IN THE NEWS

Death is not the end

Another day, another stem cell story, or so it seems. "Brain cells of corpses are grown in test tube", announces *The Independent* (UK, 3 May 2001), responding to the news that Fred Gage's research team at the Salk Institute have shown that neural progenitor cells can be propagated from adult human cadaver brains (*Nature*, 3 May 2001).

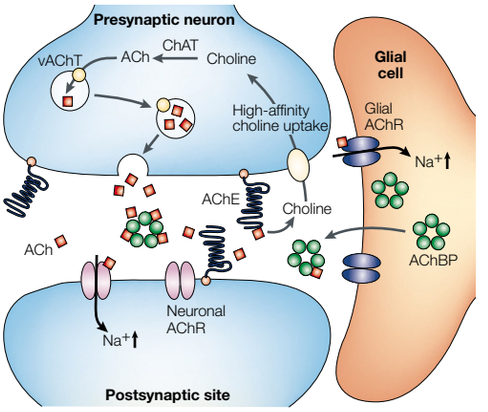
Their finding is important because it might provide an alternative to the controversial practice of deriving stem cells from embryonic tissue. However, as Peter Andrews, a stem-cell researcher from the University of Sheffield, points out, "the use of cadavers as a potential source of stem cells raises a different set of ethical issues to those associated with using stem cells from embryos" (*BBC News Online*, 2 May 2001), and Gage's team admit that "complex ethical and societal issues" (*Nature*, 3 May 2001) need to be addressed.

Some reports also raise concerns that, with all the hype surrounding stem-cell research, we might be losing sight of the science. Writing for *BBC News Online* (2 May 2001), Helen Briggs suggests that "research has been overshadowed by ethical objections about the source of the tissue". Peter Gorner in the *Chicago Tribune* (3 May 2001) says that "[Gage] is worried that the public has become so inundated by stories about embryonic stem cells … that the science that underlies the ethical debate often gets short shrift". In the same article, Gage is quoted as saying "We haven't proved that these are stem cells. They're what are known as progenitor cells… stem cells also have the ability to reproduce themselves and keep on dividing indefinitely, and we haven't yet shown that these cells will do that".

Heather Wood

GLIA

Crystal-clear glia–neuron interactions



The profound effect that glial cells have on neurotransmission continues to gain notoriety; hardly a month passes without an important breakthrough in this flourishing field. The latest development has come from the study of acetylcholine (ACh)-mediated transmission in the snail *Lymnaea stagnalis*. In this system, Smit *et al*. have identified an ACh-binding protein (AChBP) released by glia, which can directly modulate the efficacy of synaptic transmission.

The authors observed that if a presynaptic neuron was stimulated repeatedly, the presence of a glial cell around the synapse caused a reduction in the postsynaptic, ACh-dependent response. By analysing this modulation in detail, Smit *et al*. determined that the glial cell responded to ACh and released AChBP, which then acted as a molecular decoy, binding the transmitter and reducing its availability at the synapse.

AChBP has significant sequence homology to ligand-gated ion-channels (LGICs). In particular, AChBP resembles the ligand-binding site of nicotinic ACh receptors. In a companion paper, Brejc *et al*. report that they have solved the crystal structure of AChBP and, indirectly, gained new insights into the structure of the ACh-receptor binding site. As predicted for the ACh receptor, AChBP forms pentamers in which the binding site is at the interface between subunits. The authors identified the residues that form the binding site and noted that they vary among LGICs, reflecting perhaps their different binding properties. By contrast, residues conserved between AChBP and LGICs do not contribute to the binding site but seem to stabilize the global structure of each subunit.

So, in addition to re-emphasizing the influence of glial cells on synaptic transmission, the study of AChBP constitutes a double triumph, providing the first detailed three-dimensional account of the ACh binding site. This crystallographic analysis will have a great influence on structural studies of other LGICs, comparable only to the impact that the structure of KcsA has had on the study of other voltage-gated ion channels.

Juan Carlos López

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SYNAPTIC PLASTICITY

Highs and lows

Lasting changes in the strength of glutamate synapses — long-term potentiation (LTP) or depression (LTD) — occur following activity-dependent changes in calcium concentration in the postsynaptic neuron. Paradoxically, both LTP and LTD seem to depend on increases in intracellular calcium. This has led to the proposal that the direction of the change in synaptic strength is determined by the size of the increase in postsynaptic calcium concentration, with progressively higher calcium causing first LTD and then LTP.

Cho *et al*. tested this theory in rat perirhinal cortex by using different concentrations of EGTA to buffer activity-dependent increases in postsynaptic calcium to different degrees. They found that stimulation that would normally cause LTP induced LTD instead if a high concentration of EGTA was present to limit the rise in calcium concentration.

Interestingly, they also found that moderate levels of the buffer would prevent both LTP and LTD. There seems to be a 'neutral zone', between concentrations of calcium that would normally induce LTD and those that would normally induce LTP, where neither takes place. This is reminiscent of the Bienenstock–Cooper–Munro (BCM) model, which proposes that low frequencies of stimulation will cause LTD, moderate frequencies will cause no change in synaptic strength, and high frequencies will cause LTP.

Is the lack of plasticity in this neutral zone the result of LTD and LTP balancing each other out, or are they both absent? Cho *et al*. tested this by selectively blocking LTD (using the mGlu receptor antagonist MCPG) or LTP (using the protein kinase inhibitor staurosporine) and repeating the experiment. When activity-dependent calcium levels were buffered to the neutral zone levels and LTD was blocked, LTP still did not occur; likewise, blocking LTP under similar levels of calcium buffering failed to uncover LTD.

So it seems that the cessation of LTD as calcium levels rise from low to moderate is independent of the induction of LTP at still higher levels. This raises the possibility that the higher calcium levels required to induce LTP actually inhibit the mechanisms of induction of LTD. Although the full picture of the molecular mechanisms underlying long-term plasticity is far from clear, these data provide another important piece of the jigsaw.

Rachel Jones

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