This Week in The Journal

Protein Kinase C Enhances Electrical Transmission in Aplysia

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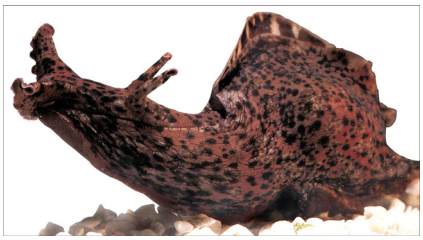
(see pages 2796–2808)

Neuroendocrine neurons produce relatively long-lasting changes in behavioral state by secreting neuropeptides into the blood. A rapid increase in circulating hormone levels is sometimes required to trigger a specific event, such as ovulation. To achieve this, many neurons must fire synchronously for an extended period (minutes to hours). Whereas prolonged changes in firing patterns can be produced by altering ion-channel function or expression, synchronous firing often relies on electrical coupling between neurons.

The neural mechanisms regulating neuropeptide secretion have been studied extensively in *Aplysia* bag cell neurons. Brief (5–15 s) stimulation of these otherwise silent neurons elicits a prolonged (~30 min) afterdischarge, during which repetitive spiking results in secretion of a hormone that stimulates egg-laying behavior. This afterdischarge requires insertion of voltage-dependent cation channels, which depends on protein kinase C (PKC) activation. Because bag cell neurons are electrically coupled via gap junctions, stimulation of inputs to just a few cells generates afterdischarges in the entire population. Gap junctions can also be phosphorylated by PKC, and in other cell types, this reduces electrical coupling. Therefore, activation of PKC during the afterdischarge might limit synchronization of bag cell neurons.

To determine whether this is the case, Beekharry et al. cultured dissociated bag cell neurons in pairs. The pairs formed electrical synapses, so spikes generated in one neuron produced electrotonic potentials in the other. Surprisingly, electrotonic potentials were much larger in the presence of a PKC activator than under control conditions. Moreover, producing an action-potential-like waveform in one neuron under voltage-clamp conditions was more likely to induce spiking in the second neuron in the presence than in the absence of PKC activation. The potentiation of electrical transmission by PKC was at least partly attributable to increased junctional current, although an increase in voltage-dependent calcium currents also contributed to the effect.

These results indicate that PKC has an unusual role in bag cell neurons: enhancing, rather than inhibiting electrical transmission. Thus, PKC not only helps generate afterdischarges in these neurons, but also helps to ensure that all neurons fire synchronously during afterdischarges. Whether PKC potentiates electrical transmission by phosphorylating the connexins that form gap junctions or through other means remains to be determined.



PKC enhances the release of egg-laying hormone in multiple ways in *Aplysia*. See Beekharry et al. Image from Columbia University, National Human Genome Resource Institute photo gallery.

AMPK Mediates Effects of Intellectual Disability Gene

Charlotte C. Bavley, Richard C. Rice, Delaney K. Fischer, Amanda K. Fakira, Maureen Byrne, et al.

(see pages 2780–2795)

Function-disrupting mutations in both copies of the gene encoding cereblon (*CRBN*) causes nonsyndromic intellectual disability in humans. Because cereblon affects the activity of many other proteins, however, the molecular links between its mutation and impaired cognitive function are unclear. One major function of cereblon is to help target proteins—including a subunit of large-conductance calcium-activated potassium channels—for ubiquitination and degradation. Elevated expression of these channels, which are required for some forms of learning, might therefore contribute to intellectual disability resulting from cereblon deficiency. Another function of cereblon is to inhibit activation of AMP-activated protein kinase (AMPK). AMPK is usually activated when cellular AMP levels are high and ATP levels are low, and it helps conserve energy by inhibiting protein synthesis. Therefore, excessive activation of AMPK resulting from cereblon deficiency might lead to cognitive deficits by preventing protein-synthesis-dependent synaptic plasticity (Kim et al. 2016 Pflügers Arch 468:1299).

Bavley, Rice, et al. tested the latter hypothesis in mice. They showed that cereblon is expressed in mouse hippocampus and that reducing *Cbrn* either globally or selectively in the dorsal hippocampus impaired performance on spatial learning and contextual fear conditioning tasks. Global *Cbrn* knock-out also reduced induction of long-term potentiation in hippocampal CA1 neurons after electrical stimulation of Schaffer collaterals, and it inhibited postsynaptic insertion of GluA1 receptors after NMDA receptor activation. As expected, activation (as indicated by phosphorylation) of AMPK was higher in hippocampal synaptosomal fractions from *Cbrn*-null mice than in controls. In contrast, activation of proteins in the mTORC1 pathway—which promotes local protein synthesis and is regulated by AMPK—was reduced. Consistent with this, levels of several synaptic glutamate receptor subunits were also reduced in *Cbrn*-null synaptosomes. Most importantly, a specific inhibitor of AMPK reversed reductions in mTORC1 pathway activation and in postsynaptic protein levels, and it rescued learning deficits in *Cbrn*-null mice.

These results suggest that hyperactivation of AMPK and downstream inhibition of synaptic protein synthesis are major contributors to learning deficits resulting from loss of cereblon function. Moreover, the results suggest that these deficits can be rescued by inhibiting AMPK function. Targeting the AMPK–mTORC1 pathway might therefore be beneficial in people with loss-of-function *CBRN* mutations.

This Week in The Journal was written by Teresa Esch, Ph.D.