Chen et al. generated transgenic mice in which RORα was depleted from PCs starting after postnatal day 10. PCs developed normally for the first two postnatal weeks, but after RORα depletion, the size and complexity of the dendritic arbor decreased. The innervation of PCs also reverted to a less mature pattern after RORα depletion: many PCs became reinnervated by multiple climbing fibers that formed synapses mainly on the soma and stem dendrites. Together, the data suggest that RORα is required not only to promote maturation and proper innervation of PCs, but also to maintain the mature state in adulthood.



At postnatal day 15 (left), Purkinje cells newly deficient in RORα look normal, but two weeks later (right), dendritic arbors are shorter, and some have greatly atrophied. See the article by Chen et al. for details.

Systems/Circuits

Different Entorhinal Regions Represent Global and Local Cues

Joshua P. Neunuebel, D. Yoganarasimha, Geeta Rao, and James J. Knierim

(see pages 9246–9258)

The medial (MEC) and lateral (LEC) areas of entorhinal cortex provide the main cortical input to the hippocampus. Like hippocampal place cells, many MEC neurons fire at particular locations in an environment. In contrast, most neurons in the LEC lack obvious spatial tuning, and instead fire in response to encountering specific objects or object locations. Together, MEC and LEC are hypothesized to represent the "where" and "what" components of episodic memories. Neunuebel et al. further characterized the selectivity of MEC and LEC neurons by recording single-unit activity as rats ran on a track, which had prominent local cues, that was enclosed in an arena containing global cues. The track and arena were then rotated in opposite directions. As expected, the firing fields of MEC neurons rotated in parallel with the arena, indicating that these neurons represent global cues. In contrast, the firing fields of the few spatially tuned LEC neurons rotated in parallel with the track, suggesting that this population represents local cues.

Neurobiology of Disease

BTA-EG4 Reduces Aβ and Improves Memory

Andrea Megill, Taehee Lee, Amanda Marie DiBattista, Jung Min Song, Matthew H. Spitzer, et al.

(see pages 9306–9318)

Benzothiazole anilines (BTAs) are a group of small molecules that disrupt interactions between β-amyloid (Aβ) peptides and other proteins, and thus might reduce pathology associated with Alzheimer's disease (AD). A tetra-ethylene glycol derivative of BTA (BTA-EG4), for example, binds to Aβ aggregates and surrounds them with a bio-resistive coating. Megill et al. found that in cultures of mouse cortical neurons, BTA-EG4 increased the proportion of amyloid precursor protein (APP) that was present on the cell surface, where APP is cleaved by α-secretase. Consistent with this, BTA-EG4 increased production of α-secretase cleavage products while reducing levels of Aβ, a product of β-secretase cleavage. In addition, BTA-EG4 improved the performance of wild-type mice on spatial memory and fear conditioning tests, increased dendritic spine density in cortex and hippocampus, and increased the frequency of miniature EPSCs in hippocampal slices, suggesting that the number of synapses increased. BTA-EG4-mediated increases in spine density required expression of APP and RasGRF1, an activator of Ras GTPase that associates with APP.