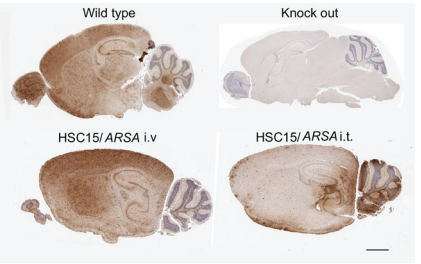
This Week in The Journal

Early Experience Accelerates Maturation of Spatial Memory

Maria P. Contreras, Julia Fechner, Jan Born, and Marion Inostroza

(see pages 3509–3519)

How do we accumulate knowledge, particularly during development? According to classical theories dating back 100 years, this process depends on current experience, time, and prior knowledge. And although still mysterious, sleep is now understood to play an important role in memory consolidation and cognitive development, which may be reflected in its complex, detectable features during slow-wave sleep—namely hippocampal sharp-wave ripples, thalamocortical sleep spindles, and neocortical slow oscillations (SOs). This week, Contreras et al. demonstrate in juvenile rats that discreet spatial experience speeds the maturation process, in keeping with previous studies. Rats were exposed on 3 d [postnatal day 25 (P25), P27, and P29] for 5 min intervals to two identical objects presented in different spatial configurations; control rats were exposed to the same objects with no change in configuration. An Object-Place Recognition (OPR) task at P31, when spatial memory has yet to develop, showed that the experience allowed rats to form OPR memory, which was not observed in control rats. The OPR memory was reflected by changes in sleep oscillatory signatures of memory processing, which were recorded as local field potentials by implanted electrodes and surface EEG signals. Specifically, rats exposed to the spatial task showed increases in ripples that were coupled to SO–spindle complexes in the parietal cortex with hippocampal ripples recorded during sleep in a 3 h retention interval between training and testing. The findings show that cognitive maturation in cortical and hippocampal networks depends on integration of new experiences with existing knowledge, which is consolidated during sleep. In support of Piaget's classical work, the authors find that prior spatial experiences can accelerate the maturation of adult-like spatial capabilities.



Brain slices stained for ARSA from wild type, *Arsa* knockout, and HSC15/*ARSA*-treated mice (intrathecally and intravenously).

Optimizing Gene Therapy Delivery for Metachromatic Leukodystrophy

Thia St. Martin, Tania A. Seabrook, Katherine Gall, Jenn Newman, Nancy Avila, et al.

(see pages 3567–3581)

Metachromatic leukodystrophy (MLD), a rare autosomal-recessive genetic disease that strikes early in childhood, first manifests as developmental delay with worsening motor and cognitive deficits, peripheral neuropathy, spasticity, and sensory impairments. This lysosomal storage disease arises from a mutation in the gene encoding arylsulfatase-A (ARSA), an enzyme responsible for breaking down sulfatides, sphingolipids found in myelin on both central and peripheral axons, and in some organs. The loss of ARSA results in toxic accumulation of sulfatides, demyelination, neurodegeneration, and neuroinflammation as well as organ dysfunction. In an existing gene therapy, called Libmeldy, the patient's own hematopoietic stem cells (HSCs) are collected from bone marrow, transduced *ex vivo* with a lentiviral vector containing the *ARSA* gene, and returned to the patient's body. Clinical trials are also testing two other therapies using intrathecal delivery of a therapeutic enzyme, in this case ARSA. This week, St-Martin et al. compare two viral capsids and routes of delivery of the therapeutic *ARSA* gene in a mouse model of MLD with striking results.

The researchers used two viral capsids: adeno-associated virus 9 (AAV9) or AAVHSC15, derived from stem cells, and carrying *ARSA*. A single intravenous injection of HSC15/*ARSA* to *Arsa* knock-out (KO) mice was significantly more effective at transducing CNS cells than was AAV9, restoring ARSA biodistribution in the mice. Intravenous delivery of HSC15/*ARSA* to mice lacking *Arsa* produced a more uniform and natural biodistribution of ARSA across the brain than an intrathecal bolus delivered to the spinal cord, which results in concentrated protein there and an "outside-in" distribution in the brain. Intravenous injection of HSC15/*ARSA* also resulted in physiological levels of ARSA activity in the brain and in peripheral organs, and corrected behavioral motor dysfunction in *Arsa* KO mice. The authors next examined three key biomarkers used in the diagnosis and tracking of MLD: levels of sulfatides, an indicator of lysosomal burden, and a marker for astrogliosis. Injection of HSC15/*ARSA* normalized sulfatide levels, rescued lysosomal burden, and prevented or ameliorated astrogliosis in the brains of *Arsa* KO mice. The results were similar in a smaller study testing HSC15/*ARSA* injection in nonhuman primates, suggesting that the findings might also translate to people.

This Week in The Journal was written by Stephani Sutherland

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