This Week in The Journal

Cell-Autonomous Role of FMRP in Auditory Brainstem

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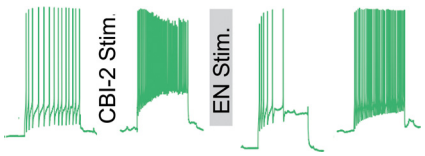
(see pages 6445–6460)

Mutations that inhibit production of fragile X mental retardation protein (FMRP) cause fragile X syndrome (FXS), the most common inherited form of intellectual disability. In addition to language and social deficits, many people with FXS are hypersensitive to sensory input, particularly sound. FXS phenotypes are thought to stem from synaptic dysfunction, because FMRP, an mRNA-binding protein, regulates translation of many synaptic proteins, and neurons lacking FMRP have excessive numbers of immature dendritic spines. Furthermore, excitatory transmission is enhanced and inhibition is diminished in several brain areas, including auditory cortex, in FMRP-deficient mice (Rotschafer and Razak, 2014 Front Cell Neurosci 8:19).

Although much is known about the effects of FMRP loss on synaptic transmission, most of this knowledge comes from studies in which FMRP was deleted from all neurons. This confounds interpretation, because cell-autonomous effects cannot readily be distinguished from those resulting from changes in circuit function. To circumvent this problem, Wang et al. transfected a subset of auditory brainstem nucleus magnocellularis (NM) neurons in embryonic chicks with short-hairpin RNAs targeting FMRP. NM neurons normally begin to extend dendrites by embryonic day (E)9, but dendritic arbors almost completely retract by E15. This pruning is required for auditory nerve fibers to form large synapses (endbulbs of Held) on NM-neuron somata at E19. Knocking down FMRP impaired dendritic growth in NM neurons, so at E11, FMRP-deficient neurons had smaller dendritic arbors than their untransfected neighbors. But FMRP knockdown also slowed retraction, so at E15, when control neurons had only 1–2 short neurites, FMRP-deficient neurons still had extensive arbors. Consequently fewer, smaller afferent terminals apposed the somata of FMRP-deficient neurons than those of control neurons. Instead, presynaptic terminals apposed the dendrites of FMRP-deficient neurons, and consequently, spontaneous EPSCs recorded in the soma were smaller, with slower kinetics than normal. In addition, fewer GABAergic terminals surrounded FMRP-deficient neurons than controls. By E19, however, most differences between FMRP-deficient and control neurons had disappeared.

These results indicate that loss of FMRP slows both growth and pruning of dendrites in NM neurons, and this disrupts the development of synaptic input to the cells. Although the FMRP-deficient neurons eventually catch up with their neighbors, this early deficiency might lead to downstream impairment in circuit development.



The excitability of B48, reflected in the number of spikes elicited by current injection, increases from baseline (trace 1) after repeated stimulation of CBI-2 (trace 2). Stimulating EN after CBI-2 temporarily reduces B48 excitability (trace 3) to below baseline levels, but after 10 min, the hyperexcitable state reemerges (trace 4). See Perkins et al. for details.

A Mechanism for Rapidly Switching Motor Patterns

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(see pages 6475–6490)

Ongoing motor behaviors must sometimes be interrupted briefly, to allow production of a competing behavior. This happens, for example, when one must jump over an obstacle while running. After the interruption, the original motor behavior often resumes immediately. What allows neural circuits controlling such behaviors to switch seamlessly from one pattern to another?

This question has been addressed using *Aplysia*. When eating, *Aplysia* ingest food by opening their food-grasping organ, the radula, while extending it, then closing the radula while retracting it, thus drawing food into the mouth. Occasionally, *Aplysia* must egest partially ingested items; to do so, they open the radula while retracting it, then close it during protraction. The motor pattern driving ingestion can be evoked *in vitro* by repeatedly activating a command neuron (CBI-2). The resulting release of neuromodulators progressively increases the excitability, and thus spiking, of B48, a motor neuron that opens the radula. The ingestive pattern persists for up to 30 min, but it can be switched temporarily to the egestive pattern by stimulating the esophageal nerve (EN). How does this affect B48?

Perkins et al. found that stimulating EN reduced excitability and spiking in B48 for ~10 min. When EN was stimulated in the absence of an ongoing motor pattern, B48 excitability returned to baseline after 10 min. But when EN was stimulated shortly after CBI-2, the 10 min period of reduced B48 excitability was followed immediately by the heightened excitability state characteristic of ingestive motor patterns. Intriguingly, increases and decreases in B48 excitability were mediated by different currents: CBI-2 stimulation increased B48 excitability by activating a tonic, cAMP-dependent inward current, whereas EN stimulation reduced B48 excitability by activating an outward current.

Together, these results indicate that the inward current that supports ingestive motor patterns is not inactivated to allow egestion. Instead, when the egestive pattern is evoked, activation of an outward current in B48 temporarily masks the ingestion-related inward current. Consequently the ingestive motor pattern can resume immediately after an egestive bout, without need for a new ingestion-inducing stimulus. This might enable animals to consume the available food as quickly as possible.

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