tion towards both the centre and plane are significant at the 2.5σ level[2]. But this would invalidate the probability calculation used above[1] (D. Hartmann, personal communication), because a concentration towards the galactic plane will produce systematically closer neighbours than expected for an isotropic distribution. Unfortunately, the use of peak count rates[2] depends sensitively on the orientation of BATSE. According to Rutledge and Lewin[4], in the final paper of the set of four, if these detector effects are removed then the significances of the concentrations towards the galactic plane and centre are substantially reduced (1.8σ and 2.4σ). Later BATSE data (using roughly triple the number of bursts) with the same selections show a slight concentration towards the galactic anticentre and no concentration towards the galactic plane[10].

So it looks like the biggest enigma in modern astrophysics remains unsolved, and new techniques will be needed. A confident counterpart identification will probably settle the question, and very rapid response by ground-based instruments may soon be possible with positions from the HETE spacecraft or the BATSE Coordinate Distribution Network. Or the distance scale could be measured from the photoelectric absorption in the soft X-ray band. These and other experiments offer hope that we in the GRB community will soon know whether we are planetary astronomers or cosmologists. □

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■ At last month's meeting of the American Astronomical Society (Washington DC, 11–15 January) a cosmological origin for gamma-ray bursts seemed to be coming to the fore. According to Jay Norris (NASA Goddard Space Flight Center), two systematic trends can be seen in the 700 or so bursts detected by the Compton Gamma Ray Observatory so far: the fainter bursts are systematically longer and 'softer' than their brighter brethren. The results remain tentative, but both effects would be consistent with (although not require) a cosmological distance scale, with fainter, more distant bursts at higher redshifts. **L.M.**

NEUROBIOLOGY

Trinity of cation channels

Thomas J. Jentsch

ONE of the most satisfying moments in science is when different lines of investigation converge to yield a beautiful picture that opens up new perspectives. This happened last year when expression cloning[1,2] of an epithelial sodium channel subunit revealed that the DNA encoding it was significantly similar in sequence to that of certain nematode genes, mutations in which lead to insensitivity to touch, neurodegeneration or both. Three reports

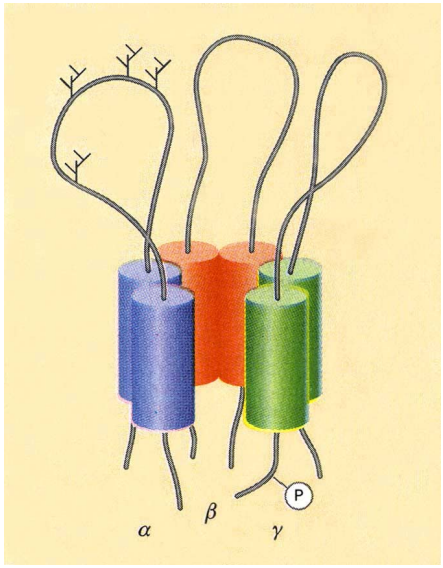

FIG. 1 Model of an epithelial sodium channel. A functional channel may contain more than one of each subunit, or other unknown subunits. Only the α-subunit is glycosylated, and the γ-subunit has an intracellular consensus site for cAMP-dependent phosphorylation. Each subunit is shown as spanning the membrane twice, but Canessa *et al.*[3] propose that additional β-sheets may participate in the formation of the pore.

on pages 463, 467 and 470 of this issue[3–5] now suggest that at least three distinct subunits are used to build channel complexes in both mammals and the nematode *Caenorhabditis elegans*. Further, the new work provides insights into the relationship between subunit structure and function, and demonstrates a remarkable degree of functional conservation between vertebrates and invertebrates.

Sodium channels allow selective diffusion of sodium ions across the plasma membrane (concentration and potential gradients will allow only net influx). Voltage-dependent sodium channels mediate the rapidly inactivating inward currents underlying action potentials. In contrast to the primarily electrical function of the voltage-dependent channels, epithelial sodium channels mediate bulk flow of Na^+ (and water, which follows osmotically) across cell layers. These channels are not strongly voltage-dependent and do not show rapid inactivation, but are subject to complex regulation (for example by aldosterone and vasopressin) on a longer timescale. They are blocked by submicromolar concentrations of amiloride; the effect of amiloride on sodium reabsorption in the distal nephron of the kidney is the basis for its clinical use as a diuretic and in the treatment of hypertension. From physiological evidence, it seems that there may be a family of related channels[6].

Whereas the first voltage-gated sodium channel was cloned by Numa's group almost ten years ago[7], the biochemical identification of epithelial Na^+ channels has proved difficult[8,9]. The approach that finally proved to be successful was expression cloning in *Xenopus* oocytes[1,2]. Expression of the single cloned complementary DNA induced currents with many of the expected properties. However, currents were smaller than those observed with expression from tissue polyA$^+$ RNA. This pointed to the involvement of other subunits, and led Rossier's group to search for them (they termed their first clone product the α-subunit of the rat epithelial sodium channel, α-rENaC)[1]. In a new triumph for expression cloning, Canessa, Rossier and colleagues have now cloned[3] two additional homologous subunits by functionally screening pools of cDNA clones expressed together with the α-subunit. Co-expression of all three subunits (α, β and γ) leads to much larger currents, and nearly all the known properties of the native channel are reproduced.

Epithelial sodium channel subunits define a new class of ion channel which is structurally unrelated to the neuronal sodium channel. They are predicted to have two hydrophobic transmembrane domains, separated by a large extracellular segment (see Fig. 1). As expected, sequence similarity is highest in the transmembrane domains, which presumably participate in forming the ion-selective pore.

It came as a pleasant surprise that the epithelial sodium channel is related by sequence to the *C. elegans* degenerins, which are encoded by the *mec-4* and *deg-1* genes among others, and which were identified in a genetic screen for touch insensitivity[10]. What Huang and Chalfie[4] have now done is to identify a new member of this family (*mec-10*); and by studying *mec* mutations and their genetic interactions in transgenic nematodes, these investigators, and Hong and Driscoll[5], have come up with an intriguing view of

degenerin activity.

In analogy to the epithelial sodium channel, MEC-4, MEC-6 and MEC-10 proteins are proposed to form heteromultimeric ion channels in *C. elegans* touch receptors (see Fig. 2*a*). These channels, which are necessary for touch sensitivity, may be directly mechanosensitive but could also function in signal amplification. Dominant mutations at equivalent positions in either the *mec-4* or the *mec-10* genes result in unregulated channel activity, which eventually leads to swelling and degeneration (lysis) of the touch cells. These gain-of-function phenotypes can be suppressed by certain loss-of-function alleles of the same genes (*mec-4* or *mec-10*), implying that several copies of MEC-4 (or MEC-10) insert into the same complex. The products of the recessive alleles thereby abolish the unregulated channel activity, without, however, restoring touch sensitivity. Surprisingly, however, most loss-of-function *mec-10* alleles enhance *mec-10*-induced degeneration, maybe indicating that these products are now unable to associate.

Although *mec-10*-induced degeneration requires both *mec-4* and *mec-6* activity, dominant *mec-4* alleles do not need *mec-10* activity to cause degeneration. This suggests that MEC-4 also participates in the formation of a different channel (lacking MEC-10) which is not involved in touch perception (Fig. 2*b*). The work of Canessa *et al.*[3] also points to variable subunit stoichiometries; here, subunit messenger RNAs show differential tissue distribution and α-subunits are sufficient to form functional channels, albeit inefficiently. Degeneration of different nematode neurons by *deg-1* mutations also depends on *mec-6* activity[11], indicating that those channels contain at least DEG-1 and MEC-6 protein (Fig. 2*c*). Additionally, rare dominant mutations in the *unc-105* gene cause severe muscle contraction[12], which can be suppressed by mutations in other genes. *unc-105* is now known to belong to the degenerin gene family (R. H. Waterston, personal communication), suggesting the existence of another, related nematode channel and a similar pathological mechanism.

The new results[4,5] also show that several loss-of-function mutants in *mec-4* and *mec-10* affect highly conserved residues in their products' second transmembrane domain. Many of these residues are predicted to lie on one side of an α-helix, suggesting that they line the pore. The region that is most fully conserved between different members of this protein family is the second transmembrane domain, and the beautiful domain-swap experiments of Hong and Driscoll[5] show that these regions of DEG-1 and α-rENaC can specifically replace the equivalent segment of MEC-4 without destroying its function.

This picture is attractive, but validating it requires more evidence. It needs to be determined by molecular cloning whether *mec-6* is a degenerin gene. Further, the stoichiometry of the channel complex (in both nematodes and mammals) will have to be elucidated. In this case, as for other multimeric channels, detailed functional analysis[13] of dominant negative mutants may be useful. Finally, there is a pressing need for an electrophysiological analysis of *mec* gene products; for instance, a demonstration that residues in the second transmembrane domain indeed line the pore will require evidence of changes in ion selectivity in mutants.

What are the broader implications of this research? First, a large channel family may now be amenable to molecular analysis, and it may include mechanosensitive channels that have some biophysical and pharmacological properties in common with epithelial sodium channels. Such channels are involved in hearing, in sensing of stretch and pressure, and possibly in regulation of cell volume. How they sense mechanical force is unclear, although the cytoskeleton has often been implicated in the process. Interestingly, touch receptors of *C. elegans* specifically express bundles of large-diameter microtubules, and mutations in *mec-7* (which encodes a β-tubulin) lead to a loss of these bundles and of touch-sensitivity[14].

Second, there are the clinical aspects. In a rare hereditary form of hypertension (Liddle's syndrome), the increased sodium reabsorption in the distal nephron could be due to defects in the epithelial sodium channel or in its regulation. The cloning of pressure-sensitive channels of baroreceptors or vascular smooth muscle could provide novel candidate genes for hypertension, and may lead to new drug-targeting strategies. Another potential area of interest is cystic fibrosis. Most symptoms of this disease result from the loss of the intrinsic chloride channel activity of the cystic fibrosis transmembrane conductance regulator (CFTR). However, sodium reabsorption is increased in lung epithelia of cystic fibrosis patients, and it will be important to see whether or how CFTR regulates the epithelial sodium channels. It would also not be surprising if some forms of human neurodegenerative disorders are caused by defects of related channels. □

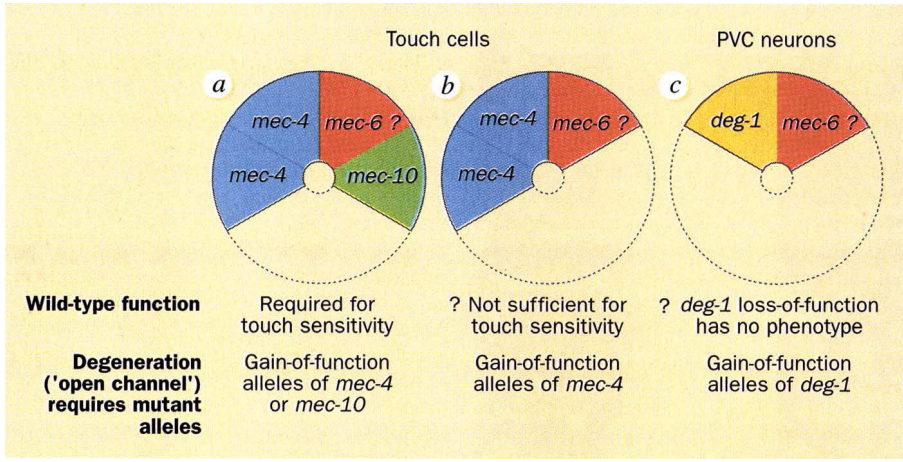

FIG. 2 Possible explanation of degenerin gene-family function in *C. elegans*. In analogy to the sodium channel, degenerins are proposed to form multimeric ion channels (in touch receptors, *a*, *b* or in other neurons, *c*); however, direct evidence for this is lacking. Each subunit is assumed to have a similar topology to that shown in Fig. 1. (The inclusion of *mec-6* in this scheme is purely hypothetical, as its membership of this gene family has not yet been established.) The fact that loss-of-function *mec-4* alleles suppress degeneration caused by gain-of-function alleles of the same gene suggests that at least two such subunits are present in a channel complex. This may also apply for *mec-10* (not shown). Other subunits may also be involved. Degeneration of cells is caused by dominant mutations, which are hypothesized to lead to nonphysiological channel opening. Degeneration of posterior ventral cord (PVC) interneurons caused by *deg-1* leads to a different form of touch sensitivity, because these cells relay signals from posterior touch cells[11].

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