ION CHANNELS

Making a submicroscopic hole in one

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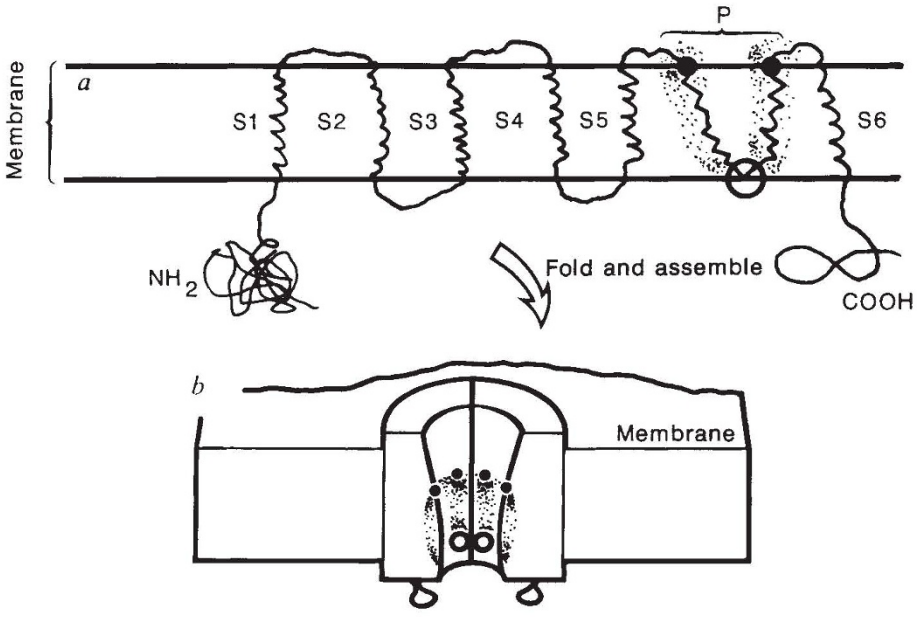
COMPLEMENTARY work in three laboratories, reported on page 700 of this issue[1] and in this week's *Science*[2,3], has provided the best answer yet to one of neurobiology's central questions: what is the structure that constitutes an ion-selective pore?

A special class of proteins, called channels, is responsible for the electrical activity of neurons. These channels work by opening and closing the gate that permits ions to flow through a submicroscopic pore. Members of one large subclass of channels have their gate regulated by the voltage difference across the neuron's membrane and are all products of a gene superfamily.

The pores of these voltage-gated channels have the amazing ability to distinguish between ions. For example, the crystal radius of potassium ions is 0.13 nm and that of sodium ions is 0.1 nm, yet various channel types have pores that can tell these chemically very similar ions apart. Potassium channels permit potassium ions to pass through their pore while effectively excluding sodium ions, whereas sodium channels have the opposite selectivity. The structural basis for this selectivity, a phenomenon at the very heart of all electrical excitability, has perplexed electrophysiologists for half a century. Now molecular biological techniques have almost certainly identified the amino-acid sequence that constitutes the ion-selective pore of potassium, sodium and calcium channels. And the pore is not what some would have expected — it contains no charged residues, and the pore-forming sequence is not particularly hydrophilic.

The voltage-gated channels all have a structure like the one illustrated in the figure. Six transmembrane helices, designated S1 to S6, have been identified (although not yet actually proved to have that structure); the segment of sequence between S5 and S6 is labelled in the figure as P.The recent experiments[1-3] identify P as the pore-forming sequence. Although the current evidence directly links P to the ion-permeation pore only in several specific members of the family, the P region surely must have the same function in all members of the superfamily. Because some family members select for sodium ions, others for potassium and still others for calcium, one can anticipate that the specific structural elements responsible for ion selectivity will now be quickly identified.

The first experimental clues that the P region might constitute the pore came from experiments that used site-directed mutagenesis to modify the sensitivity of ion channels to certain toxins[4-7]. Pharmacological agents have long been known to block the function of ion channels by plugging them up, much like a cork plugs a bottle, and several laboratories had identified mutations in P that alter the



Structure of a voltage-gated channel showing, *a*, one subunit of a potassium channel with six transmembrane helices (S1–S6) and the newly identified pore-forming region (P); ● and ○ are the sites that bind tetraethyl ammonium (TEA) ions from the outside and inside respectively, the second site being part of the selectivity filter. *b*, A channel is assembled from four subunits, two of which are shown here. Four P regions make up the ion-selective pore.

RÉSUMÉ

Headbangers

BLIND, subterranean mole rats truly feel the presence of their fellows, E. Nevo *et al.* report (*Proc. natn. Acad. Sci. U.S.A.* **88**, 1256–1260; 1991). Mole rats of the species group *Spalax ehrenbergi* use a crude but effective method to communicate over long distances — thumping their flattened heads against the walls of their tunnels. The seismic signals so generated travel well and help to mediate the territorial behaviour of the rodents. It has been thought that the vibrations are detected as sounds, transmitted through the bones to the ear. But Nevo *et al.* show that the signals can be detected independently of the auditory system, presumably by mechanosensors near the animals' surface.

Inside out

THE 'Dupal' isotopic signature, found in basalts from ocean islands throughout much of the Southern Hemisphere, is probably derived from deep in the Earth's mantle, according to D. Weis *et al.* (*Geology* **19**, 99–102; 1991). The Dupal anomaly is identified by its isotopically unusual lead and strontium content. The question, since it was discovered by Dupré and Allègre, has been where it comes from. The new results are from the Ninetyeast Ridge, a 5,000-km-long rise below the Indian Ocean. Geochemical sampling shows that the basalts forming the ridge are related to those of Heard island in the Antarctic. If the hot mantle plume currently generating the Heard magmatism was also responsible for Ninetyeast Ridge, which started to form 115 million years ago, it must be deep seated, the authors argue, originating at least at the 670-km-deep boundary between the upper and lower mantle, if not deeper.

Red-blooded reindeer

THE combined efforts of laboratories in Italy, Norway and Finland have brought to light another example of evolutionary fine-tuning in haemoglobin. R. Petruzzelli *et al.* (*Biochim. biophys. Acta* **1076**, 221–224; 1991) have determined the sequence of reindeer haemoglobin, to assist in interpretation of its function. It has a markedly low affinity for oxygen, and its heat of oxygenation is highly exothermic in the deoxy (R) state and close to zero after the conformational switch (T state). This means that oxygen delivery to the peripheral tissues in the winter (ambient temperature down to −40 °C) remains efficient. The cofactor, 2,3-DPG, plays no part in the physiology, for it hardly binds; this is a consequence of mutations at its β-chain site, and also of enhanced competition from Cl^-. If release of Cl^- by the R state is endothermic it will tend to cancel the heat of the intrinsically exothermic oxygenation process.