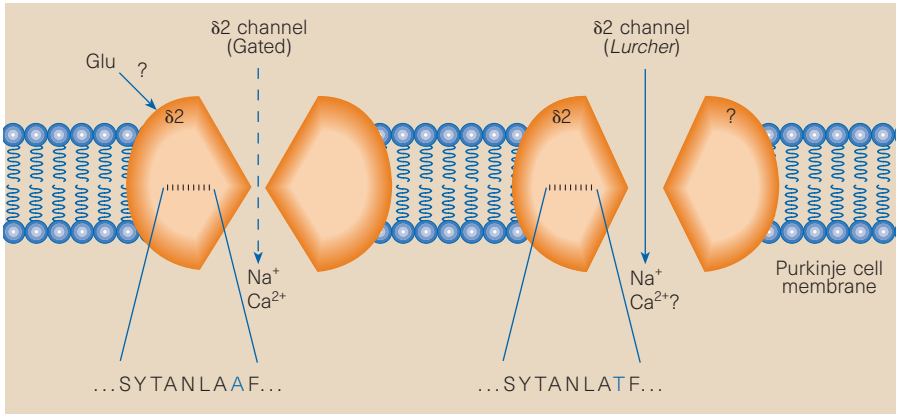

Figure 1 **Purkinje cells in the cerebellum express the glutamate receptor (GluR) δ2 subunit which, possibly together with an unknown subunit partner, forms a cation channel that is activated by glutamate or by a related excitatory transmitter. The gated channel is permeable to Na^+ and it may also be 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 δ2, magnified to show the actual sequence) activates the δ2 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 δ2 — a lesser-known member of the GluR family. From the molecular signature of δ2 we might predict that it is operated by glutamate, even though the recombinantly expressed protein lacks all channel activity[5,6]. Expression of δ2 seems to be confined to a subset of dendritic spines[7] in cerebellar Purkinje cells, and knock-out of the δ2 gene leads to aberrant innervation and altered synaptic physiology of these large, cerebellar neurons[8].

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 δ2 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 δ2 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 glutamate[3].

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 δ2, 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 δ2 has been documented in Purkinje cells, the massive neuronal loss in the mid- and hindbrain of homozygous mouse embryos indicates that δ2 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. □

Peter H. Seeburg is at the Max Planck Institute for Medical Research, Department of Molecular Neuroscience, Jahnstrasse 29, D-69120 Heidelberg, Germany.

1. Zuo, J. *et al. Nature* **388,** 769–773 (1997).
2. Olney, J. W. & Sharpe, L. G. *Science* **166,** 386–388 (1969).
3. Choi, D. W. *Neuron* **1,** 623–634 (1988).
4. Hollmann, M. & Heinemann, S. *Annu. Rev. Neurosci.* **17,** 31–108 (1994).
5. Araki, K. *et al. Biochem. Biophys. Res. Commun.* **197,** 1267–1276 (1993).
6. Lomeli, H. *et al. FEBS Lett.* **315,** 318–322 (1993).
7. Landsend, A. S. *et al. J. Neurosci.* **17,** 834–842 (1997).
8. Kashiwabuchi, N. *et al. Cell* **81,** 245–252 (1995).

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 "surfisk," 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 "surfisk," 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.