This Week in The Journal

Dystroglycan Selectively Affects CCK-Expressing Synapses

Simon Früh, Jennifer Romanos, Patrizia Panzanelli, Daniela Bürgisser, Shiva K. Tyagarajan, et al.

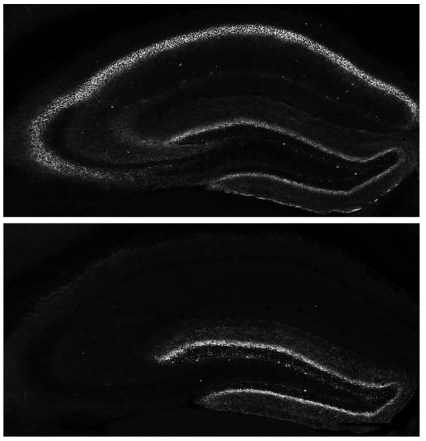
(see pages 10296–10313)

The dystrophin glycoprotein complex—comprising the intracellular actin-binding protein dystrophin, the transmembrane protein ß-dystroglycan, and the extracellular matrix-binding protein α-dystroglycan, along with other proteins—forms a structural link between the cytoskeleton and the extracellular matrix (ECM). This complex stabilizes muscle membranes, preventing damage during contraction, and it contributes to ECM-dependent signaling cascades. Mutations that disrupt this complex cause muscle degeneration in muscular dystrophy.

The dystrophin glycoprotein complex is also expressed in the CNS, where it contributes to neuronal migration and clusters adjacent to GABAergic terminals in the somata of mature cortical and hippocampal pyramidal neurons. Although α-dystroglycan binds to neurexins, which interact with neuroligins to induce clustering of $GABA_A$ receptors ($GABA_ARs$), GABAergic synapses still form in dystroglycan-deficient neurons, leaving the role of dystroglycan at these synapses unclear (Waite et al. 2012 Trends Neurosci 35:487).

To address this question, Früh et al. knocked out *Dag1*, the gene encoding both α- and ß-dystroglycan, selectively in pyramidal neurons. Unexpectedly, loss of *Dag1* affected only the synapses between cholecystokinin-expressing interneurons and pyramidal cells; synapses with parvalbumin-expressing basket cells appeared normal. *Dag1* knockout reduced the density of markers of cholecystokinin-expressing synaptic terminals on pyramidal cell bodies and reduced the density of cholecystokinin-positive somata in the hippocampus. In addition, staining for cholecystokinin, but not parvalbumin, was reduced throughout the somatosensory cortex. Consistent with loss of cholecystokinin-expressing inhibitory synapses, the amplitude and frequency of spontaneous IPSCs were reduced in hippocampal pyramidal cells. Furthermore, a cholinergic agonist, which excites cholecystokinin-expressing neurons and increases sIPSC frequency in wild-type pyramidal neurons, had no significant effect on *Dag1*-null neurons.

Knocking out *Dag1* in adult mice also reduced the density of cholecystokinin synaptic markers, suggesting dystroglycan is required for synaptic maintenance as well as synaptogenesis. Surprisingly, however, a mutation that abolishes interactions between dystroglycan and neurexins and causes intellectual disability in humans did not affect markers of cholecystokinin synapses, suggesting that dystroglycan does not promote cholecystokinin synapse formation and maintenance by binding to neurexins. Future work should identify dystroglycan partners that support cell-type-specific synaptic development and maintenance, as well as determining how loss of cholecystokinin synapses affects hippocampal function.



Cannabinoid receptors are expressed in the terminals of cholecystokinin-expressing interneurons surrounding pyramidal cell bodies in the hippocampus (top). Knocking out dystroglycan in pyramidal neurons (bottom) reduces the density of these synapses. See Früh et al. for details.

Cholinergic Fibers Compensate for Loss of Entorhinal Input

Jean-Bastien Bott, Céline Héraud, Brigitte Cosquer, Karine Herbeaux, and Julien Aubert

(see pages 10472–10486)

Mild cognitive impairment (MCI), along with loss of entorhinal cortical neurons, often occurs with age. Although MCI often precedes Alzheimer's disease (AD), not all people with MCI develop AD, and cognitive function sometimes improves. Mechanisms that compensate for loss of entorhinal inputs to the hippocampus—possibly including upregulation of cholinergic signaling—likely underlie such improvement.

The risk of developing AD is highest in people expressing the ε4 allele of the lipid-transporting protein apolipoprotein E (*APOE4*). *APOE4* may increase AD risk partly by impairing synaptic maintenance and remodeling, which require lipid transport. Previous work by Bott et al. (2013 Neurobiol Aging 34:2683) revealed that while mice expressing human *APOE3* exhibited cholinergic sprouting and recovery of spatial memory function after partial lesion of the entorhinal cortex, mice expressing human *APOE4* did not. These results suggested that APOE4 impairs cholinergic sprouting, which otherwise compensates for loss of entorhinal neurons.

The authors now provide additional support for these hypotheses. They compared the extent of behavioral recovery to the extent of glutamatergic and cholinergic axon sprouting in the hippocampus at different times after entorhinal lesions in male and female mice expressing *APOE3* or *APOE4*. In all cases, restored memory function was associated with sprouting of glutamatergic or cholinergic fibers. In male *APOE3* mice, behavioral recovery occurred by 70 days post lesion (70 dpl), when cholinergic sprouting was extensive and glutamatergic innervation was restored. Cholinergic sprouting never occurred in *APOE4* males, however, and behavioral recovery and glutamatergic re-innervation were delayed until after 70 dpl. Unlike males, neither *APOE3* nor *APOE4* females showed spatial memory deficits even at 30 dpl. Notably, cholinergic sprouting was apparent at this time in both genotypes, but glutamatergic innervation was never restored in *APOE4* females. Finally, entorhinal lesions led to bursts of high-amplitude activity in the dentate gyrus of mice expressing channelrhodopsin in cholinergic neurons, and optical stimulation of cholinergic fibers restored activity to normal levels.

These results support the hypothesis that cholinergic sprouting compensates for loss of entorhinal neurons in the early stages of MCI. The results also suggest that *APOE4* increases AD risk by reducing growth of both cholinergic and glutamatergic fibers, and importantly, that the effects are sex dependent, at least in mice. Therefore, sex differences should be considered when developing and evaluating potential therapies for treating MCI.

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