the rest of the ion-conduction pathway, leading to channel opening.

In a companion article, Jiang *et al.* explored the validity of this radically different gating model by replacing different residues of the paddle with cysteine, biotinylating this amino acid, and testing whether avidin, a molecule with high affinity for biotin, would bind the paddle extra- or intracellularly during channel opening. They found that avidin could bind to the S3 residues only from the outside of the cell and only if the channel was open. In the case of S4, avidin had access to some residues only from the outside (upon channel opening), to others only from the inside (when the channel was closed) and to a third class from both sides. These data imply that the paddle indeed experiences a large displacement across the lipid bilayer following voltage changes. This movement might simply pull the S5 domain to open the channel.

So, K^+-channel gating involves a fundamentally different operational principle that could not have emerged from mutational analysis alone. The publication of these two papers constitutes an important landmark for the field and will undoubtedly be hailed as one of the breakthroughs of the year.

Juan Carlos López

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stimulation of these inputs depends on the context of that stimulation. It is possible that this effect results from a refractory period that restricts the Purkinje cells' response to the additional input and is related to the electrical response properties of these neurons.

As Kim points out in a related article, this work helps to answer some unresolved questions in functional imaging. For example, the careful analysis demonstrates that it is possible to infer changes in postsynaptic field potential from haemodynamic signals, even though the latter are much slower than the former. Step by step, we are coming closer to a full understanding of just what functional imaging can tell us about brain activity.

Rachel Jones

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REPAIR

No Nogo — grow/no grow?

Nogo is a myelin-associated protein that is expressed in the central, but not the peripheral, nervous system, and is thought to be partly responsible for the inability of central axons to regrow after injury. But three studies of Nogo-knockout mice published in *Neuron*, rather than clarifying the role of Nogo in preventing regeneration, have confused matters by finding different phenotypes.

Evidence from several studies has led to the view that Nogo, with other myelin-associated proteins, inhibits outgrowth of axons. Perhaps if this inhibition could be blocked or removed, injured axons in the central nervous system could regenerate. Three groups have generated mice that lack one, two or all three isoforms of Nogo, to see whether these mice show improved regeneration of central axons.

Nogo-A is the main isoform found in oligodendrocytes, so it has attracted the most attention in studies of regeneration. The first study, by Kim *et al.*, used mice with a mutation that prevents expression of Nogo-A and B. After spinal cord injury in young adult mice, they found that the knockout mice showed increased sprouting of corticospinal axons and also improvements in motor function — a promising result.

The second study, by Simonen and colleagues, used a Nogo-A knockout mouse and found a smaller increase in axonal growth. By contrast, Zheng *et al.* found that neither a Nogo-A/B mutant nor a Nogo-A/B/C mutant mouse showed any improvement in axonal regeneration or sprouting after spinal cord injury.

There is no obvious explanation for the difference in results. Although Kim *et al.* found that sprouting was greatest in young Nogo-A/B knockout mice, rather than older adults, the mice used by Zheng and colleagues were also young. The fact that Nogo-A knockout mice show a smaller increase in sprouting than the Nogo-A/B knockouts used by Kim and colleagues could be due to a compensatory increase in Nogo-B expression following the Nogo-A mutation, but the lack of regeneration in the mice used by Zheng *et al.* is puzzling. Clearly, much more work is needed before we will understand the role of Nogo in preventing regeneration; and a good starting point will be to find the reasons for the different phenotypes seen in these studies.

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