EDITOR'S CHOICE

HUNTINGTON'S DISEASE: new cells for old

The role of neural stem cells in neurodegenerative disorders has been something of a passion of mine for many years, as abnormalities in this process may have important implications for therapy both in terms of innate repair and exogenous cell transplants in disorders of the CNS. Furthermore, understanding the processes of neurogenesis in diseased brains may also provide us with a better understanding of abnormal signalling pathways involved in disease pathogenesis. This new paper from the van der Kooy group raises some very interesting questions on how disease processes may influence stem cell behaviour in one of the neurogenic regions of the adult brain (the subventricular zone [SVZ]) in the R6/2 transgenic mouse model of Huntington's disease. They report that in this mouse, which contains the expanded exon 1 CAG repeat of human Huntington's disease gene:

1. There is an increase in neural precursor cell/neurospheres generated from the SVZ in R6/2 mice compared to wild type with increasing age and the development of symptoms.
2. There is an increase in BrdU in the SVZ 30 days after injection in the R6/2 mice compared to the wild type, implying there is an increase in stem cells at this site which is confirmed using EM and the demonstration of more precursor 'B' cells in the SVZ in the R6/2 mice.
3. There is an increase in proliferation with age which occurs *in vitro* with cloning but only at a time when such abnormalities in proliferation have been seen in the R6/2 mouse *in vivo*.
4. The increase which is seen *in vitro* is clearly primed *in vivo* and cannot be mimicked by growing early stage neurospheres for longer periods of time *in vitro*.
5. There is no change in the fate potential of the precursor cells *in vivo* or *in vitro*.
6. There is a decrease in olfactory bulb BrdU positive cells with an increase the BrdU positive cells in the striatum, suggesting a switch in migration of the stem cells to sites of more pathology.

These series of observations suggest that, with disease progression in this mouse model of Huntington's disease, there is a steady increase in the number of stem cells in the SVZ which, once primed and induced *in vivo,* is maintained *in vitro*. This suggests that the stem cell changes its properties with the evolving disease process in the brain. This would therefore imply that, in neurodegenerative disorders of the CNS, there are signals that cause a fundamental switch in the properties of proliferating neural stem cells which attempts to compensate for the pathology. Obviously if this process can be properly harnessed, then it will have important implications for CNS repair, but the key question remains as to what that signal is and how can we manipulate it to effect better repair in conditions such as Huntington's disease. - ***RAB***

Batista CM, Kippin TE, Willaime-Morawek S, Shimabukuro MK, Akamatsu W, van der Kooy D.

A progressive and cell non-autonomous increase in striatal neural stem cells in the Huntington's disease R6/2 mouse.

JOURNAL OF NEUROSCIENCE

2006;26:10452-60.

HUNTINGTON'S DISEASE: up and down or side to side?

Huntington's chorea is characterised by cognitive decline and chorea, but patients often display other deficits, including abnormalities of eye movement. Blekher et al have carried out a detailed and sensitive series of oculomotor tests in a group of patients with HD. Clinical evaluation was carried out using the standardised clinical rating scale UHDRS (Unified Huntington's Disease Rating Scale). The study included 215 individuals grouped into four classes depending on the presence or absence of motor abnormalities representative of HD. All the individuals in this study had a parent affected with HD and followed one of two patterns: they were either at risk of HD but not yet diagnosed or they had been diagnosed with HD within the past two years. Both vertical and horizontal saccadic readings were recorded using a video eye tracking system. Eye movement measures included visually-guided, anti-saccade, predictable, memory-guided (two versions) and fixation tasks. None of the participants reported significant eye problems and all had normal or corrected visual acuity. The authors showed that HD gene carriers – but not nongene carriers - had impaired saccades and were particularly poor in anti-saccade and memory-guided tasks, and this when standard clinical assessments currently used in HD were normal. The improved sensitivity provided by these quantitative saccadic measures may open a new chapter in the diagnosis of disease onset and also may enable researchers to ascertain whether disease modifying therapies are just that. - ***CA***

Blekher T, Johnson SA, Marshall J, White K, Hui S, Weaver M, Gray J, Yee R, Stout JC, Beristain X, Wojcieszek J, Foroud T.

Saccades in presymptomatic and early stages of Huntington disease.

NEUROLOGY

2006;67:394-9.

STROKE: a pit of vipers

If you get bitten by a Malaysian pit viper, you may bleed to death. A key component of the venom is Ancrod which splits fibrinopeptide A from fibrinogen. Ancod has been used in several trials as a treatment for ischaemic stroke. The previous North American Stroke Treatment with Ancrod Trial (STAT) showed that Ancrod outperformed placebo if given within three hours of a stroke. This study looks at its ability to improve stroke outcome if given later, within six hours. The result, perhaps unsurprisingly given what we know of TPA, is that later treatment is not beneficial. Normally such a pedestrian study would not make it onto the review pages of *ACNR*, but it is the vipers in the last paragraph of the report that merit attention:

"Preliminary data from this trial were first presented at the World Federation of Neurology Congress in London in 2001. Soon thereafter, the sponsor company, which was always supportive of the scientific outcomes of this trial, was sold. In the meantime, data from the study were not fully available to the investigators, and further analysis was difficult. Only with the support of many dedicated investigators and after careful reassessment of the material finally provided, could the members of the executive and safety committees prepare this report on behalf of the investigators. This situation illustrates the understandable but often regrettable divergences between sponsor and investigators' interests, leading to scientific losses and unethical waste of patients' and investigators' efforts. The bias towards easier publication of successful trials, sometimes at too early a stage, is another important issue to consider: the publication of this report is therefore an important recognition of the scientific and medical value of all clinical trials."

The moral is that it is critical that investigators have free access to data accumulated in their trial. It has always amazed me that some investigators are prepared to work in any other way. - AJC

Hennerici MG, Kay R, Bogousslavsky J, Lenzi GL, Verstraete M, Orgogozo JM; ESTAT investigators.

Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial.

LANCET

2006 Nov 25;368(9550):1871-8.

PARKINSON'S DISEASE: First gene therapy trial

This very short abstract buried at the back of an issue of Movement Disorders is one that was presented at the 20th Annual Symposium on the Aetiology, Pathogenesis and Treatment of Parkinson's Disease and Other Movement Disorders. This gives a very brief account (as one would expect) on 12 patients who have received open label unilateral subthalamic viral vector (AAV-GAD) injection as a treatment for their Parkinson's disease. This open label study involves 12 patients with an average age of 58.2 years and in this abstract the authors report on their FDG PET studies using this approach. The strategy involves trying to convert the excitatory subthalamic nucleus to an inhibitory one by changing the phenotype of the projection neurons from this structure and builds on earlier experimental work reported in Science in 2002 (see *ACNR* 2.5). Five patients appeared to respond to this virally delivered therapy and seven did not. In those that responded, there were clearly changes in FDG metabolism as one would anticipate, namely a decline in the internal globus pallidum and ventral lateral thalamus ipsilateral to the delivery of the viral vector and increased metabolism in the premotor and supplementary motor regions. These changes appear to correlate with improvements in their UPDRS scores. Whilst this is an abstract, it is important because this is the first ever gene therapy trial in Parkinson's disease and clearly gives us hope that this approach may have a future. - ***RAB***

Feigin A, Tang C, During M et al.

Gene therapy for Parkinson's disease with subthalamic nucleus AAV-GAD: FDG PET results.

MOVEMENT DISORDERS

2006;21:1543-4.

PARKINSON'S DISEASE: Get the rhythm

The role of dopamine in the control of movement is well known (*see for example the historical article in this issue of the ACNR by Oleh Hornykiewicz*), but how exactly dopamine achieves this is not altogether clear. The classical model of basal ganglia function has nigral dopamine stimulating the direct and indirect pathways through the striatum by activation of the D1 and D2 receptors on the projection neurons respectively. This then changes the outflow of the basal ganglia (the internal part of the globus pallidum and the substantia nigra pars reticulata) to the thalamus and so cortex, especially motor areas and by so doing contributes to the initiation of movement. As a result, in diseases such as Parkinson's disease (PD) there is a loss of the nigrostriatal dopaminergic projection with a decrease in activation of cortical areas, causing akinesia amongst other symptoms, presumably through a failure of motor cortical activation. However, a recent paper suggests that it may not be as simple as this and that dopamine may be more important in coordinating activity between the striatum and motor cortex, so that in PD the problem is more a loss of this synchronous activity. The work leading to this suggestion uses a dopamine transporter (DAT) knock out mouse in which dopamine levels can be easily manipulated such that:

a) a hyperdopaminergic state with hyperactivity can be achieved by placing the DAT knock out mouse in a novel environment;
b) a hypodopaminergic state with akinesia can be achieved by blocking dopamine synthesis using alpha methyl-p-tyrosine (AMPT) [as there are no dopamine stores to compensate for this synthetic block];
c) restoration of dopamine in the hypodopaminergic state can be achieved using L-dopa.

Using this system the authors show that there are differences in firing frequency (both at the single level and local field potential level) in the striatum and motor cortex with differing levels of dopaminergic tone. More importantly though, they show that with dopamine depletion the degree of synchrony between striatum and cortex is enhanced whilst the hyperdopaminergic state is characterised by asynchronous activity in corticostriatal networks. This is an interesting study given the recent work on the mechanisms underlying the beneficial effects of deep brain stimulation in PD and its postulated functions on changing corticostriatal rhythmicity and synchrony. However, this paper more importantly raises fundamental questions about how diffusely projecting neurotransmitters may work in the normal brain and how they fail in disease across networks and as such this work has implications on how best to treat conditions such as PD. - ***RAB***

Costa RM, Lin SC, Sotnikova TD, Cyr M, Gainetdinov RR, Caron MG, Nicolelis MA.
Rapid alterations in corticostriatal ensemble coordination during acute dopamine-dependent motor dysfunction.
NEURON
2006;52:359-69.

nvCJD: Its in the blood

★★★★ RECOMMENDED

Almost anything, however trivial, about variant CJD gets straight into the media, but this report probably deserves to, because it is very worrying. It describes the case of a 22-year-old man who, after several years of symptoms of inflammatory bowel disease, had an ileostomy. Complications of its reversal some time later were so severe that he required 22 units of blood transfusion. Unfortunately one of the donors of this blood died 20 months afterwards of variant CJD. The recipients were all informed there was a slight risk of developing CJD, which cannot have been an easy message to relay or receive. All was well for six years, and then the patient developed progressive limb pain, balance and cognitive deficits. He died nearly nine years after the vCJD implicated transfusion (age 32 years). Prior to death, a MRI had shown the pulvinar sign, which had not been seen on a scan done at the onset of symptoms. Deposition of type 4 PrP, the hallmark of vCJD, was seen post mortem throughout the cortex and cerebellum, and likewise in the tonsils. There are two other such cases in the literature, which does not amount to a whole lot of beans until you consider that the long incubation period of vCJD, and lack of reliable blood test, means that much of the transfusion stock may be contaminated. As Collinge told listeners of Radio 4's Today programme, we really need to know the results of the National Anonymous Tonsil Archive's screening of 100 000 tonsils for disease-associated PrP. It is still not clear whether vCJD is going to be a ghastly pandemic or a fascinating rarity. - ***AJC***

Wroe SJ, Pal S, Siddique D, Hyare H, Macfarlane R, Joiner S, Linehan JM, Brandner S, Wadsworth JD, Hewitt P, Collinge J.
Clinical presentation and pre-mortem diagnosis of variant Creutzfeldt-Jakob disease associated with blood transfusion: a case report.
LANCET
2006 Dec 9;368(9552):2061-7.

EPILEPSY: The cost of misdiagnosis

You all know that in everybody else's clinic, not your own of course, the chronic misdiagnosis of epilepsy is 20-25%. You all want to help those other neurologists resolve their diagnostic problems and the only way to do so is to have video-EEG-telemetry. You go to your friendly, local health care commissioner and tell them that epilepsy misdiagnosis causes misery, psychosocial deterioration, inappropriate treatment, lack of appropriate treatment and all those clinical things that medical practice is supposed to help. The response is: "That is all very interesting but how will you save money?" So here is the answer. Using standard prevalence and misdiagnosis rates, these authors calculate a misdiagnosis rate of 1,769 cases per million population. The cost of medical resources allocated to these patients was taken from another paper, including inappropriate admissions (45%), AEDs (26%), outpatient attendances (16%) and GP care (8%). The total they came to is £316 per patient. This is similar to the NICE guidelines calculation of £263 and works out as £559,076 per million population per year. I reckon it is still an underestimate, considering that a new AED for a year costs about £1,000. What we don't know from this calculation, is how much it will cost to treat the patient's true diagnosis, but so far my managers have not thought of this and I am not going to tell them. So now you have the data you can help all those other guys who can't diagnose fits. Good luck. Any other tips on managerial bamboozling, please email to mark.manford@addenbrookes.nhs.uk. - ***MRAM***

Juarez-Garcia A, Stokes T, Shaw B, Camosso-Stefinovic, Baker R.
The costs of epilepsy misdiagnosis in England and Wales.
SEIZURE
2006;15:598-605.

EPILEPSY: Sliced resistance to carbamazepine

★★★ RECOMMENDED

Antiepileptic drugs often don't work and epilepsy associated with hippocampal sclerosis is particularly resistant to medical treatment. Hypotheses for the mechanism of this resistance include failure of drugs to cross the blood brain barrier, but perhaps the varying effect of different drugs in different types of epilepsy make an alteration intrinsic to the tissue more likely. This study explored that possibility by applying carbamazepine directly to the mesial temporal lobe slices from 28 patients with mesial temporal lobe epilepsy and from 6 patients with extrahippocampal tumours. The resected tissue was sliced and stimulated until spontaneous discharges occurred. Then carbamazepine was applied and finally washed off. Different types of epileptic activity were induced in different slices. The slices from patients with mesial temporal lobe epilepsy showed little change in spike activity when carbamazepine was applied but tissue from those with extrahipocampal tumours showed a reduction of abnormal activity by about 90%. Tissue showing lower drug resistance generally came from patients with a shorter duration of epilepsy and clinically less resistant epilepsy, suggesting that this model is clinically relevant. Seven per cent of patients who were carbamazepine-sensitive in the model, where the drug could gain access to tissue, had been resistant *in vivo*, suggesting that this subgroup may have had a different mechanism of resistance, perhaps at the blood brain barrier. The authors speculated on the mechanism of resistance. They found from voltage clamp experiments that there was reduced sensitivity of voltage dependent sodium channels to the effects of carbamazepine in resistant slices. The authors argue that, since carbamazepine acts on the sodium channel on the outer surface of the cell, cellular transporters which increase efflux of the drug are unlikely to have any impact on resistance. They speculated on the possibility that synaptic reorganisation in the hippocampus may be a factor in drug resistance but had no direct evidence for this hypothesis. This new finding moves a step closer to understanding why the drugs we use act so differently in different patients, but clearly this kind of work is limited by the availability of human experimental tissue. - ***MRAM***

Jandova K, Pasler D, Antonio LL, Raue C, Ji S, Njunting M, Kann O, Kovacs R, Meencke HJ, Cavalheiro EA, Heinemann U, Gabriel S, Lehmann TN.
Carbamazepine resistance in the dentate gyrus of human hippocampal slices.
BRAIN
2006;129:3290-306.

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