

EDITOR'S CHOICE

PARKINSON'S DISEASE: A stimulating new approach

Electrical stimulation of the brain has been explored in PD for some time, most notably in the form of deep brain stimulation of the subthalamic nuclei. However other targets and approaches have been sought including cortical stimulation and now, in a recent paper in *Science*, the spinal cord! Fuentes et al have used dorsal column stimulation (DCS) in the treatment of experimental PD. They have done this using a number of different animal models but in all cases they have implanted electrodes in the upper thoracic cord, which are stimulated at a frequency of around 300Hz. In their first experiment, they show that knocking out dopamine synthesis using inhibitors of the pathway (i.p. alpha-methyltyrosine) causes deficits in locomotion and abnormalities in corticostriatal neuronal activity both in terms of local field potentials and single unit recordings. They then show that high frequency stimulation of the upper thoracic cord increases locomotor activity both in the dopamine depleted and non-depleted animals, but that the effect is much greater in the depleted state. This improvement in locomotion was accompanied by a move towards normalisation of neuronal activity, as assessed immediately after the period of stimulation, a series of benefits that were also seen in the DATKO mice with acute dopamine depletions. The next experiments involved chronic lesions using 6-OHDA striatal terminal lesions in rats and stimulating the thoracic cord for 30 sec-

onds every 10 minutes with the animals in an open field test chamber (as a way of looking at locomotion). The stimulation improved locomotion for the duration it was on and for about 100 seconds afterwards. Thus the authors conclude "that stimulation of the dorsal column pathways using epidural implanted bipolar electrodes can restore locomotive capability". The method by which this is achieved is unknown, but the authors propose that it works through ascending effects via the thalamus and from there to the corticostriatal system, rather than by non-specific brainstem arousal effects or effects on spinal cord locomotor circuits. In other words dorsal column stimulation works by activating large cortical areas which then activate the striatum in such a way as to overcome the block to the motor system that the striatum mediates in response to its lost nigral dopaminergic input. This is all very interesting and will stimulate much debate especially with respect to how it works. Indeed until this is better understood, it may well remain as a curious experimental observation. – **RAB**

Fuentes R, Petersson P, Siesser WB, Caron MG, Nicoletis MA.

Spinal cord stimulation restores locomotion in animal models of Parkinson's disease.

SCIENCE

2009;323:1578-82.

PARANEOPLASIA: Yet another limbic antibody

There was a time when the only antibody that mattered in neurology was the acetylcholine receptor antibody. Those days are long gone. First we had a range of antibodies against channels in the peripheral neuromuscular junction... which we could just about get our head around. But in recent times, more and more antibodies have been identified against targets with incomprehensible names... and it is getting pretty bewildering... Does it really matter if you have an antibody against "collapsin response-mediator protein-5"? None of this is helped by some pretty shoddy research in the lower-tier journals. Nor is the situation clarified when different centres use different assays and get different results, so that – for instance – a positive "anti-basal ganglia antibody" in the US is one thing, and in the UK is quite another... And why do anti-GluR3 antibodies do different things in Israel than other countries...?

Josep Dalmau is the Pennsylvania King of Paraneoplastic Neurology, and has characterised many weird and wonderful antibody-associated paraneoplastic syndromes. And his team has come up with yet another one: against AMPAR, a glutamate receptor. I think we can quite reasonably ask: "so what"? Well, first of all, he is looking at an important-not-to-miss disease: the potentially treatable limbic encephalitis, which may be mistaken for untreatable conditions like the degenerative dementias. Roughly speaking, three-quarters of such patients will have antibodies which recognise the surface of neurones in the laboratory; and, of these, less than half will be directed to the potassium channel. The rest will be a rag bag of antibodies against NMDA, GAD, Hu, Ma, amphiphysin, CV2 and CRMP5.... and a lot will remain uncharacterised. So the Dalmau lab went through its freezers and identified 10 patients with limbic encephalitis, without defined autoantibodies, whose

sera bound the brain and cerebellum of rats in a similar way. Clinically, they were kosher cases of limbic encephalitis: with encephalopathy, seizures and medial temporal MRI abnormalities. 9/10 were women and 7/10 had had tumours of the lung, breast, or thymus. 9/10 improved dramatically after the presenting episode, with immunotherapy, but there was a tendency to relapse. The Dalmau team soaked some hippocampal neurones in the patients' sera and then immunoprecipitated the antigens, and ran them through a mass spec. The resulting signature suggested the antigens came from the GluR1 and GluR2 subunits of the AMPAR. Some juggling with transfectants led to the conclusion that some patients had antibodies to GluR1, some to GluR2 and some to both. And, when they took the sera back to the neuronal cultures, they found that it specifically reduced the number of GluR2-AMPA clusters at the synapse, with a much lower effect on the overall AMPAR cluster density. In answer to the "so what?" question: Dalmau has potentially identified a new test for "anti-VGKC negative" limbic encephalitis patients; and a positive result should lead to a hunt for cancer. His team has also shown how this antibody might be working: by effectively shunting AMPARs away from the synapse... now that is both useful and interesting! – **AJC**

Meizan Lai, Ethan G. Hughes, Xiaoyu Peng, Lei Zhou, Amy J. Gleichman, Huidy Shu, Sabrina Matà, Daniel Kremens, Roberta Vitaliani, Michael D. Geschwind, Luis Bataller, Robert G. Kalb, Rebecca Davis, Francesc Graus, David R. Lynch, Rita Balice-Gordon, Josep Dalmau.

AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location (p NA).

ANNALS of NEUROLOGY

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EPILEPSY: and head-nodding

I am always impressed to hear of clinicians who are able to identify a new disease, especially in a context where clinical services are stretched beyond the comprehension of most Western physicians. I usually assume that when something is new to me, that is just my ignorance, a fairly safe assumption as a rule. In fact, head-nodding disease was originally identified in about 1960, in Tanzania but has become more widely known in Africa in the last decade. It is not the involuntary response of a beleaguered populace to an oppressive military regime, but a clinical condition characterised by head nodding, mental retardation, clinical signs and other seizures as well. In this study of 62 patients, only about ten underwent MRI or EEG as this would have involved travelling 300km to Dar es Salaam but clinical data were available in all, skin biopsies in many and CSF in about three quarters. The onset was usually between the ages of six and ten years and 45% of patients had only head nodding but the same number also had other seizures, especially tonic clonic seizures. In some patients seizures were triggered by food. Some patients had focal signs and others "brain damage", although this is not clearly defined. There was evidence of onchocerciasis in 84% on blood tests or skin biopsy, the authors do not comment on the background rate in the community. Hippocampal sclerosis was present in 42% of those who underwent MRI. This is not an epilepsy syndrome I recognise in patients with hippocampal sclerosis and the geography points to a local predisposition; genetic or environmental, as yet to be determined with certainty. I await further studies with interest. – **MRAM**

Winkler AS, Friedrich K, König R, Meindl M, Helbok R, Unterberger I, Gotwald T, Dharsee J, Velicheti S, Kidunda A, Jilek-Aall L, Matuja W, Schmutzhard E.

Head nodding syndrome – Clinical classification and possible causes.

EPILEPSIA

2008;2008-2015.

PARKINSON'S DISEASE:

Oh Glia! Where is the problem?

The loss of the dopaminergic nigrostriatal pathway is the core event in Parkinson's disease (PD), but what causes the death of these cells is unclear. There is though an emerging consensus that part of the problem is intrinsic to the cells, but that this may not be the whole story and the glia may contribute to the disease process. This evidence includes:

- Histological data on microglia activation in pathological specimens of PD brains;
- Microglia activation in vivo using PK11195 PET;
- Pathology in grafted dopaminergic cells in patients who have had fetal ventral mesencephalic grafts for their advanced PD; and
- The proven role of glia in other neurodegenerative disorders such as MSA and motor neuron disease.

Adding to this is the recent data from Chen et al in which they show that astrocytes are important in the loss of dopaminergic cells in MPTP treated animals. The experiments begin by showing that mice treated with MPTP using their dosing regime have reduced nigrostriatal dopamine and increased GFAP astrocytosis in these same areas – namely the striatum and nigra. They then sought to follow the transcription of genes containing the antioxidant response element (ARE). ARE regulates many cytoprotective genes via the transcription factor Nfe2 related factor (Nfe2) and using a reporter system they showed that MPTP increased Nfe2-ARE signalling in the nigra and decreased it in the striatum.

In order to study what this meant, MPTP was then given to Nfe2 knock-out mice (Nfe2^{-/-}) as well as normal wild type mice (Nfe2^{+/+}). It was found that in the Nfe2^{-/-} mice there was an increased toxic effect of MPTP and that this was NOT related either to major baseline changes in the integrity of the dopaminergic nigrostriatal system nor the capacity to generate more MPP⁺ (the toxic metabolite of MPTP). However there was an increase in the astroglial response in the Nfe2^{-/-} mice in response to MPTP. Furthermore, when they overexpressed Nrf2 in GFAP positive cells

(astrocytes), they dramatically protected the animals from the toxic effects of MPTP and attenuated the astroglial response and this included in Nfe2^{-/-} mice. Thus it appears that MPTP induced dopaminergic loss involves a major astroglial component and oxidative stress. Of course whether this is relevant to patients with PD remains unproven. – **RAB**

Chen PC, Vargas MR, Pani AK, Smeyne RJ, Johnson DA, Kan YW, Johnson JA.

Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: critical role for the astrocytes.

PNAS

2009; 106: 2933-2938.

SLEEP DISORDERS: what next after RBD?

REM sleep behaviour disorder (RBD) is mainly characterised by a loss of the normal muscle atonia that accompanies REM sleep. Patients with RBD present with excessive motor activity while sleeping, and this includes kicking or crying during dreaming. Recent studies have shown that RBD appears to be a feature of α -synucleinopathies, presumably mediated by degeneration of sleep regulating nuclei in the brain stem such as the pontine tegmentum. As such there is great interest that RBD can occur long before the development of Parkinson's disease (PD), dementia with Lewy bodies (DLB) or multiple system atrophy (MSA) (all α -synucleinopathies). If this is the case then there is the possibility of studying patients with RBD to see the extent to which they go onto develop one of these disorders, especially PD.

Postuma et al therefore studied patients with RBD and quantified the risk of subsequently developing a neurodegenerative disorder. They used 93 patients who had attended a sleep disorders clinic and met inclusion criteria for RBD as well as a life table analysis to define disease risk over 5, 10 and 12 years. Some of the inclusion criteria included a polysomnogram confirming RBD, complex motor behaviours during REM sleep, absence of any neurodegenerative disorder confirmed on a baseline neurologic examination. Interestingly, 26 out of the 93 patients developed a neurodegenerative disease; 15 developed parkinsonism and 11 dementia. Out of the 15 who developed Parkinsonism, 14 were diagnosed with idiopathic PD and one with multiple system atrophy (MSA). For the 11 patients with dementia, seven met clinical criteria for LBD and four met clinical criteria for AD. There was no difference in RBD duration between those who did or did not develop disease.

The current study has clearly demonstrated that the risk of developing a neurodegenerative disorder such as PD is lower than previously reported in other studies – this may relate to issues of sample size, follow up periods, diagnostic criteria and so on. Thus it will be essential to continue follow up in all cases of RBD using bigger sample sizes to see if a clearer picture may emerge on why some patients with synucleinopathies have RBD and how this differs from idiopathic RBD. – **CA**

Postuma, R, Gagnon, J, Vendette, M, Fantini, M, Massicotte-Marquez, J, Montplaisir, J.

Quantifying the risk of neurodegenerative disease in idiopathic REM sleep behaviour disorder.

NEUROLOGY

January 7 2009 [EPUB].

EPILEPSY: the risk from head injury

In this study the authors used the Danish National Registry to identify all patients born from 1977-2002 who developed epilepsy or who had a head injury. This association does not prove causation in every case, there may have been a few whose head injury was the consequence of a seizure and some who had a head injury and were going to develop epilepsy anyway, but in the great majority it is likely that the association was causative. They defined a mild head injury as one with loss of con-

sciousness for less than 30 minutes, post-traumatic amnesia for less than 24 hours and GCS no less than 14. Severe head injury included evidence of intracerebral contusion or haemorrhage. They analysed patients with skull fracture separately. They were then able to measure the relative risk of developing epilepsy against the remainder of that birth cohort. It is not clear how they categorised patients who may have had more severe clinical markers of head injury than the mild group but did not have evidence of intracranial haematoma, and these may not have been analysed. This differs from the previous standard study of Annegers, in which they were considered moderately severe.

The authors followed about 1.6 million individuals for nearly 20 million person years and found that the risk of epilepsy was approximately doubled by a mild brain injury or a skull fracture and increased seven-fold by a severe head injury. The risk was highest in those over the age of 15 and persisted for more than ten years after injury. The risk was maximal in the first year for those with brain injury but did not seem to be related to time, for those with a skull fracture. For those with a mild brain injury, a family history of epilepsy substantially increased the risk of seizures, with an effect that was between additive and multiplicative. For severe head injuries it appeared to be closer to additive.

This study confirms findings in previous studies and adds to them by clarifying the issues in relation to mild head injuries in the era of neuroimaging. It also, for the first time, describes in a large cohort, the contribution of genetic factors to the risk of epilepsy. It will be of great use to those advising patients with head injury and great profit to the medicolegal fraternity. It will also provide a valuable baseline for any studies which may be undertaken in the future with anti-epileptogenic drugs, if they become available. It must be remembered however, that it is restricted to patients under the age of 25 at the time of their trauma. – **MRAM**

1. Annegers JF, Hauser WA, Coan SP, Rocca WA.

A population based study of seizures after traumatic brain injury.

N Engl J Med

1998;338:20-24.

Christensen J, Pedersen MG, Pedersen CB, Sidenius P, Olsen J, Vestergaard M.

Long-term risk of epilepsy after traumatic brain injury in children and young adults: a population-based cohort study.

LANCET

2009 Mar 28;373(9669):1105-10.

EPILEPSY: anti-epileptic drugs in pregnancy affect the baby's IQ

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, the children exposed to valproate in utero had 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. 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 under-treat 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.

NEJM

2009; 360:1597-1605.

MULTIPLE SCLEROSIS: A convenient pill?

Time was when people with multiple sclerosis would have been content with anything that was effective as a treatment for their disease, no matter how unpalatable. Over the years, people ingested snake venom, stung themselves with bees, drunk bottles of coke laced with venlafaxine, immersed themselves in hyperbaric chambers.... But now the concept of convenience has crept into the lexicon of multiple sclerosis therapeutics. And what could be more convenient than a pill? No more needles in the bathroom, or monthly visits to the hospital to spend all day waiting for the Tysabri infusion. And there is no shortage of contenders to be the first pill to be licensed for multiple sclerosis: fingolimod, cladribine, and now fumarate.

What is fumarate? Nothing to do with smoking. It activates the nuclear-factor-E2-related factor-2 (Nrf2) transcriptional pathway, -as you can tell from another review in this journal ("Oh Glia!") - may mean that the drug could be both anti-inflammatory and neuro-protective, which would be handy. 257 patients with relapsing-remitting multiple sclerosis were given fumarate in three different doses, and compared to a placebo, for 24 weeks then there was a "safety extension study" where everyone got active drug. The principal outcome measure was the total number of gadolinium-enhancing lesions added up from four scans done throughout the first 24 weeks. On the highest dose of fumarate (240mg tds) there was a statistical difference from placebo: a reduction in new lesion total by 70%. Before getting too excited, let me remind you that this is about the same as interferon-beta's effect on MRI scans. The lower doses did not make the statistical cut. There was no effect on any clinical outcome, although to be fair the group taking the highest fumarate dose trended towards the lowest relapse rate. Taking the drug did not seem to cause much bother; some flushing and GI upset only. My bottom line is that fumarate, for all its Nrf2-thingummy, shows no sign of being any more efficacious than the interferons, so far at least. So, a lot of time and money is being put into phase 3 trials, plans to get the drug licensed and all the rest.... for convenience. But it is not exactly convenient to have inadequately treated multiple sclerosis. – **AJC**

Kappos L, Gold R, Miller DH, Macmanus DG, Havrdova E, Limmroth V, Polman CH, Schmierer K, Yousry TA, Yang M, Eraksoy M, Meluzinova E, Rektor I, Dawson KT, Sandrock AW, O'Neill GN; BG-12 Phase IIb Study Investigators

Efficacy and safety of oral fumarate in patients with relapsing-remitting multiple sclerosis: a multicentre, randomised, double-blind, placebo-controlled phase IIb study.

LANCET

2008 Oct 25;372(9648):1463-72.

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