

EDITOR'S CHOICE

EPILEPSY: Valproate is bad news for the foetus

This multicentre UK and USA study recruited over 300 pregnant women taking monotherapy with common antiepileptic drugs; phenytoin, carbamazepine, lamotrigine and valproate. They evaluated these women at baseline and found them to be similar for maternal IQ, epilepsy severity, folate use and gestational age at birth. For children exposed in utero to phenytoin, carbamazepine or lamotrigine, the main determinant of IQ at 3 years of age was maternal IQ. However this relationship was broken in the women taking valproate whose children suffered a dose-related reduction in IQ. On average, children exposed to valproate had an IQ score 9 points lower than those exposed to lamotrigine, 7 points lower than those exposed to phenytoin and 6 points lower than those exposed to carbamazepine. These results were statistically significant but there was no significant difference between the other drugs. A further analysis will be made when the children are six. The authors point out that these drugs are used frequently for indications other than epilepsy and, although this study was only in women with epilepsy, they would expect the results to be similar for other groups. This study provides convincing evidence of the dangers of valproate to the foetus over and above obvious major malformations.

They will cause increasing headaches to those of us who find ourselves with a limited choice of medication in patients with generalised epilepsy, especially juvenile myoclonic epilepsy. When do these problems arise? Is it safe to start valproate in the 2nd-3rd trimester for patients where no other drug will do? I guess we shall never know. Do you undertreat the mother to save harm to the foetus? It must be remembered that in one confidential enquiry into maternal mortality, the risk of maternal death in women with epilepsy was ten times expected. Treating mothers remains the first priority and sometimes the risks may be unavoidable. What about other drugs? Can one justify giving levetiracetam? The balance of the hope of the future against the devil you know. A balanced decision needs to be made with each mother prior to conception. This new knowledge is crucial but the decisions just get harder. – **MRAM**

Meador KJ, Baker G, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW for the NEAD Study Group.

Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs.

**NEW ENGLAND JOURNAL OF MEDICINE
2009;360:1597-1605.**

LEARNING: Adult hippocampal neurogenesis a phenomena looking for a function?

The role of adult neurogenesis in the dentate gyrus of the hippocampus is an area of intense debate. The fact that new neurons are born in this area of the mature CNS is not in doubt, but the question is what do these cells do once they have matured and been incorporated into new circuits? A couple of papers have added to the literature in this area.

The first by Kim et al investigated the consequences of preventing the death of these cells using a Bax-KO mouse. Bax is pro-apoptotic and its absence prevents programmed cell death in newly born neurons. Using this model (which of course assumes that most new neurons born in the dentate gyrus are lost through apoptosis), they found that there was a readjustment of synaptic connections with impairments in both electrophysiological and behavioural hippocampal function. In other words, if a population of new born neurons in the hippocampus are not removed by natural cell death, they clog up the system and cause deficits which behaviourally involve memory acquisition and consolidation.

This is consistent with the study of Trouche et al who followed the fate of newly dividing (BrdU positive) neurons in terms of their integration and functional abilities. In this study the authors used the activity dependent protein Zif268 in combination with high resolution confocal imaging and co-labelling with BrdU and the neuronal marker NeuN, to follow the fate of cells in the context of controlled behav-

iours involving the water maze.

They found that these newly born neurons are recruited into neuronal networks involved with spatial memory and that once incorporated are involved in the updating and strengthening of that memory and thus contribute in part to its durability. Thus these cells are recruited under experience-specific conditions and store those conditions as part of their contribution to the spatial memory of the hippocampus.

Quite how this information is then used, updated and modified in the long term is not clear, but this and the other study of Kim et al does highlight that these new neurons do make a significant contribution to some aspects of hippocampal memory. – **RAB**

Kim WR, Park OH, Choi S, Choi SY, Park SK, Lee KJ, Rhyu IJ, Kim H, Lee YK, Kim HT, Oppenheim RW, Sun W.

The maintenance of specific aspects of neuronal function and behaviour is dependent on programmed cell death of adult-generated neurons in the dentate gyrus.

**EUROPEAN JOURNAL OF NEUROSCIENCE
2009;29:1408-21.**

Trouche S, Bontempi B, Rouillet P, Rampon C. Recruitment of adult-generated neurons into functional hippocampal networks contributes to updating and strengthening spatial memory.

**PNAS
2009;106:5919-24.**

Journal reviewers

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SPINAL CORD INJURY: Too much of a good thing

It seems obvious: if physiotherapy improves the outcome after spinal cord injury, and so does a drug, then combining the physio and the drug should be better still, shouldn't it? Well, no...

The drug in question is the antibody to Nogo-A, the neurite growth inhibitor, which is in human trials. In this paper, the discoverer of Nogo-A, Martin Schwab and colleagues, investigated the efficacy of step training or intrathecal delivery of an anti-Nogo-A antibody on the recovery of rats from a surgical cord lesion at T8. The outcome measure was stunningly simple and beautifully illustrated: the animals' gait was analysed by 3-D video recording using four cameras monitoring 5 reflective markers on each hindlimb. After a spinal cord injury, the animals' steps are irregular and disordered. This is restored to near-normal by the antibody to Nogo-A. Locomotor training has a less dramatic, but nonetheless clear effect in regularising the gait. But the combination of antibody and training leads to more dragging and more irregularity of gait than with the antibody alone. In other words: the training has interfered with the effect of the antibody. By far the best group were those animals who had received the antibody and been left to "self-train" in their cages.

As you might expect from these careful scientists, the paper is brimming with data and careful analysis. But the bottom line is that they cannot work out why these two treatments of spinal cord injury should interfere with one another. So the obvious is not always right and we need to be careful about combining treatments of spinal cord injury... and the prospects of anti-NogoA antibody being efficacious seem to increase with each study. Roll on the clinical trials. – *AJC*

Maier IC, Ichiyama RM, Courtine G, Schnell L, Lavrov I, Edgerton VR, Schwab ME.

Differential effects of anti-Nogo-A antibody treatment and treadmill training in rats with incomplete spinal cord injury.

BRAIN

2009;132(Pt 6):1426-40.

BRAIN INJURY: Rise and shine

The recent short lived excitement surrounding the potential for zolpidem to "wake" patients in a minimally conscious state demonstrated the power that this concept exerts on the public imagination. Faced with the seemingly hopeless situation of a patient with a severe brain injury who will not wake up, there is often an overwhelming need to "try something" to facilitate a return to consciousness. Because patients and their brains are frustratingly heterogeneous, no single approach or treatment has yet been shown to reliably offer itself as a therapeutic option with a consistent evidence base.

This case report describes a young man in a minimally conscious state following a brain injury sustained in a road traffic accident. The authors describe an initial 100 day period during which he received trials of methylphenidate followed by bromocriptine without evidence of increased wakefulness. Both agents have been previously reported as eliciting a therapeutic response in the management of low awareness states. A subcutaneous apomorphine infusion was then initiated with immediate (within a week) improvements in Disability Rating Scale, Extended Glasgow Outcome Scale and Coma-Near Coma Scale. An interesting (unintended) withdrawal of the apomorphine resulted in a deterioration of cognitive and physical functioning after 18 days of treatment. Resumption of treatment then maintained previous improvements. After 180 days, the infusion was stopped and the patient reportedly managed to return to relatively normal activity within another year.

The study also has information on tractography performed on the patient. This leads to speculation about specific "pathway" involvement in minimally conscious states. Unfortunately the imaging studies are not correlated with the response to the apomorphine and seem to have come from another paper.

This case study raises a number of interesting and contentious points. Should all patients in minimally conscious states have a trial of dopamin-

ergic medication? Could imaging studies guide suitability for these trials? Will it ever be possible to carry out a properly controlled study of these medications in such a heterogeneous patient group? The increasing weight of accumulating evidence certainly provides grounds for cautious optimism. – *LB*

Fridman EA, Calvar J, Bonetto M, Gamzu E, Krimchansky BZ, Meli F, Leiguarda RC, Zafonte R.

Fast awakening from minimally conscious state with apomorphine.

BRAIN INJURY

2009;23(2):172-7.

BRAIN REPAIR: Repairing the brain in Alzheimer's disease – a role for BDNF?

BDNF was the second neurotrophic factor to be discovered after NGF* and has long been known to be involved in CNS plasticity especially in the hippocampal complex. As a result it has been a favoured therapeutic target as it may improve memory and cognition in disorders such as Alzheimer's Disease (AD). This ability to use BDNF for therapeutic benefit is not just restricted to exogenous delivery (see below) but it could also be endogenously upregulated by environmental enrichment and some drugs, such as anti-depressants. However, the recent study by the group of Mark Tuszynski (who brought us a trial of NGF for AD) has investigated the extent to which BDNF delivered to the entorhinal cortex can restore hippocampal function in aging, diseased and lesioned animals.

The entorhinal cortex (ECx) provides the major input to the hippocampus via the perforant pathway and the integrity of this system is needed for some aspects of normal learning and memory. BDNF is anterogradely transported along this pathway and as AD pathology involves this part of the brain early on in the disease course, it would be logical to see if manipulating BDNF levels affects the functional capabilities of this system. The team therefore explored this to show that:

- Lentiviral (LV)-BDNF delivery to the ECx of the APP transgenic mouse models of AD ameliorated some hippocampal dependent behavioural deficits with anatomical and microarray profile correlates of cell rescue without there being any effect on pathology;
- Bilateral infusion of recombinant BDNF into the medial ECx had similar effects on aged rats through restoring age related deficiencies in synaptic integrity mainly through an action on the Erk signalling pathway;
- BDNF did not only rescue neuronal atrophy and synaptic loss but also has the capacity to rescue cells "lesioned" in vitro by beta-amyloid and in vivo following perforant pathway transections and LV-BDNF delivery into the ECx;
- The same was then done in non-human primates. Here the perforant pathway was again lesioned and LV-BDNF injected into the ECx with the rescue of cells;
- Finally the same viral vector delivery system was used to rescue the aged ECx in non-human primates at both the anatomical and functional level.

These series of experiments therefore suggest that BDNF may help in rescuing aspects of hippocampal function which in turn has implications for the treatment of disorders such as AD. The translation of this work to the clinic is though not straightforward given (i) the extensive pathology seen in all neurodegenerative disorders including AD; (ii) the problems of long term targeted delivery of growth factors and (iii) the risk of the patient developing neutralising antibodies to the growth factor. Nevertheless, studies such as this rekindle the hope that growth factors could be useful in treatment of neurodegenerative disorders of the CNS. – *RAB*

Nagahara AH et al.

Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease.

NATURE MEDICINE

2009;15:331-7.

[* Happy Birthday to Rita Levi-Montalcini, one of the discoverers of NGF who was 100 years old this April].