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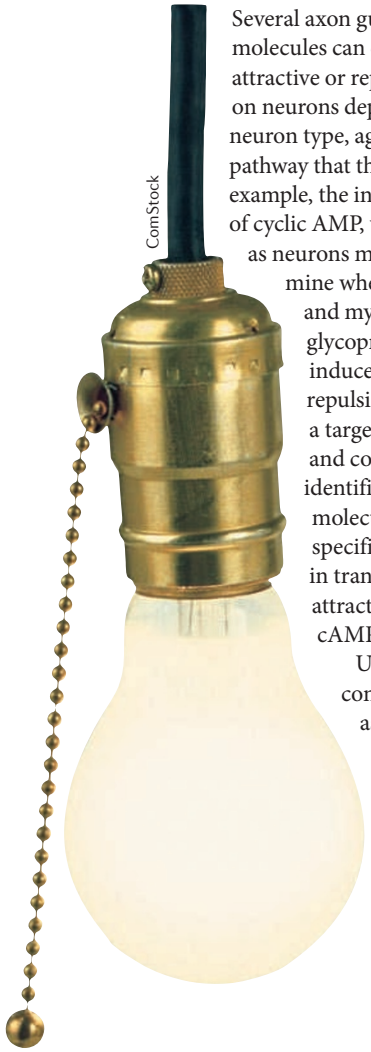
AXON GUIDANCE

A developmental switch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Several axon guidance molecules can exert either attractive or repulsive actions on neurons depending on the neuron type, age or signalling pathway that they trigger. For example, the intracellular levels of cyclic AMP, which decrease as neurons mature, determine whether netrin 1 and myelin-associated glycoprotein (MAG) induce attraction or repulsion towards a target. Shewan and colleagues have identified two key molecules that are specifically involved in transducing the attractive or repulsive cAMP signal.

Using growth cone turning assays, the authors showed that embryonic dorsal root ganglia (DRG) neurons, which are normally attracted towards an extracellular cAMP gradient, were repulsed by cAMP when transfected with small interfering RNA (siRNA) against EPAC, a cAMP-dependent guanine nucleotide exchange factor. Activation of protein kinase A (PKA), which has previously been implicated in mediating both attraction and repulsion to cAMP, led to repulsion in this assay, and the response was blocked with siRNAs against PKA but not blocked with siRNAs against EPAC. Furthermore, the authors showed that EPAC, but not PKA, was required for growth cone attraction to both a netrin 1 and MAG gradient.

Next, the authors investigated adult DRG neurons, which contain low levels of cAMP and are repelled by netrin 1 and MAG gradients. Bath application of an EPAC-selective activator blocked the repulsive response to these guidance cues. Knocking down EPAC with siRNA did not affect the repulsive response, but knockdown of PKA switched growth cone repulsion to attraction, indicating that PKA is a key mediator of adult growth cone repulsion from both netrin 1 and MAG gradients.

Finally, the authors used fluorescence resonance energy transfer and calcium imaging to further examine the developmental switch from attraction to repulsion by netrin 1 and MAG. They found that netrin 1 activated EPAC in embryonic growth cones, leading to an increase in intracellular calcium levels and BRAF activity, whereas PKA was preferentially activated in postnatal cells.

These findings suggest that, as neurons mature, the switch from attraction to repulsion downstream of cAMP depends on a switch from EPAC- to PKA-mediated signalling. It will be interesting to determine whether EPAC activation might be able to promote axon regeneration following injury to adult neurons.

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ORIGINAL RESEARCH PAPER Murray, A. J., Tucker, S. J. & Shewan, D. A. cAMP-dependent axon guidance is distinctly regulated by Epac and protein kinase A. *J. Neurosci.* **29**, 15434–15444 (2009)