

NEURODEGENERATION: Keeping active is good for the brain

Mouse models of Huntington's disease have been used as a way of testing novel treatments to see if the natural history and progression of the disease can be modified. In this study a different approach is undertaken which examines how environmental enrichment delays disease progress in mouse models of disease. Over the last three to four years it has been shown that if you place mouse transgenic for the Huntington's disease gene into environments in which they are stimulated both from a motoric and cognitive point of view there is slowing of disease progression in terms of pathology as well as behavioural deficits. The origin of this is not known but in this recent paper it is hypothesised and demonstrated that it may relate to the secretion of BDNF. In particular this group have shown by Western blot that BDNF levels in two specific areas namely the hippocampus and striatum are reduced in the R6/1 transgenic HD mice, and that this can be restored using environmental enrichment. However, other areas of the brain do not show any changes in BDNF suggesting that it is relatively region specific, and in addition other trophic factors (i.e. NGF) are unaffected so showing that it is specific for this trophic factor as well.

This is an interesting study because the effect of enrichment to date is not known. Our own group is interested in knowing whether the effects of enrichment relate in some way to neural stem cell proliferation given that this is a known proliferative stimulus to the adult neural precursor cell. This study, however, has taken a different tack and demonstrates changes in trophic factor which are influenced by environmental stimulation.

Whether this translates into clinical benefit is not known but it does clearly raise the important issue that physical and mental activity at least in animal models governs the trophic factor secretion and therefore neuronal support within the adult CNS. In the diseased state this may be important in promoting or at least maximising the potential of neurons which are either borne through neural precursor cells or dependent on trophic factors for their persistent survival. Thus whilst it is not clear whether this has a clinical correlate it once more lends weight to the notion that it is good for patients with diseases of the brain to be physically and mentally active. -RAB

Environmental Enrichment Rescues Protein Deficits in a mouse model of Huntington's disease indicating a possible disease mechanism.

Spires TL, Grote HE, Varshney NK, Cordery PM, van Dellen A, Blakemore C, Hannan AJ.

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REHABILITATION: Eyes closed for better balance after stroke

Methods for rehabilitation of balance after stroke are poorly developed. Therapists typically follow one of two strategies. They might try to get patients to react to perturbation by pushing them or by sitting on a ball or standing on a wobble board, or they may try to encourage activity of postural muscles in anticipation of a task such as reaching. There has been little examination of the use of sensory information in balance to guide therapy. An investigation of the use of sensory information in chronic stroke led a French research group to think that patients are too reliant on visual information in maintaining balance. They subsequently tested the effects of balance retraining with visual cue deprivation (eyes closed) in a small randomised controlled trial. The trial and the preceding investigation of the effects of sensory information and the trial are published in two parts in the February edition of Archives Physical Medicine and Rehabilitation.

Twenty patients over one year post stroke who were able to walk without assistance were recruited to a four week balance training course of 5 one hour sessions a week. Patients without joint position sense in the affected leg were excluded. The patients were randomly allocated to train with visual deprivation (blind folded) or to train with vision (control group). Balance was assessed before and after the training course using a clever posturographic evaluation. The patient stood barefoot on a platform and sway angle of the centre of gravity was measured under conditions in which the platform and the surroundings could be stable or could be moving. Gait velocity, ease of gait and stair climbing time were also assessed. After the training program balance, gait velocity and self assessment of gait improved significantly in all patients. Balance improved more in the vision deprived group.

Depriving patients of vision probably forces patients to increase their use of somatosensory and vestibular information. Of course this method needs testing further to confirm the results and to see if they apply to more acute patients; however the method is promising and would be very easy to use in clinical practice. -AJT

Reliance on visual information after stroke. Part II: Effectiveness of a balance rehabilitation program with visual cue deprivation after stroke: a randomised controlled trial.

Bonan IV, Yelnik AP, Colle FM, Michaud C, Normand E, Panigot B, Roth P, Guichard JP, Vicaut E.

ARCHIVES PHYSICAL MEDICINE AND REHABILITATION

2004; 85: 274-8.

PAIN: Integrins are integrally involved in mediating pain states

Chronic pain is a common neurological problem that is largely intractable to current therapies, despite improvements in the understanding of mechanisms contributing to pain following tissue and nerve injury. This study investigates a role for integrins in mediating such pain.

Integrins are adhesion molecules that bind extracellular matrix (ECM) proteins, including laminin and fibronectin. They are transmembrane heterodimers (comprised of α and β subunits) that mediate signalling in both directions across the membrane. They are present on primary afferent nociceptors and are thus optimally located to sense changes in the ECM environment, which accompany inflammation and injury.

In this study, several strategies were used to disrupt integrin signalling, which concomitantly inhibited the development of hyperalgesia in rat models. Peptide fragments of laminin or monoclonal antibodies against the α_1 and β_3 integrin subunits (involved in laminin binding) blocked the hyperalgesia triggered by the injection of prostaglandin E2 (PGE2), and carageenan (a longer-lasting model of inflammatory pain), but not by adrenaline. Fibronectin peptides and antibodies against the α_5 subunit of integrin (involved in fibronectin binding) blocked hyperalgesia induced by adrenaline, but not by PGE2 or carageenan. The α_1 subunit is involved in both laminin and fibronectin binding. Monoclonal antibodies and antisense deoxynucleotides against this subunit prevented hyperalgesia induced by all the above triggers. The α_1 subunit antisense molecules also inhibited taxol-mediated hyperalgesia, which is a model of neuropathic pain. Thus, it appears that integrins in fact mediate pain through several pathways.

This demonstration that integrins play a significant role in cell signalling pathways mediating sensitisation of nociceptors, not only adds to our knowledge of chronic pain mechanisms, but also offers hope for the development of better therapies for those suffering from inflammatory and neuropathic pain. -LMS, SJT.

Integrin signaling in inflammatory and neuropathic pain in the rat.

Dina OA, Parada CA, Yeh J, Chen X, McCarter GC, Levine JD

EUROPEAN JOURNAL OF NEUROSCIENCE

2004; 19: 634-42

☆☆☆ RECOMMENDED

MOTOR NEURON DISEASE: Dysfunctional Glutamate Receptors in Sporadic ALS

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurodegenerative disorder resulting from selective loss of motor neurons in the brain and spinal cord. 90% of cases are sporadic and of unknown aetiology. This report from Kawahara *et al*, describes defective editing of messenger RNA (mRNA) encoding the GluR2 subunit of the glutamatergic AMPA receptor in ALS patients. RNA editing of the GluR2 subunit leads to the exchange of a glutamine for an arginine residue in the second of its membrane-spanning domains. This GluR2 RNA editing is not only essential for the correct functioning of the AMPA receptor but is also crucial for neuronal survival. Thus Kawahara proposes that the mechanism underlying motor neuron death in ALS may be the failure to edit the GluR2 Q/R site.

The GluR2 editing efficiency in various neurons from several neurodegenerative diseases was assessed by studying the enzymatic digestion of GluR2 mRNA; a process which occurs only in the edited version of the subunit. Cerebellar Purkinje and motor cortical cells of ALS patients, as well as DRPLA and normal control cells, displayed complete GluR2 Q/R site editing. However, motor neurons dissected from ALS patients showed very variable editing efficiency at this site; 56% of the motor neurons being incompletely edited. This indicates a defect specific to ALS spinal motor neurons. The toxicity of the unedited form of the GluR2 subunit is thought to relate to its ability to promote transport of the AMPA receptor to the membrane and to enhance the permeability of the AMPA receptor to calcium ions.

Further investigation of the mechanism underlying reduced RNA editing at the GluR2 Q/R site should identify rational therapeutic targets specific for ALS. -LMS, SJT

RNA editing and death of motor neurons.

Kawahara Y, Ito K, Sun H, Aizawa H, Kanazawa I, Kwak S

NATURE

2004; 427; 801

EPILEPSY: When nocturnal seizures wake up

Seizures whilst you are asleep are bad enough but if they evolve into waking attacks the social consequences may be much greater. So what is the risk? In this study children with benign rolandic epilepsy or any patients with frontal lobe epilepsy which are known to be nocturnal syndromes, were excluded. This left 161 consecutive patients with pure nocturnal attacks, aged 11-83 with two thirds male. Duration of epilepsy ranged from 1-514 months. Focal

seizures affected 15% and GTCS 85%. Sixteen patients had generalised EEG abnormalities and 31 had focal changes. Seizures were mild (<1/yr) in 37%, moderate (1-6/yr) in 54% and severe (>6/yr) in 9%. Follow-up was 24-72 months during which time 14 were lost to follow up and 5 patients died. Those lost to follow-up had been observed for a mean for 25 months before they were lost to the study. Retention was 149 at 2 years, 107 at 3 years, 79 at 4 years and 42 at 5 years. Seventy-eight percent became seizure-free for at least 2 years.

All patients who developed daytime seizures did so within 55 months of follow-up. Eighteen patients (11%) developed seizures whilst awake, about two thirds of these within the first two years of follow-up. By far the strongest identifiable risk factor for conversion to waking seizures was sudden withdrawal of treatment, which was voluntary in all cases. Phased withdrawal did not carry an excess risk. The other significant identified factor was a high seizure frequency at inclusion. Patients can be reassured that it is uncommon for waking seizures to develop on a long background of nocturnal epilepsy, especially if their epilepsy is mild and they do not stop treatment suddenly.

- MM

Risk of seizures while awake in pure sleep epilepsies. A prospective study
D'Alessandro R, Guarino M, Greco G, Bassein L for the Emiglia Romana study group on clinical and epidemiological problems in neurology.

NEUROLOGY
2004;62:254-7.

CREUTZFELDT-JAKOB DISEASE: Diagnosis of sporadic disease

The clinical diagnosis of sporadic Creutzfeldt-Jakob (sCJD) disease may be difficult. Peripheral biomarkers which may support the diagnosis include CSF 14-3-3 protein and EEG periodic complexes, but neither has perfect sensitivity or specificity. This paper suggests another possible biomarker: deposition of pathological prion protein (PrP^{Res}) in olfactory epithelium.

In sCJD, PrP^{Res} is found exclusively in the CNS, unlike the situation in vCJD where it may be found in reticuloendothelial tissues (hence the utility of tonsil biopsy in the diagnosis of vCJD). Having demonstrated that PrP^{Res} may be shown in olfactory epithelium of sCJD cases post mortem but not in AD or other neurodegenerative diseases (N Engl J Med 2003; 348: 711-9), the authors undertook olfactory biopsy in a patient with suspected sCJD 45 days after disease onset. PrP immunostaining of cilia and basal cells of olfactory epithelium was found. At postmortem, pathological confirmation of sCJD was made.

The findings relate to only one patient and hence need to be confirmed in larger studies. However, if deposition of PrP^{Res} in olfactory epithelium is

proved to be an early event in sCJD, this may have implications for early diagnosis and, possibly, for early therapeutic intervention. -AJL

Prion deposition in olfactory biopsy of sporadic Creutzfeldt-Jakob disease.

Tabaton M, Monaco S, Cordone MP, Colucci M, Giaccone G, Tagliavini F, Zanusso G.

ANNALS OF NEUROLOGY
2004;55(2):294-296

☆☆☆ RECOMMENDED

EPILEPSY: Buzzing the pleasure centre

Those of us who treat many epileptic patients will remember the occasional one who admits that their epileptic aura is really quite pleasant. If you ask them how pleasant, you get a coy look and an admission that it is really embarrassingly pleasant. Not surprisingly, non-compliance with treatment is reported to be quite high in this group. The current paper explores the localisation of pleasurable sensation in 11 patients undergoing presurgical evaluation. Seven patients were male, which differs from most previous reports in which females predominate and 7 had right-sided abnormalities. Most patients described a very visceral sensation of pleasure, 3 describing a feeling akin to orgasm. All three had temporal lobe discharges, two on the right and one on the left. Previous series have ascribed this sensation to the right hemisphere. All except one of the other patients also had temporal lobe abnormalities on investigation, in 8 pointing to the basal temporal lobe. The other patient experienced a feeling of euphoria – perhaps a more emotional and less visceral sensation. She had biparietal atrophy on MRI and discharges, assessed by intracranial electrodes started in the right basal temporal region and rapidly spread to the parietal cortex. Lesions were hippocampal sclerosis in 3 cases and a variety of foreign tissue lesions in the remainder, including astrocytomas and cavernomas.

If intracranial stimulators can help Parkinson's disease, how many more people would benefit from having their pleasure centre buzzed? I can see a lucrative, if not entirely ethical private practice for an entrepreneurial neurosurgeon. However, the down side is that 6 of the 11 experienced interictal depression. -MM

Ictal pleasant sensations: cerebral localization and lateralization.

Stefan H, Schulze-Bonhage A, Pauli E, Platsch G, Quiske A, Buchfelder M and Romstöck J.

EPILEPSIA
2004;45:35-40