This Week in The Journal

● Cellular/Molecular

Palmitoylation Allows LTP-Induced Translocation of AKAP150

Dove J. Keith, Jennifer L. Sanderson, Emily S. Gibson, Kevin Woolfrey, Holly R. Robertson, et al.

(see pages 7119 –7136)

Many extracellular ligands activate receptors linked to adenylyl cyclase, which produces cAMP and thus activates protein kinase A (PKA). Different signaling molecules can produce different cellular effects because PKA is clustered with distinct upstream activators and downstream mediators in different subcellular domains. This targeting and clustering depends on A-kinase-anchoring proteins (AKAPs). In rodent neurons, AKAP150 targets PKA, protein kinase C, and phosphatases to postsynaptic densities in dendritic spines, where they regulate activity-dependent insertion and removal of AMPA receptors. Induction of long-term potentiation (LTP) promotes translocation of AKAP150 to spines, and experiments by Keith et al. reveal that this requires AKAP150 palmitoylation. Surprisingly, however, preventing palmitoylation by mutating palmitoylation sites increased basal translocation of AKAP150. As a result, the number of synapses increased and subsequent treatment to induce LTP decreased synaptic number. The data suggest palmitoylation is necessary for retaining AKAP150 in recycling endosomes until LTP-inducing stimuli trigger its translocation to spines.

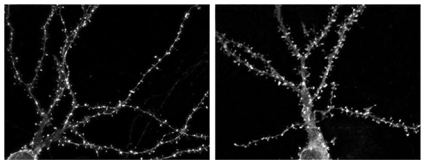
▲ Development/Plasticity/Repair

Potentiation of Recurrent Inhibition Produces Habituation

Indulekha P. Sudhakaran, Eimear E. Holohan, Sahar Osman, Veronica Rodrigues, K. VijayRaghavan, et al.

(see pages 7225–7231)

Like all animals, *Drosophila* exhibit habituation to repeated presentation of the same stimulus; for example, prolonged exposure to an aversive odor reduces subsequent avoidance of that odor. This habituation involves calcium-dependent signaling in



Rat hippocampal neurons expressing a human form of AKAP150 lacking the palmitoylation site (right) have more glutamatergic synapses than neurons expressing the wild-type form (left). See the article by Keith et al. for details.

GABAergic local interneurons (LN1s) of the antenna lobe, packaging of glutamate by LN1s, and expression of NMDA and $GABA_A$ receptors in antennal lobe projection neurons (PNs). Previous work indicated that persistent activation of LN1s is sufficient to reduce aversive responses to odors. Sudhakaran et al. extend these findings, showing that neurotransmitter release from PNs is also necessary for odor-induced habituation. Moreover, persistent activation of PNs that respond to a given odor was sufficient to induce habituation to that odor in the absence of peripheral input. Habituation also required functional electrical synapses between excitatory local interneurons and LN1s. Together, these data indicate that odor-specific habituation in *Drosophila* is mediated by NMDAR-dependent potentiation of recurrent inhibitory synapses from LN1s to PNs.

■ Behavioral/Systems/Cognitive

Cannabinoid Signaling Influences Responses to Threat

Mathilde Metna-Laurent, Edgar Soria-Gomez, Danièle Verrier, Martina Conforzi, Pierrick Jégo, et al.

(see pages 7109 –7118)

In threatening situations, animals can either try to minimize injury passively or actively attempt to escape. For example, mice conditioned to associate a tone with receiving a shock initially freeze (a passive response) when hearing the tone, but with repeated exposure, they switch to active responses, such as rearing or digging. Individuals differ in how quickly they make this switch, and those that exhibit fewer passive responses in a closed chamber are quicker to learn to escape when it is possible, suggesting their tendency to respond actively is consistent across conditions. Metna-Laurent et al. present evidence that endocannabinoid signaling in glutamatergic and GABAergic neurons has differential effects on this tendency. Mice lacking type-1 cannabinoid receptors (CB1) in telencephalic glutamatergic neurons exhibited more passive responses, whereas those lacking CB1 in GABAergic neurons exhibited more active responses. Additionally, low doses of CB1 agonist promoted active responses in wild-type mice, whereas high doses promoted passive responses.

♦ Neurobiology of Disease

Tau Mutations Decrease Microtubule Stability

Donna M. Barten, Patrizia Fanara, Cathy Andorfer, Nina Hoque, P. Y. Anne Wong, et al.

(see pages 7137–7145)

Microtubules are in a state of "dynamic instability" in which tubulin subunits are continually added and removed from the tips. In neurites, microtubule associated proteins (MAPs), such as tau, increase microtubule stability. Mutation, abnormal phosphorylation, and/or aggregation of tau is associated with several neurodegenerative diseases, including frontotemporal dementia (FTD). Such tauopathies are generally thought to result from microtubule destabilization, but this had not been confirmed *in vivo*. To do so, Barten et al. fed mice ^2H_2O, allowed ^2H to become incorporated into newly synthesized tubulin, then purified brain microtubules and determined what fraction of free and microtubule-associated tubulin subunits were labeled. Microtubules from mice harboring FTD-linked tau mutations incorporated more newly synthesized tubulin than those of wild-type mice, suggesting subunit turnover was indeed increased. Treating mice with a microtubule-stabilizing drug reduced turnover to normal levels and reversed learning deficits in mutant mice. Interestingly, however, cognitive improvements required shorter treatment duration than increases in stability.