IN THE NEWS

Are sheep safe?

BSE rarely makes the headlines these days, but that looks set to change after a report in *Nature* that lamb might present an even greater risk to human health than beef. At present, the 'risk' is purely theoretical, and is based on two uncorroborated assumptions: that BSE has passed into sheep, and that it has spread through the United Kingdom's national flock. If this has happened, it is estimated that up to 100,000 people could die from eating contaminated lamb.

In fact, nobody really knows whether sheep have been affected by BSE. As the *Daily Telegraph* (UK, 10 January 2002) points out, this is partly because of "the recent fiasco in which scientists looking for BSE in the national flock spent four years studying cows' brains". There is concern that the symptoms of BSE could be mistaken for those of the related sheep disease scrapie, thereby masking the true extent of the problem.

The researchers stress that their data represent a worst-case scenario, although team leader Neil Ferguson warns that "there has been rather too much complacency. That there is a potential risk has been known for the past five years" (*The Mirror*, UK, 10 January 2002).

The Food Standards Agency's official line is that "the risk of BSE in sheep remains theoretical and the agency is not advising against the consumption of lamb" (*BBC News*, 10 January 2002). However, those who remember similar statements being made about beef during the BSE crisis might not feel reassured. Frances Hall from the Human BSE Foundation says "a lot of families have been changing over to eating more lamb because of fears of BSE. If anyone in the future is found to have acquired the disease from sheep, they will have good reason to be extremely angry" (*The Mirror*).

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would then act trans-synaptically to activate soluble guanylate cyclase in the Purkinje cell, leading to an increase in cyclic GMP. From other work, we know that such an increase, if it occurs simultaneously with a rise in postsynaptic calcium levels (which could follow activation of postsynaptic glutamate receptors), can decrease the postsynaptic sensitivity to glutamate, leading to synaptic depression. The result of all this will be that the presynaptic NMDA receptors select repetitive inputs as candidates for depression, with the final decision depending on concurrent depolarization of the Purkinje cell by climbing fibre inputs.

There is much more work to be done before we can complete this particular puzzle — but perhaps finding this piece will help us to see the overall picture.

Rachel Jones

References and links

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http://www.els.net/
cerebellar plasticity | long-term depression and depotentiation

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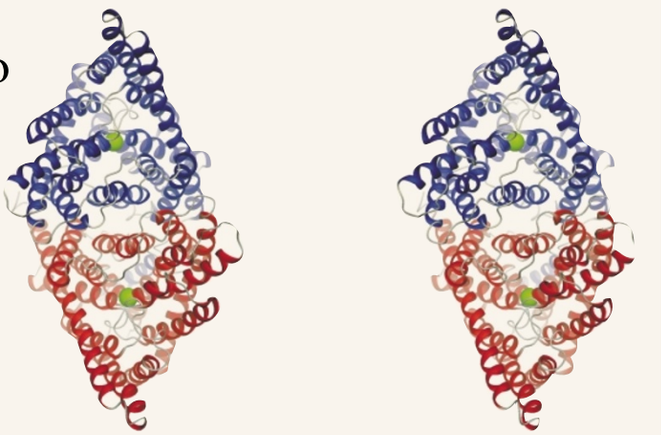
ION CHANNEL STRUCTURE

Looking right into the double barrel



Stereo view of a bacterial ClC channel. Reproduced from Dutzler *et al*. © 2002 Macmillan Magazines Ltd.

ClC chloride channels are a widespread family of anion-selective channels. Many examples underscore the relevance of ClC channels: mutations in ClC-1 produce myotonia, and loss of ClC-5 causes Dent's disease, a renal pathology in which abnormal amounts of protein appear in the urine. In the nervous system, the absence of ClC-3, which is normally expressed in synaptic vesicles, leads to retinal and hippocampal degeneration in mice.

Like every other channel, ClC channels have been extensively mutated and studied under the electron microscope in attempts to unravel their structure. But unlike several cation channels, neither ClC nor any other anion channel had succumbed to the power of crystallography. Now Dutzler and his colleagues report on their success in solving the crystal structure of two prokaryotic ClC channels. Their data provide us with unprecedented details on the structure of these proteins, and help us to explain some of our previous biophysical findings. The new structure takes our understanding of the chemical and physical basis of anion selectivity to new heights.

ClC channels are thought to be dimeric and to have two pores. Dutzler *et al.* confirmed this prediction and obtained unequivocal evidence that each pore is formed independently by one monomer. Moreover, the authors found a structural peculiarity within each monomer: the amino- and carboxy-terminal halves are structurally similar, giving rise to an internal repeated pattern that had not been identified in the primary sequence. Importantly, the two halves have opposite orientations in the membrane: they run antiparallel to create a pseudo axis of symmetry. This arrangement allows the amino-acid residues that constitute the chloride-binding site to be in close proximity, despite being in different halves of the molecule. Similar to what had been found in potassium channels, the chloride-binding site in ClC channels is made of partial (not full) charges, providing a favourable electrostatic environment for anions, but preventing them from binding too tightly to the pore.

In addition to locating the chloride-binding site, Dutzler *et al.* identified another negative charge in the conduction pathway — the side chain of a glutamate residue. The authors speculated that this glutamate must move out of the way for conduction to occur, and reasoned that chloride entry into the pore might elicit this structural rearrangement. This idea makes perfect sense in view of previous observations that chloride is necessary for ClC channel gating.

The structures of these two ClC channels are a real breakthrough in the study of anion channels. They will pave the way for a deeper understanding of anion conduction and selectivity, placing it on a par with our modern insights into the workings of cation channels.

Juan Carlos López

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chloride channels