This Week in The Journal

How Sensory Axons Invade the Spinal Cord

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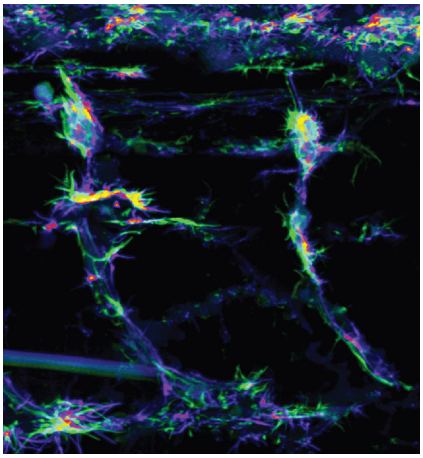
(see pages 6617–6636)

The brain and spinal cord are surrounded and protected by a multilayered sheath composed of specialized extracellular matrix (basement membrane), glial processes (forming the glia limitans), and meninges. During development, components of this barrier guide and restrict neuronal migration and neurite growth: only sensory and motor axons extend across the boundary, and they do so only at defined motor exit points (MEPs) and dorsal root entry zones (DREZs). To penetrate the barrier at these sites, growth cones of growing sensory and motor axons form specialized actin-based protrusions called invadopodia, which secrete matrix metalloproteases to degrade the basement membrane locally. What causes invadopodia to form at MEPs and DREZs has been unclear.

To address this question, Kikel-Coury et al. tracked the formation of invadopodia as growth cones of zebrafish dorsal root ganglion (DRG) neurons invaded the spinal cord. They found that invadopodia did not form exclusively at the DREZ, but the number and stability of invadopodia increased when growth cones reached this site. Notably, the increase in invadopodia was balanced by a decrease in the length of filopodia, the actin-based structures that probe the surroundings as growth cones navigate to their targets. Consistent with previous results, the number of invadopodia in growth cones navigating toward or present at the DREZ was reduced by photoactivation of the small GTPase Rac1; this was accompanied by an increase in filopodia length. Conversely, inhibiting Rac1 increased the number of invadopodia and reduced filopodia length. Importantly, Rac1 inhibition also reduced the number of DRG axons that entered the spinal cord. The effects of inhibiting Rac1 were mimicked by knocking out the netrin receptor dcc, and the effects of both manipulations were rescued by treating fish with sp-cAMP, an activator of protein kinase A (PKA).

Based on these and previous results, the authors propose that netrin secreted by the spinal cord floor plate binds to dcc on DRG growth cones, leading to PKA-dependent activation of Rac1, which limits stabilization of invadopodia. As axons grow dorsally along the glia limitans, the netrin signal declines, allowing invadopodia to stabilize and break down the basement membrane at the DREZ, thus allowing axons to enter the spinal cord.



As the growth cones of DRG axons reach the DREZ of the spinal cord, actin shifts from forming long filopodia to forming stable invadopodia. See Kikel-Coury et al. for details.

Roles for Oxytocin and Dopamine in Paternal Behaviors

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(see pages 6699–6713)

Newborn mammals depend on parents for food, warmth, and protection. In most species, such care is provided exclusively by the mother: fathers provide essential care in only 3–5% of species. Much is known about the hormones and neural circuits that govern maternal care. Central to these is the median preoptic area (MPOA) of the hypothalamus, whose activity is regulated by pregnancy-related hormones, including oxytocin. Oxytocin also supports maternal behaviors through actions in the ventral tegmental area (VTA) and nucleus accumbens (NAc), which likely enhance the rewarding properties of caregiving. Although the neural underpinnings of paternal care are less well studied, the central role of the MPOA is retained (Feldman et al., 2019, Nat Rev Neurosci 20:205). He et al. now provide evidence that oxytocin signaling in the VTA and NAc also promotes paternal behaviors in mandarin-vole fathers, which normally assist in pup care.

The authors expressed a calcium indicator or designer receptors exclusively activated by designer drugs (DREADDs) in oxytocin-expressing neurons in the hypothalamic paraventricular nucleus (PVN). They selectively targeted neurons that project to the VTA or NAc. Calcium imaging revealed that both VTA-projecting and NAc-projecting oxytocin neurons were activated when fathers approached and groomed their pups, but not when they simply crouched over pups or engaged in nonparental behaviors. VTA-projecting neurons were also active when fathers ate carrots. DREADD-mediated activation of either VTA-projecting or NAc-projecting oxytocin neurons increased grooming of pups and caused fathers to retrieve displaced pups more quickly than normal. In contrast, inhibition of either population reduced pup grooming without affecting pup retrieval. DREADD-mediated inhibition of VTA-projecting oxytocin neurons also reduced dopamine release in the NAc during pup grooming and carrot consumption, although activation of the neurons did not affect dopamine release. Finally, channelrhodopsin-mediated activation of VTA projections to NAc increased pup grooming, whereas inhibition of these projections reduced grooming.

These results suggest that oxytocin-releasing PVN neurons promote paternal behaviors both through direct projections to the NAc and through projections to the VTA that promote dopamine release in the NAc. This circuitry partially overlaps with that promoting food consumption. How activation of the circuitry differs in males that do not exhibit paternal behaviors should be investigated in future studies.

This Week in The Journal was written by Teresa Esch, Ph.D.
https://doi.org/10.1523/JNEUROSCI.twij.41.31.2021