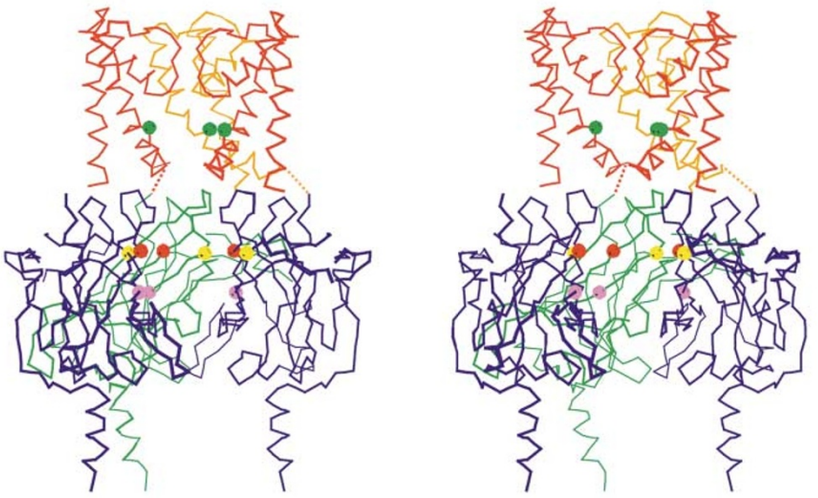
ION CHANNEL STRUCTURE

Rectifying an IRKsome finding



Stereo view of a channel consisting of the transmembrane pore of the MthK channel docked with the cytoplasmic pore of mGIRK1. The front subunit of the tetramer has been removed to provide a clearer view of the pore structure. The coloured spheres indicate positions where mutations affect ion conduction or blocking by impermeant cations.Reproduced, with permission, from Nishida & MacKinnon © 2003 Elsevier Science.

It is easy to envisage ion channels simply as holes in the cell membrane through which ions can pass freely in both directions, and this is indeed the case for many channels. However, there is a subset of K^+ channels that conduct ions more efficiently into than out of the cell. These are known as inward rectifier K^+ (IRK) channels. A new study published in *Cell* identifies the unique structural features of these channels that account for this property.

IRK channels are important for restoring the resting potential of neurons after electrical activity. During an action potential, Na^+ ions flow into the neuron, and if all the K^+ channels were open, K^+ ions would be expelled, thereby dissipating the positive charge that is generated inside the neuron. To stop this from happening, the IRK channels become blocked by intracellular cations, such as polyamines, which can bind inside the channel but cannot pass through. As the action potential subsides, the neuron transiently becomes hyperpolarized, and the IRK channels re-open to allow K^+ ions to enter and restore the cell to its resting potential.

What are the structural properties of the IRK channels that cause them to function as rectifiers? It was suspected that part of the answer lay in the carboxyl terminus, because mutations in this region affected the binding affinity of blockers. Nishida and MacKinnon examined the crystal structure of the amino and carboxyl termini of mGIRK1, a G-protein-gated IRK channel from the mouse. Both termini lie inside the cell, and the authors found that they assemble into a tetramer to form a pore-like structure that extends the total length of the channel to nearly 60Å. The pore is lined with negatively charged amino acid side chains, which provide an excellent binding substrate for polyamines.

The efficacy of blocking by polyamines is higher at positive membrane

STEM CELLS

Cells under surveillance

Embryonic stem (ES) cells are a promising source of new neurons to replace those that are lost through disease and injury. Functional recovery is the ultimate goal, but the cells must first be targeted to the right place, differentiate appropriately, and become integrated into functional circuits. Previously, the fate of ES cells that were transplanted into the brain could only be assessed retrospectively, through the examination of post-mortem tissue. However, Hoehn *et al.* have now developed a magnetic resonance imaging (MRI) technique that allows them to follow the movements of grafted cells in the living brain.

In a study reported in the *Proceedings of the National Academy of Sciences*, the authors induced ischaemia in the right cerebral hemisphere of the rat brain by transiently blocking the middle cerebral artery. They labelled an ES cell line with an MRI contrast agent, grafted these cells into the intact left hemisphere, and tracked their migratory behaviour using MRI. They found that they could detect clusters containing as few as 40 labelled cells — a higher resolution than has previously been achieved with this type of approach.

It has long been suspected that stem cells are preferentially targeted to damaged tissue, and the experiments of Hoehn *et al.* provide a striking confirmation of this phenomenon. In spite of the relatively large distance between the graft site and the site of brain injury, a large proportion of the grafted ES cells migrated directly across the corpus callosum, which bridges the two hemispheres, and headed straight for the lesioned area. This raises the possibility that ischaemic tissue might release a long-range chemoattractant that directs ES cell migration.

So, Hoehn *et al.* have developed a high-resolution imaging method for tracking the movements of grafted ES cells in the brain. This should prove to be extremely valuable for gauging the success of stem cell transplantation in experimental studies, and perhaps even in the clinic. Also, studying the migratory behaviour of grafted cells might provide some important clues to the nature of the endogenous signals that influence their migration, making it possible to develop more effective transplantation protocols.

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References and links

ORIGINAL RESEARCH PAPER Hoehn, M. *et al.* Monitoring of stem cell migration *in vivo*: a highly resolved *in vivo* magnetic resonance imaging investigation of experimental stroke in rat. *Proc. Natl Acad. Sci. USA* **99**, 16267–16272 (2002)
FURTHER READING Rossi, F. & Cattaneo, E. Neural stem cell therapy for neurological diseases: dreams and reality. *Nature Rev. Neurosci.* **3**, 401–409 (2002)