

EDITOR'S CHOICE

MOTORNEURON DISEASE: helpful neighbours

Amyotrophic Lateral Sclerosis (ALS) is a form of motorneuron disease characterised by the loss of lower and upper motorneurons. It is a fatal condition for which effective therapies are desperately needed. In this study in *Nature Neuroscience*, it has been shown that non-neuronal cells can help- namely astrocytes when transplanted into the cervical spinal cord of SOD mutant rats caused increased motor neuronal survival with accompanying functional benefits in the grafted animal.

In this study, a particular type of astrocyte was used- GRPs, which represent a lineage-restricted precursor cell derived from the developing spinal cord. These cells were then labelled with GFP and transplanted into the cervical cord of 90 day old SOD rats. This site for grafting was chosen because one of the major causes of death in ALS is respiratory failure secondary to diaphragmatic weakness.

After grafting, about a third of the cells survived and differentiated into astrocytes with little evidence that they proliferated post implantation. There was some time-dependent migration of the cells away from the graft site but the benefits were largely restricted to the

forelimb and diaphragm- both of which improved with the cell grafts.

So how do astrocyte transplants help protect neurons from death? Well the answer relates to the fact that the grafted cells express a glutamate transporter (GLT1, which is equivalent to EAAT2 in humans) which is normal and functionally active, unlike the host astrocytes. In addition these cells can reduce microgliosis but do not produce growth factors for the motorneuron.

This study is therefore of interest as it shows that cell therapies for neurodegenerative disorders of the CNS may need to use cells other than those directly targeted by the disease process. So given the recent interest in glial mediated cell death, what disease is next going to be treated by astrocyte, rather than neuronal, grafts?

– RAB

Lepore AC, Rauck B, Dejea C, Pardo AC, Rao MS, Rothstein JD, Maragakis NJ.

Focal transplantation-based astrocyte replacement is neuroprotective in a model of motor neuron disease.

**NATURE NEUROSCIENCE
2008;11:1294-301.**

REHABILITATION: Memories are made like this

We all take photographs and even sometimes make home videos so that we will have reminders of events or moments in our lives. The pictures also provide a way of sharing past experiences and can sometimes trigger memories we haven't thought about in ages.

These aide memoirs are often used to try to bring back memories in those who have amnesia due to head injury or conditions such as Alzheimers disease. Now a group in Cambridge has shown how using photographic film shows of significant days in an amnesic patient's life can help to consolidate autobiographical memory.

Their case, 'Mrs B', a 63 year old well educated woman with bilateral hippocampus lesions following limbic encephalitis, has marked amnesia. She usually has no memory of events after a couple of days. The Cambridge group developed a camera, called SenseCam, which is worn on the chest and takes images every 30 seconds. The resulting film, shot from the point of view of the first person can be replayed, discussed and shared.

The effectiveness of using the SenseCam films was compared with keeping a diary record of special days. After six viewings 80% of events were recalled from the Sensecam days and 49% were recalled from the diary

days. While it might not be surprising that the films were better for recall it was remarkable how effective they were over the long term. Retention of events was maintained three months later and without viewing SenseCam images in the mean time. Events from days recorded using the diary were not remembered at all even at one month.

The camera training was welcomed by Mrs B and her husband. Importantly it enabled them to share experiences and it also helped her to be less anxious about forgetting important times.

This is a very simple and effective strategy for aiding memory but it proved to be more than that. It also demonstrates how important context is in consolidating memories. I look forward to seeing how this works with other amnesic patients. – AJT

Berry E, Kapur N, Williams L, Hodges S, Watson P, Smyth G, Srinivasan J, Smith R, Wilson B, Wood K.

The use of a wearable camera, SenseCam, as a pictorial diary to improve autobiographical memory in a patient with limbic encephalitis:

**A preliminary report
NEUROPSYCHOLOGICAL REHABILITATION
2007;17:4,582-601.**

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COGNITION: muscling in on memories

Long Term Potentiation (LTP) in the hippocampus was described for the first time over 30 years ago and since then much has been written about it in terms of its molecular/synaptic basis. The phenomenon describes the increase in synaptic transmission at the CA1 synapse in response to an intense afferent input. Whilst the exact mechanism causing it is not fully understood, key players have been identified and include the post-synaptic NMDA and AMPA receptors, with activation of the former leading to an increase in the latter via a calcium-dependent process. A recent paper by Wang et al suggests a mechanism. They show that the influx of calcium through the NMDA receptor activated myosin Vb, which in turn recruit recycling endosomes in the dendritic spine that move to the cell membrane where they cause spine growth and the insertion of more AMPA receptors. This transportation of receptors and membrane is done via actin filaments, which is a calcium dependent process.

This work uses a number of different approaches to confirm that this network is causally linked to LTP at this synapse, and as such provides a fascinating new insight into LTP. In particular it highlights the extent to which neurons can restructure small parts of their dendritic tree and by so doing mediate focal synaptic changes reflecting if you like a degree of "microplasticity". This brings with it a level of complexity to the dynamic remodelling of the CNS that could not have been conceived of when LTP was first coming to scientific attention. – **RAB**

Wang Z, Edwards JG, Riley N, Provance DW Jr, Karcher R, Li XD, Davison IG, Ikebe M, Mercer JA, Kauer JA, Ehlers MD. Myosin Vb mobilizes recycling endosomes and AMPA receptors for postsynaptic plasticity.

CELL

2008;135:535-48.

STROKE: My brother had a bleed in his brain....

It is a standard conversation in clinic: what are my risks of having a subarachnoid haemorrhage (SAH), given that my [XXX relative(s)] had one? It is pretty clear that the risk of having an unruptured aneurysm, or a subarachnoid haemorrhage, is marginally increased if a first-degree relative has had a SAH. But what about the risk of a SAH if two or more first-degree relatives have had one? Up until now, there has been no clear answer, because you need a huge study to identify sufficient numbers of people with lots of affected relatives.... Step up the nation of Sweden. By using the Swedish Inpatient Register and the Swedish Multi-generational Register, 130,373 relatives of people with SAH were identified. The headline result is that your chance of having a SAH with one relative affected is increased by 2.15 and for those with two affected first-degree relatives, the odds ratio was 51.0. The absolute risk is still pretty low.... around 10 per 100 000 person-years. And the odds-ratio of 51 is not as hard as might first appear; it is based on only 1 affected in the controls and 10 affected in the "multi-relatives" group. We should not moan: it is unlikely we will ever have a bigger study to address this question. The clear result is that we should take people seriously when they ask for aneurysm screening, if more than one first-degree relative has had a SAH. And then we get into the thorny issues of how frequently to screen, with what modality, and quite what to do with unruptured aneurysms... Not easy. – **AJC Bor AS, Rinkel GJ, Adami J, Koffijberg H, Ekblom A, Buskens E, Blomqvist P, Granath F.**

Risk of subarachnoid haemorrhage according to number of affected relatives: a population based case-control study.

BRAIN

2008 Oct;131(Pt 10):2662-5. Epub 2008 Sep 26.

HEADACHE: The new kid on the block for migraine

Triptans have been the mainstay of acute migraine treatment since the 1990s. Since sumatriptan, there have been innumerable other agonists of the serotonin 5-HT_{1B/1D} receptors, with some seriously improbable names ("eletriptan" is my favourite). They are genuinely useful drugs, albeit expensive. Eletriptan costs over £3 a tablet, whereas three aspirin (which my wife finds just as effective) costs 5p. The triptans also cause alarming chest pain, which is probably not due to cardiac ischaemia, and there are worries about using them in cardiovascular disease, uncontrolled hypertension, and focal migraine subtypes such as hemiplegic and "basilar migraine". Now, something genuinely new: an antagonist of the calcitonin gene-related peptide receptor. It turns out that CSF CGRP concentration is increased during a migraine attack and intravenous CGRP triggers migraine-like headaches in people with migraine.... So now, does blockade of CGRP help people with migraine? Merck funded this phase 3 RCT of 1380 patients given telcagepant, zolmitriptan, or placebo. Telcagepant was as effective as zolmitriptan at reducing migraine frequency and severity, and had fewer adverse events (37% for telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo). Quite where telcagepant acts is a bit mysterious. Lars Edvinsson, in the commentary suggests whether it works on the CGRP-containing sensory nerves of the intracranial vessels, or the trigeminal nerve, or yet more centrally... This all sounds terrific. I hate to be a party-pooper, but I would like to see a trial of telcagepant versus a NSAID. – **AJC**

Ho TW, Ferrari MD, Dodick DW, Galet V, Kost J, Fan X, Lebensperger H, Froman S, Assaid C, Lines C, Koppen H, Winner PK.

Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial.

LANCET

2009;372(9656):2115-23

Brain Awareness Week 16-22 March, 2009

Every March the European Dana Alliance for the Brain (EDAB) coordinates Brain Awareness Week, a major collaboration celebrating the wonders of the brain and brain research through hundreds of public events worldwide.



Dr Fabio Carmello

EDAB is an organisation that is committed to enhancing the public's understanding of why brain research is so important.

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