Figure 1 This hypothetical structure was proposed for an aluminosilicate zeolite⁷, but has only now been realized as a cobalt phosphate. The new material has cobalt, aluminium and phosphorus at the blue sites, and oxygen at the red sites. The method of synthesis should yield a great number of new microporous materials, opening up a wider range of chemistry for these open framework catalysts.

works is to find a recipe that at least partially dissolves and transports the components in the reaction solvent, and also causes a microporous framework to form rather than an undesirable non-porous structure. The significance of the new phases¹ lies in their open structures (including one novel form) and their compositions, and in the discovery of a new synthesis procedure that made these materials possible.

The authors chose a clever combination of a new cobalt reagent, CoCO_3 , and a largely non-aqueous ethylene glycol solvent system to create conditions that lead to the ready synthesis of the cobalt phosphates. The pores within the crystallized products are filled with organic ammonium cations and water, which stabilize the structure during crystallization by space filling and charge compensation. But whether this metal carbonate route is more generally applicable to other divalent transition metals is not yet clear.

Another intriguing aspect of the cobalt

Figure 2 Cubic framework of the building block in Fig. 1. The pseudo-octagonal micropores in this structure are 3.8 Å in diameter and permeate the structure in three dimensions.

phosphates is the formation of an unprecedented structure that Stucky and colleagues have called ACP-1, for aluminium cobalt phosphate 1 (Fig. 1). This structure was erroneously proposed for one of the synthetic aluminosilicate zeolites, known as cubic zeolite P, by R. M. Barrer *et al.*⁷, in 1959. Nearly 40 years have passed between Barrer's proposal and the successful synthesis of the hypothetical structure, albeit in a completely different composition. The ACP-1 structure is an array of nine cube-shaped building blocks arranged at the corners and in the centre of a larger cube. Repeating this structure produces a framework that contains a three-dimensional network of 3.8-Å channels (Fig. 2).

A key question that always arises when a new family of frameworks is discovered is whether the latent microporosity of the materials can be accessed. The porosity remains latent until a method is devised to remove the space-filling, charge-compensation molecules without destroy-

ing the framework. Without the removal of this 'stuffing', much of the promise of novel or improved applications is diminished. Achieving access is a crucial step in the application of the cobalt phosphates — if successful it will allow study of the redox chemistry of the frameworks and of their potential as selective oxidation catalysts. The cobalt phosphates may also be good at adsorptive separations of gases and ion exchange processes. □

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Neurodegeneration

A silent channel opens its gates

Peter H. Seeburg

Many human neurodegenerative diseases, such as amyotrophic lateral sclerosis (also known as Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease and Huntington's chorea, lead to the demise of distinct nerve-cell populations. Yet in no case is the selective vulnerability of the affected cells, nor the underlying damaging principle, understood.

A popular view is that these sinister diseases are caused — or at the very least exacerbated — by the unphysiological activity of cation-selective membrane channels operated by glutamate, which is the most abundant excitatory neurotransmitter in the brain. Now, the discovery by Zuo *et al.*¹ (page 769 of this issue) provides the first direct evidence in support of this view. The authors have traced the selective neurodegeneration that occurs in a spontaneous neurological mouse mutant (*lurcher*) to the constitutive activation of a member of the glutamate-receptor-channel family.

First described in 1960, the *lurcher* (*Lc*) mouse derives its name from a peculiar gait that is characteristic of heterozygous carriers of the mutant gene. These mice develop a lack of balance (ataxia), because all of the Purkinje cells in the cerebellum — a brain structure that is important for motor coordination — are lost. Mice that are homozygous for the *Lc* gene die shortly after birth, due to a massive loss of hindbrain neurons during embryonal development. These neurons include the trigeminal motor nucleus, which controls the muscles required for suckling. So, the neurological phenotype of the *lurcher* gene is characterized by selective neuronal

cell death. In a collaborative effort¹ between the labs of Nathaniel Heintz and David J. Linden, the molecular cause for this neuronal death has now been unravelled.

Ever since John Olney and Lawrence Sharpe² reported that infant rhesus monkeys develop brain lesions when exposed to glutamate, attention has been directed towards how the abundant excitatory neurotransmitter L-glutamate might become a culprit in acute and degenerative cell death in the brain. In an elegant series of experiments, Dennis Choi³ and colleagues showed that this glutamate-evoked cell death can be mimicked *in vitro*, and that the onset and extent of cell death are critically dependent on the influx of Ca^{2+} into neurons.

Our mechanistic understanding of these observations was boosted by the molecular characterization of the various receptor channels that are activated by L-glutamate in central neurons⁴. These cation-selective channels are composed of sequence-related subunits. They form a family of glutamate receptors (GluRs) which have distinct properties, commensurate with their particular roles in synaptic physiology. The best-characterized GluRs are the AMPA (amino-hydroxymethylisoxalate propionic acid) and NMDA (*N*-methyl-D-aspartate) receptor channels, which mediate fast excitatory neurotransmission.

Whereas most AMPA receptors are permeable only to monovalent cations, NMDA receptors are designed for the controlled synaptic influx of Ca^{2+} ions. Most neurons carry both types of GluR, not only in synapses

Figure 1 Purkinje cells in the cerebellum express the glutamate receptor (GluR) $\delta 2$ subunit which, possibly together with an unknown subunit partner, forms a cation channel that is activated by glutamate or by a related excitatory transmitter. The gated channel is permeable to Na^+ and it may also be permeable to Ca^{2+} ions. Zuo *et al.*¹ have found that, in the *lurcher* mouse, an amino-acid substitution in a short sequence that is conserved in all GluR subunits (dotted line in $\delta 2$, magnified to show the actual sequence) activates the $\delta 2$ channel in the absence of neurotransmitter, leading to neurodegeneration of Purkinje cells.

but also on dendrites and cell bodies. This explains why the cell death that is encountered in acute neurological insults such as stroke and head trauma is delayed: injured cells release glutamate which opens the gates of AMPA- and NMDA-receptor channels. This leads to an ultimately deadly influx of Ca^{2+} to the neurons that surround the main site of injury.

Experimental evidence implicating glutamate in acute neuronal cell death came easily (for example, refs 2, 3). However, a link between neurodegenerative diseases and genetically determined alterations in signalling cascades operated by glutamate or other excitatory neurotransmitters has not yet been forged. Enter $\delta 2$ — a lesser-known member of the GluR family. From the molecular signature of $\delta 2$ we might predict that it is operated by glutamate, even though the recombinantly expressed protein lacks all channel activity^{5,6}. Expression of $\delta 2$ seems to be confined to a subset of dendritic spines⁷ in cerebellar Purkinje cells, and knock-out of the $\delta 2$ gene leads to aberrant innervation and altered synaptic physiology of these large, cerebellar neurons⁸.

Zuo *et al.*¹ have completed a technical *tour de force* by positionally cloning the *Lc* gene. On doing this, they saw that what they had cloned was the $\delta 2$ gene, carrying a single nucleotide substitution (Fig. 1). This nucleotide change indicated the substitution of an amino-acid residue in a small region that is highly conserved between all known GluR subunits. When the authors expressed the mutant $\delta 2$ subunit *in vitro*, they found that the channel was active in the absence of glutamate — in other words, the mutation had resulted in a gain of function. Indeed, Purkinje cells in heterozygous *Lc* mice show a resting membrane potential that is well above that of their wild-type counterparts, indicating that the affected cells experience a constant influx of cations. So the death of these cells is closely related to

the excitotoxic cell death that is brought about by excess glutamate³.

What have we learned from these findings and what remains enigmatic? We finally have a demonstration that a molecular alteration in a transmitter-gated channel can cause the degeneration of the neurons that express it. The consequence of the single amino-acid change indicates that the highly conserved region in which it occurs is a major determinant in channel activation, following the binding of a neurotransmitter. We do not know the subunit composition of the native channel that incorporates $\delta 2$, how this channel operates normally, or which ligand — glutamate or a related transmitter — gates it.

It remains to be seen whether the channel is also permeable to Ca^{2+} ions. Perhaps the entry of Ca^{2+} into Purkinje cells that are heterozygous for the *Lc* gene is due to depolarization, mediated by the entry of Na^+ through the constitutively open channel. Furthermore, although expression of $\delta 2$ has been documented in Purkinje cells, the massive neuronal loss in the mid- and hindbrain of homozygous mouse embryos indicates that $\delta 2$ is also expressed in these structures — at least transiently during embryonal development. Finally, the finding by Zuo *et al.*¹ should now give considerable impetus to screening for other GluR mutations in familial neurodegenerative disorders. □

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NATURE

100 YEARS AGO

An interesting memoir, by C. T. Mörner, has recently appeared in the *Zeitschrift für physiologische Chemie*, dealing with a method of preserving fish, much employed in northern Sweden. The fish are washed, and placed in wooden casks, and are then covered with brine. The casks are then closed and made airtight, and placed in the open air in a sunny place, and allowed to remain there for from five to six weeks. The process of fermentation, which soon ensues, is controlled by means of a small vent-hole, which is opened from time to time.... As soon as the requisite stage in the process has been reached, the casks are opened, and the now-finished article is packed in smaller vessels for storage and distribution. This article of diet, known in Swedish as "surfsk," is eaten either raw or toasted.... As accounting for the disagreeable odour which characterises this preparation, Mörner found amongst the gases emitted during fermentation the offensive-smelling methylmercaptan. Amongst the organic acids discovered in the "surfsk," whilst absent in the fresh fish, succinic acid, butyric acid, formic, acetic, and valeric acids were detected.... Curiously indol, skatol, phenol, putrescine and cadaverine, so characteristic of putrefactive processes in general, were absent in this preparation. From *Nature* 19 August 1897.

50 YEARS AGO

The Seventeenth International Physiological Congress was held in Oxford during July 21–25. It was attended by about 1,200 physiologists, including welcome delegates from the USSR and China.... Perhaps the most important work reported has been in independent research, in which, after Prof. E. G. T. Liddell's phrase, after seven years, members were showing an active post-inhibitory rebound. An outstanding paper was given by A. L. Hodgkin and A. F. Huxley, who suggested that during the rising phase of the action potential in nerve, the membrane becomes highly permeable to sodium ions which then enter the cell. Potassium ions leave the cell during the falling phase and later restorative processes occur linked with energy-producing mechanisms. There was considerable indirect evidence in favour of this view. From *Nature* 23 August 1947.