This Week in The Journal

● Cellular/Molecular

With Estradiol Loss, Also Loss of Hippocampal Spines and LTP

Ricardo Vierk, Günter Glassmeier, Lepu Zhou, Nicola Brandt, Lars Fester, et al.

(see pages 8116 – 8126)

Women with breast cancer who receive the drug letrozole, an aromatase inhibitor that halts production of estradiol, often complain of memory problems. Investigations into estradiol's effects in the rat hippocampus have shown that it induces spine and spine synapse formation between CA1 and CA3 neurons and boosts long-term potentiation (LTP). Now Vierk et al. have shown the correlate: letrozole treatment led to a rapid and lasting reduction in LTP and in spine synapses. In acute hippocampal slices from systemically letrozole-treated female rats, LTP was diminished within 6 hours; after a week of treatment, LTP was gone. Cofilin is an actin-associated protein that promotes spine stability and is required for LTP in mice. Here, it was dephosphorylated in conjunction with the synaptic alterations. Similar but more modest findings were seen in male and ovariectomized rats. The work confirms that estradiol loss compromises spine and synapse stability as well as LTP.

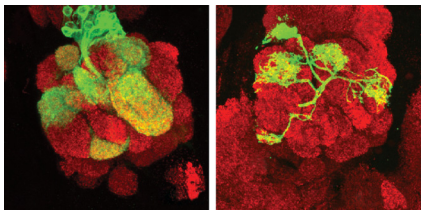
▲ Development/Plasticity/Repair

Projection Neuron Dendrites "Lost" without Novel SUMO Protease

Daniela Berdnik, Vincenzo Favaloro, and Liqun Luo

(see pages 8331 – 8340)

The *Drosophila* brain, with its relatively simple organization, has yielded important clues about how neural systems wire themselves during development. Olfactory projection neurons (PN) target one of ~50 glomeruli in the *Drosophila* antennal lobe via previously identified cell-autonomous molecules, but post-translational modifications also appear to contribute to targeting.



Wild-type PN dendrites target a stereotypical set of glomeruli (left). "Lost" dendrites of a single *Velo* mutant neuron mistarget multiple glomeruli within the antennal lobe (right). See the article by Berdnik et al. for details.

Berdnik et al. used a mosaic forward genetic screen to identify a novel predicted small ubiquitin-like modifier (SUMO) protease that seems to be required for dendrite targeting and for axon morphogenesis. In mutants, PN processes appeared "lost," prompting the authors to give the gene the German name *Verloren* (*velo*). Dendritic target innervation and axon formation were rescued by introduction of a *velo* transgene, indicating a cell-autonomous role for the protease. Velo's catalytic subunit was required for rescue, and related SUMO proteases compensated for dendritic targeting but not axon arborization defects. Genetic interactions suggested that Velo deconjugates poly-SUMO chains rather than promoting maturation.

■ Behavioral/Systems/Cognitive

Birdsong Processing Modulated by Endogenous Neuroestrogen

Luke Remage-Healey and Narendra R. Joshi

(see pages 8231 – 8241)

The auditory-information stream in a songbird's brain flows not in a straight, concrete channel but rather along a winding path subject to modulation. Endogenous neuroestrogens are among the factors that can influence the flow, according to Remage-Healey and Joshi. The authors previously showed that neuroestrogens are elevated in the zebra finch caudal nidopallium (NCM) in response to song stimuli; they now show that neuroestrogens enhanced song selectivity in the so-called high vocal center (HVC). This downstream sensorimotor-processing nucleus receives indirect input from NCM. The authors combined dual extracellular recordings and retrodialysis to determine that NCM estrogen rapidly modulated song selectivity of HVC neurons via a membrane-bound estrogen receptor. Aromatase inhibitors delivered to the NCM weakened song selectivity, whereas estrogen applied directly in the HVC or another adjacent area did not affect neurons' responses. The findings suggest an endogenous, specific, transsynaptic neuromodulation by estrogen. The modulation seen in adult males was absent in juvenile birds, reflecting a developmental requirement.

♦ Neurobiology of Disease

Biphasic Roles Revealed for JNK after Cerebral Ischemia

Yoshihiro Murata, Norio Fujiwara, Ji Hae Seo, Feng Yan, Xiangrong Liu, et al.

(see pages 8112 – 8115)

Acute stroke treatments must come within a critical time window, but a picture emerging from animal models suggests that later treatments might cause more harm than good. A growing list of molecules appears to act biphasically, contributing to cell death in the acute phase but necessary for later repair and recovery. Murata et al. now show that these include the neuronal death regulator c-Jun-N-terminal kinase (JNK). A JNK inhibitor delivered 10 minutes after transient occlusions of the middle cerebral artery significantly reduced infarct size. But when the inhibitor was given 7 days after occlusion, the damage was worse than in untreated animals. Late treatment with the JNK inhibitor reduced brain markers of neurovascular remodeling and diminished tube formation in an *in vitro* model of angiogenesis, suggesting a recovery role for the stress-activated protein. The biphasic nature of JNK—and other molecules—must be considered in the development of potential stroke therapeutics.