This Week in The Journal

For Axons, Repulsion Is Repulsion

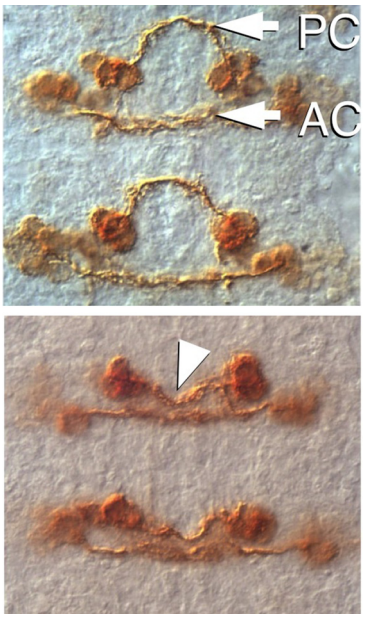
Hong Long, Shingo Yoshikawa, and John B. Thomas

(see pages 1140–1150)

As axons grow, they are guided along specific trajectories by environmental cues that are recognized by receptors in the axonal growth cone. The extracellular domains of these receptors determine which cues the axon responds to, while the intracellular domains determine whether the axon turns toward or away from the cue. These responses are classified broadly as attractive or repulsive, respectively. Whether different receptors promote different degrees of attraction or repulsion remains unclear, however.

Long et al. addressed this question by examining the effects of chimeric receptors in embryonic *Drosophila* neurons. Each chimera comprised the extracellular domain of one repulsive receptor and the intracellular domain of another. If the receptors cause different degrees of repulsion, one would expect expression of each chimeric receptor to have a different effect. This was not the case, however. For example, when chimeric receptors composed of the extracellular domain of Unc5 and the intracellular domain of Roundabout (Robo) or Derailed (Drl) were expressed in axons that normally extend along the ventral nerve cord parallel to the midline, the axons turned away from the midline, often exiting the nerve cord. Importantly, the effects of the chimeras were indistinguishable from each other and from the effects of Unc5 itself. Likewise, when chimeras comprising the extracellular domain of Drl and the intracellular domain of Robo or Unc5 were expressed in axons that normally cross the midline in the posterior commissure, the axons instead entered the anterior commissure in trajectories indistinguishable from those produced by expression of intact Drl. Finally, chimeras composed of the extracellular domain of Robo and the intracellular domain of either Unc5 or Drl fully rescued axonal mistargeting in *robo* mutants. Thus, the intracellular domains of these repulsive receptors appear to be entirely interchangeable.

These results suggest that Unc5, Robo, and Drl produce repulsion in similar ways. At what point do the intracellular signaling pathways activated by each receptor converge? Would subtle differences in repulsion be detected if chimeric receptors were expressed in neurons growing under more controlled conditions *in vitro*? Given the large differences in the structure of these proteins' intracellular domains, some distinct functions seem likely. Future work should identify these functions and investigate whether these proteins govern processes beyond repulsion.



Drosophila EW axons normally (top) cross the midline in the posterior commissure (PC), but when Drl–Unc5 chimeric receptors are expressed in these neurons (bottom), the axons cross in the anterior commissure (AC). See Long et al. for details.

Accumbens Shell Reflects Reward Devaluation

Elizabeth A. West and Regina M. Carelli

(see pages 1128–1139)

Taking action to obtain a reward involves multiple neural processes. One must recognize when a reward is available, know how much and what type of effort is required to obtain the reward, and be motivated to exert the required effort at the appropriate time. These processes depend on the nucleus accumbens (NAc), which is thought to promote specific instrumental actions when reward-associated cues and appropriate internal drives are present. The precise function of the NAc in coordinating these processes remains obscure, however,

To further elucidate the functions of the NAc, West and Carelli asked how neurons in shell and core subregions responded to reward-associated cues under different motivational conditions. Rats first learned that pressing a lever after a cue was presented would yield a specific food. The rats' motivation to seek the reward was then manipulated by giving them free access to that food (thus devaluing it) or a different food. As shown previously, subsequent lever pressing was lower for a devalued reward than for the same reward that was not devalued.

Subsets of neurons in both core and shell responded to cue presentation with increased or decreased firing. Neuronal activity in the core was correlated with performance during testing: the greater the proportion of neurons that responded to the cue in fully trained rats, the sooner the rat stopped seeking the devalued reward. Although similar proportions of shell neurons responded to the cue, the proportion of responsive shell neurons was not correlated with subsequent performance. Interestingly, however, the proportion of shell neurons that responded to the cue was lower after the associated reward was devalued than when it was not. Reward devaluation did not alter the proportion of cue-responsive core neurons, however.

These results are consistent with previous work indicating that NAc core and shell have different roles in goal-directed action. Specifically, they suggest that neuronal ensembles in the core respond when cues predict that a particular reward is available, regardless of the current desirability of that reward, whereas ensembles in the shell respond only when the current motivational value of the anticipated reward is high. Together, these regions may help animals choose which reward to pursue when multiple options are present.

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