This Week in The Journal

Visualizing Calcium in Endoplasmic Reticulum

Yohei Okubo, Junji Suzuki, Kazunori Kanemaru, Naotoshi Nakamura, Tatsuo Shibata, et al.

(see pages 15837–15846)

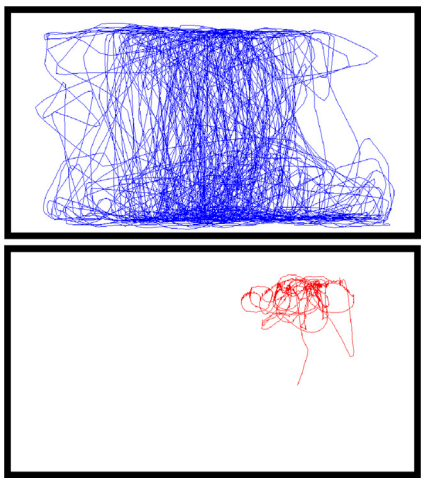
Calcium regulates numerous neuronal processes, including neurite growth, gene expression, and long-term plasticity. Ca^{2+} can enter neurons through ligand- and voltage-gated channels, and it is removed from the cytoplasm by Ca^{2+} pumps in the plasma membrane and endoplasmic reticulum (ER). Ca^{2+} can also be released from the ER via inositol trisphosphate (IP_3) and ryanodine receptors in the ER membrane. This release boosts cytosolic Ca^{2+} levels after activation of metabotropic glutamate receptors (mGluRs, which increase IP_3 production) or NMDA receptors (which trigger Ca^{2+}-induced Ca^{2+} release), and thus helps to activate downstream signaling pathways.

Cytoplasmic Ca^{2+} levels are spatially restricted by Ca^{2+} buffers and the presence of barriers, such as the necks of dendritic spines. In contrast, Ca^{2+} is thought to diffuse rapidly in ER. Studies of ER Ca^{2+} dynamics have been hindered by the lack of good reporters, however. To overcome this obstacle, Okubo et al. targeted a genetically encoded fluorescent Ca^{2+} sensor to the ER using an ER retention signal. They used the sensor to measure ER Ca^{2+} changes resulting from synaptic stimulation of mouse Purkinje cells in cerebellar slices.

Stimulating parallel fibers (which activate mGluRs) caused a local decrease in ER fluorescence, indicating that the stimulation caused spatially restricted Ca^{2+} release as expected. Local ER Ca^{2+} levels were restored by diffusion within the ER, with only a slight contribution from the ER Ca^{2+} pump (SERCA). ER Ca^{2+} readily diffused from the dendritic shaft into spine heads, suggesting that the spine neck does not present the same barrier to ER Ca^{2+} diffusion as it does to cytoplasmic diffusion.

In contrast to parallel-fiber stimulation, stimulation of climbing fibers—which induce dendritic Ca^{2+} spikes—led to SERCA-dependent increases in ER Ca^{2+} levels throughout dendrites. ER Ca^{2+} levels returned to baseline within minutes, but in the meantime, mGluR1-induced Ca^{2+} release was enhanced.

These results not only confirm that Ca^{2+} readily diffuses in the ER lumen, but also demonstrate that ER Ca^{2+} uptake and release enable climbing-fiber inputs to potentiate Purkinje cell responses to parallel-fiber inputs. The ability to visualize changes in ER Ca^{2+} may help researchers discover other ways the ER contributes to synaptic integration, as well as how dysregulation of Ca^{2+} leads to neurodegeneration.



Adult zebrafish swim-paths show that fish with left-lateralized parapineals (blue) explored a larger proportion of the tank than fish with right-lateralized parapineals (red). See Facchin et al. for details.

Behavioral Effects of Reversed Asymmetry

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(see pages 15847–15859)

Asymmetries in brain structure and function are found throughout vertebrate species. They have been hypothesized to improve processing efficiency and reduce interhemispheric competition. Although similar efficiency could theoretically be gained regardless of which hemisphere controls any given function, the fact that many functions are lateralized to the same hemisphere across individuals of a species (e.g., language in the left hemisphere in humans) suggests that such directional asymmetries are evolutionarily advantageous. In fact, hemispheric specializations are conserved even across vertebrate species. For example, the left hemisphere typically specializes in focused attention, categorization, and sequential processing, while the right hemisphere contributes more to stimulus differentiation, strong emotions (especially fear), and social cognition (Rogers, 2014, Genesis 52:555). Still, the benefits of directed asymmetry remain poorly understood.

Zebrafish are an excellent animal model for addressing this question. In 95% of zebrafish, the parapineal (a photosensitive structure not found in higher vertebrates) is located on the left side of the pineal and projects exclusively to the left habenula. This lateralization helps drive asymmetrical development of the habenula, a structure involved in reward, anxiety, and stress responses. In 2–5% of zebrafish, both parapineal and habenular asymmetry are reversed. Facchin et al. found that axons projecting from the parapineal to the habenula were stunted in these fish. Furthermore, fish with reversed parapineal asymmetry (R_{PP}) released more cortisol in response to stress than fish with normal asymmetry (L_{PP}).

Reversing parapineal lateralization also caused behavioral abnormalities. Compared to L_{PP} fish, R_{PP} fish took longer to begin swimming when placed in a new tank, and they were less likely to enter the top half of the tank. In tanks with mirrored sides (where reflections were probably interpreted as other fish), R_{PP} fish tended to stay near the edges, whereas L_{PP} fish often crossed the middle of the tank. Interestingly, treating R_{PP} fish with an anxiolytic agent eliminated these behavioral differences.

These results suggest that reversing parapineal asymmetry increases physiological and behavioral responses to stress in zebrafish. They thus lend some credence to the hypothesis that abnormal asymmetry contributes to neurodevelopmental disorders such as dyslexia, autism, and schizophrenia in humans (Rogers, 2014, Genesis 52:555).

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