

EDITOR'S CHOICE

Presenilin 1 gene mutation causing Pick's disease

Over 100 mutations in the presenilin 1 (PS1) gene causing Alzheimer's disease (AD) have been described in the past decade (molgen-www.uia.ac.be/Admutations). Cell biological and animal models show these mutations increase production of the long variant of amyloid ϵ -peptide (A β 42) by increasing gamma-secretase cleavage of amyloid precursor protein (APP). This report from Belgium broadens the clinical phenotype of PS1 mutations, reporting a novel mutation (G183V) associated with the clinical features of frontotemporal dementia (FTD) and, uniquely, a neuropathological substrate typical of Pick's disease.

The proband presented aged 54 with apathy, disinhibition and frontal release signs. Memory functions were intact. Brain imaging showed predominant frontotemporal atrophy. The clinical-radiological diagnosis was FTD. However, unusually for FTD, he had an abnormal EEG (slow and sharp waves in the temporal regions) and later developed dyspraxia (not further specified). He died at age 62. Brain pathology showed tau positive Pick bodies and Pick cells but no amyloid deposits. No mutation was found in the genes encoding APP, tau, PS2, or prion protein, but a novel mutation was identified in PS1, which was also found in 3 other family members, 2 with lesser degrees of cognitive and neuroradiological change.

Although the clinical phenotype of FTD has previously been reported with PS1 mutations (L113P, insR352), this is the first case with neuropathological evidence of Pick's disease. Although the neurogenetic finding might be a novel polymorphism, the cosegregation with clinical and neuroimaging abnormality suggests pathogenicity. The proposed mechanism is a dominant negative effect, resulting in loss of gamma-secretase activity; if correct, treatment of such patients with gamma-secretase inhibitors would be contraindicated. -AJL Dermaut B, Kumar-Singh S, Engelborghs S, Theuns J, Rademakers R, Saerens J, Pickut BA, Peeters K, van den Broeck M, Vennekens K, Claes S, Cruts M, Cras P, Martin JJ, Van Broeckhoven C, De Deyn PP. *A novel presenilin 1 mutation associated with Pick's disease but not ϵ -amyloid plaques.*

ANNALS OF NEUROLOGY
2004;55(5):617-626

★★★ RECOMMENDED

NEUROIMMUNOLOGY: anti basal ganglia antibodies – what do they signify?

There have recently been a whole series of articles on the role of anti basal ganglia antibodies in neurological disease, in particular PANDAS (Paediatric Autoimmune Neuropsychiatric Disorders After Streptococcal infections) and related disorders. Gavin Giovannoni and colleagues in London were one of the first groups to demonstrate antibodies against the basal ganglia in patients with a range of neurological disorders following streptococcal infections, suggesting that the humoral mediator of the condition could be isolated and act as a diagnostic test. They now extend these findings to encephalitis lethargica (EL) by describing 20 new cases of this condition in which a range of immunological abnormalities were seen including antibodies against a range of neural epitopes (but not just in the basal ganglia). In addition they demonstrated that these antibodies can be seen pathologically in brain specimens from a patient who died from this condition, and argue that they are pathogenic and thus that EL is therefore related to Sydenham's chorea and PANDAS. However, despite this convincing account, it is often difficult to prove causality with antibody mediated disorders, and a couple of recent papers in Movement Disorders take on this challenge. The first of these papers by Singer *et al* demonstrates that the striatal microinfusion of PANDAS sera (as well as that from patients with Tourettes syndrome) is without effect, suggesting that the antibodies contained within the sera are non-pathological. Indeed this group then go on to report in this same issue of Movement Disorders that their ELISA method for detecting anti

basal ganglia antibodies cannot differentiate between PANDAS and controls, suggesting a "lack of major antibody changes in this disorder", a conclusion that is largely embraced by the accompanying editorial by Roger Kurlan.

So how does one reconcile all these different findings and what does it mean when one has a positive anti basal ganglia result in a patient? I think for the moment it is not clear, but it is important to remember that assays such as those employed in these studies are very operator dependent and certainly in the hands of Giovannoni *et al* they appear to have very low false positive results. Therefore results from this laboratory are probably significant, but quite how they cause disease is unclear at this stage given that the passive transfer of disease has not been achieved – analogous to the situation that is seen with most antibody associated paraneoplastic syndromes. This failure to prove causality also creates issues of treatment, in that whilst antibiotics to treat the underlying streptococcal infection are clearly important, it is not clear what, if any, immunosuppressive therapies should be advocated....but that is the subject of future studies and I also suspect yet more controversy! -RAB Dale RC, Church AJ, Surtees RAH, Lees AJ, Adcock JE, Harding B, Neville BGR, Giovannoni G (2004)

Encephalitis lethargica syndrome: 20 new cases and evidence of basal ganglia autoimmunity.

BRAIN
2004;127:21-33

Kurlan R

The PANDAS hypothesis: losing its bite?

MOVEMENT DISORDERS
2004: 19:371-374

Loiselle CR, Lee O, Moran TH, Singer HS

Striatal microinfusions of Tourette Syndrome and PANDAS sera: Failure to induce behavioral changes.

MOVEMENT DISORDERS
2004: 19:390-396

Singer HS, Loiselle CR, Lee O, Minzer K, Swedo S, Grus FH.

Anti-basal ganglia antibodies in PANDAS.

MOVEMENT DISORDERS
2004: 19:406-415

MULTIPLE SCLEROSIS: Transplant drug helps aggressive disease

The interferon-failure era has well and truly begun. The enthusiasm for interferons as a treatment for multiple sclerosis has waned on both sides of the Atlantic and the hunt is on for more effective treatments. There are many new agents at one stage or other in the development pipeline. One of the most interesting is daclizumab, a monoclonal antibody that binds to – and blocks the function of –, CD25, the alpha chain of the IL2 receptor. IL2 is a pivotal cytokine in the survival and proliferation of T cells. This antibody has a proven track record at inhibiting rejection in organ transplantation and, like several drugs before it, translation into the autoimmune field made good sense.

Roland Martin's group at the NIH have reported a pilot study of treating just 10 patients with daclizumab, all of whom had "failed" interferon by virtue of having had one relapse, or progressing by just one EDSS point, in the previous eighteen months. (In itself, that is a provocative definition as it does not take account of pre-treatment relapse frequency). The patients were required to demonstrate a high degree of new MRI lesion formation before treatment was given as a monthly infusion over 6 months. During this time, new MRI lesion formation was reduced by 78%. So the drug is effective at reducing inflammation in the brain... as have been many novel agents.

So far, so good. But what makes this study special is that, as the trial was taking place, high expression of the CD25 molecule was discovered to be a marker of regulatory T cells, whose job it is to suppress autoimmunity. So daclizumab potentially might have exacerbated disease activity, by releasing the control of autoaggressive T cells. Almost certainly, daclizumab would be considered too dangerous if the trial were being

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planned now. So, once again, the treatment of multiple sclerosis has thrown up a confusing result that sends us back to the immunological drawing board. -AJC

Bielekova B, Richert N, Howard T, Blevins G, Markovic-Plese S, McCartin J, Wurfel J, Ohayon J, Waldmann TA, McFarland HF, Martin R. *Humanised anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon-beta*. PROC NATL ACAD SCI U S A. 2004;101:8705-8708.

REHABILITATION: What happens to Head Bangers?

This group have published several papers in this field in recent years but this one adds significantly to the picture of short to medium term outcome in children after a head injury (HI). Their study population of nearly a thousand was identified from a comprehensive local Register linked to the trauma centre admissions. A postal questionnaire was used, based on a new outcome scale derived from the Glasgow Outcome Scale for adults, the Kings Outcome Scale for Childhood Head Injury (KOSCHI) and covering a wide variety of symptoms, behaviour, personality and performance. This was sent out to the parents of children up to six years since injury. Amazingly they were able to retrieve GCS and/or duration of loss of consciousness in all patients (as there is another ongoing study in trauma) – most studies report routine recording of GCS in only up to 60% of cases.

They formed a control group of 45 children by asking some parents of the study group to identify a child of the same age and sex but without a history of head injury (but one wonders about the possibility of parents choosing a “role model” child in their area and thus the validity of this control?) There was a nearly 60% response rate (thus over 500 children), higher in the more severe groups and no noted differences in characteristics between responders and non-responders.

Some surprising findings include that only 30% of the study group had any follow-up and only 8% received any form of therapy. Current teachers were aware of the child's head injury in only 40% of cases. Nearly half the children had moderate disability according to the KOSCHI outcome score and worryingly 43% of those with mild HI were in this group. Not surprisingly symptoms were more frequent in the more severely injured groups and worse outcome was associated with poor socio-economic status (which is already recognised as a risk factor for acquiring head injury in the first place).

As they mention, up to 3,000 children each year in the UK acquire significant new neurological or cognitive disability as a result of head injury. Clearly given their young age and impact on development there is a huge potential for improvement in quality of life with appropriate assessment and intervention. The authors suggest a postal questionnaire follow-up to identify those that may benefit from follow-up assessment. However, one wonders whether an information/advice sheet to parents on discharge with relevant contacts as has been advocated for adults might be more efficient? -JJMACF

CA Hawley, AB Ward, AR Magnay, J Long.
Outcomes following childhood head injury: a population study. JOURNAL NEUROLOGY NEUROSURGERY PSYCHIATRY 2004, 75:737-742

☆☆☆ RECOMMENDED

EPILEPSY: Telephone-induced seizures!

One of my wise teachers once said that if the history is odd, consider psychiatric causes but if it is truly bizarre then think organic. Few people could make up a story like these three patients who described typical complex partial seizures triggered by answering the phone and occurring a few seconds into the conversation. The effect was described with both land lines and mobile phones. For one patient the attacks seemed to come on most frequently when her best friend phoned her but when she was admitted for video-EEG-telemetry, it was a nurse phoning her that triggered the seizure after seven unsuccessful phone calls. The simultaneous EEG showed a right temporal seizure discharge. Recording seizures was unsuccessful in the other two patients but one had an interictal epileptiform disturbance over the right frontotemporal region and the other more non-specific changes over the left temporal lobe.

Neuroimaging was normal in all three. All responded to a greater or lesser degree to carbamazepine. I see this as a strong justification to leave on my answerphone 24 hours per day.

Michelucci R, Gardella E, de Haan GJ, Bisulli F, Zaniboni A, Cantalupo G, Alberto Tassinari C, Tinuper P, Nobile C, Nichelli P, Kasteleijn-Nolst Trenite DG.

Telephone-induced seizures: a new type of reflex epilepsy. EPILEPSIA 2004;45:280-3

☆☆☆ RECOMMENDED

REHABILITATION: Neighbourhood Watch and the Leylandia

The two hemispheres of the brain are like a lot of neighbours; most of the time they co-operate and are quite amicable across the garden fence (corpus callosum), getting on with tasks that require involvement of both parties, but occasionally there are elements of competition and even downright antagonism! Yes I agree, a rather crass analogy but one which helps me interpret Pascual-Leone's paper on a rather surprising effect of inhibiting the motor cortex. By applying low frequency (1Hz) repetitive transcranial magnetic stimulation (rTMS) a target area of cortex can be temporarily switched off ('virtual lesioning'). This Harvard group performed this on one hemisphere and measured speed and accuracy of a motor task (index finger key tapping) pre and post rTMS of both hands. Not much happened to the execution time or accuracy in the contralateral hand, ie the hand supplied directly by M1 receiving the rTMS, however, the ipsilateral hand on performing the same motor task appeared to be significantly quicker in executing the task without compromising accuracy (same error rate) post TMS. A case of leaving the Leylandia unchecked(?). [Editor's note: this analogy defeats me].

There are various confounders that have to be taken on board but the study does seem to have controlled pretty well for these, e.g. ensuring a plateau in performance with practice of the motor task before performing the experiment. The hypothesis from this study is that a bidirectional inhibitory transcallosal pathway between motor areas can be suppressed with TMS on one side, releasing the contralateral M1 to work faster. The paper also supported this proposed mechanism by studying inhibition directly with a paired TMS study. Interestingly the effect is not equal, with the dominant hemisphere generating greater inhibition.

There is evidence from both stroke patients and rat lesioning that a paradoxical increase in function can occur in the unaffected hemisphere. If this TMS method has a long lasting effect, then a therapeutic application in rehabilitation may be possible. At the moment 600 pulses affords about 10 minutes of increased speed. Maybe I will have to give their protocol a go and see if my mobile text messaging is any quicker! -JLR M.Kobayashi, S.Hutchinson, H.Theoret, G.Schlaug, and A. Pascual-Leone.

Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements.

NEUROLOGY 2004; 62: 91-98.

HUNTINGTON'S DISEASE: Induction of autophagy by rapamycin slows progression

Huntington's disease (HD) is an autosomal dominant inherited disorder caused by a polyglutamine tract expansion in the Huntingtin protein (Htt). HD is characterised neuropathologically by intraneuronal inclusions, which amongst other proteins, are comprised of aggregates of the N-terminal fragment of mutant Htt.

This work by Ravikumar and colleagues demonstrates that within these inclusions, mutant Htt associates with a cellular kinase, mTOR. mTOR is responsible for the regulation of cellular processes through the control of mRNA translation, such as maintenance of cellular volume and inhibition of autophagy. Sequestration of mTOR within such inclusions impairs its kinase activity and induces the autophagy process, which breaks down aggregation-prone proteins including mutant Htt. Several lines of evidence point to the cellular toxicity of intraneuronal inclusions in HD. However, there is also evidence of a possible protective role for these inclusions. This study employed rapamycin, a specific inhibitor of mTOR, to stimulate autophagy. This drug successfully

reduced mutant Htt accumulation and neurodegeneration in vitro and in vivo models of HD and improved performance in four behavioural tasks of mouse models of the disease.

It is hopeful that rapamycin will be available shortly to treat human disease since it is already used as an immunosuppressant and its ester analogue, which has fewer side effects, is undergoing evaluation in clinical trials for cancer. This pre-clinical study suggested that rapamycin loses efficacy when aggregate pathology is advanced, thus in the clinic it would be important to start therapy early to slow progression of HD. In those individuals with a genetic susceptibility, starting therapy before the onset of symptoms may stall the disease beyond normal life span and thus represent a cure.

These trials suggest a huge therapeutic potential for mTOR inhibition in the treatment not only of HD, but other neurodegenerative diseases associated with protein aggregation. -LMS, SJT

Ravikumar B, Vacher C, Berger Z, Davies JE, Luo S, Oroz LG, Scaravilli F, Easton DF, Duden R, O'Kane CJ, Rubinsztein DC

Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of Huntington disease.

NATURE GENETICS

2004; 36 (6) ; 585-95

★★★ RECOMMENDED

STROKE: asymptomatic carotid stenosis

In 1991, the European and North American carotid surgery trials (ECST and NASCET) demonstrated a long-term net benefit of carotid endarterectomy in patients with a recent stroke and significant ipsilateral carotid stenosis. But the data was less robust for surgery for asymptomatic carotid stenosis, hence the MRC Asymptomatic Carotid Surgery trial, of which this is the 5 year report. 3120 patients were included with carotid stenosis of at least 60% on ultrasound and no attributable cerebrovascular event in the preceding 6 months. 1560 were allocated immediate surgery and 1560 randomised to deferred surgery, of which 201 patients had had an endarterectomy within the 5 year period, for one reason or other. Overall the surgical risk of perioperative stroke or death was 3.1%. It took two years before this risk was outweighed by the benefit from surgery. But, by 5 years, there was a clear benefit for early endarterectomy: a risk of 6.4% of any stroke (including peri-operative) or death in the surgical arm compared to 11.8% for medical treatment. This benefit was seen for stenoses greater than 70%. The trial will continue to run for a further 5 years, so it may be that surgery to lesser stenoses will yet prove beneficial in the long-term.

Halliday A, Mansfield A, Marro J, Peto C, Peto R, Potter J, Thomas D; MRC Asymptomatic Carotid Surgery Trial (ACST) Collaborative Group.

Prevention of disabling and fatal strokes by successful carotid endarterectomy in patients without recent neurological symptoms: randomised controlled trial.

LANCET

2004;363:1491-502

REHABILITATION: Invasive motor cortex stimulation to help recovery from stroke

Recently it has been demonstrated that in animal models of stroke, improved function can result from subthreshold cortical stimulation when combined with motor training. This has led to a feasibility trial in human stroke patients in the US (Northstar Neuroscience). Results from the first patient in the study were published alongside reports of the pre-clinical studies in the December issue of Neurological Research last year. And since invasive methods of stimulation have not really been considered as an option for stroke rehabilitation in the UK, it is worth drawing attention to this article.

A 65 year old man with a subcortical infarct was recruited to the study 19 months after stroke. At the time of recruitment he was unable to move his fingers but could extend his wrist against gravity. He underwent surgery to create a cranial flap. The site, identified by fMRI, was over the cortical motor representation of wrist flexion. A plate carrying an array of electrodes was implanted and stimulation through selective electrode contacts evoked contralateral finger flexion. The flap was replaced and

three days after surgery the patient began an intensive 3 week programme of occupational therapy involving the paretic hand and arm and aimed at improving activities of daily living. During these sessions an external pulse generator was worn and subthreshold cortical stimulation was delivered concurrent with Occupational Therapy. At the end of the three weeks his score on the Fugl-Meyer motor assessment was improved by 10 points and he was reported to be able to pick up a pencil and print block letters.

Of course this case report is not controlled and we cannot be sure that the reported changes would not have occurred without the stimulation. We will have to wait for the results of the trial. However, as well as the possibility that this treatment may be effective it is interesting to consider how the stimulation might have helped. The authors speculate how recovery may have occurred. The patient was unable to move the fingers voluntarily when the electrode plate was implanted but the stimulation delivered during the operation evoked individual finger flexion. This means that the corticospinal projections to the motoneurons of the finger flexors were intact but the patient could not access them. It is possible that the stimulation delivered during the patient's attempts to use the hand may have depolarised the underlying neurons to a level that allowed the movement to be executed. As the practice and stimulation continued so synaptic circuits were reinforced and voluntary movement was regained.

This invasive treatment might seem rather extreme, but if the results are good many patients might be prepared to have the surgery. However, if the cortical stimulation proves effective there may be ways in which the cortex could be stimulated by non-invasive means. -AJT

Brown JA, Lutsep H, Cramer SC, Weinand M.

Motor cortex stimulation for enhancement of recovery after stroke: case report.

NEUROLOGICAL RESEARCH

2003; 25: 815-818

PARKINSON'S DISEASE: Neurogenesis as a treatment for PD?

D3 receptors are widely expressed in the development and persist in neurogenic areas in adulthood (subventricular zone and hippocampus). D3 receptor activation promotes mitogenesis in vitro via G protein activation of the Ras pathway, which promotes phosphorylation of mitogen activated protein kinases (MAPK).

The authors sought to examine the role of D3 activation on precursor cells in vivo. D3 activation by 7-OH-DPAT (via intraventricular infusion for 2 weeks) increases BrdU incorporation into cells in the SVZ, RMS (rostral migratory stream, the migration path of neuroblasts to the olfactory bulb), and striatum. BrdU incorporates into dividing cells and is used as a marker for cell proliferation, and persist so cells can also be double labelled with other cell markers and thus the cell's fate can be examined. BrdU immunoreactivity in the striatum decreases as a function of the distance from the ventricle, suggesting the cells had migrated from the SVZ, or the proliferation was in response to a dose dependent effect according to the agonist gradient. The increase in BrdU was specific to D3 activation as it was not mirrored by a D1 agonist, and abolished by co-infusion of a D3 antagonist. The authors did not explore whether D3 blockade reduced basal BrdU incorporation.

Proliferation in the striatum may represent stimulation of endogenous in situ precursors. PCNA, another marker for proliferation, represents cells that are dividing only at the time of killing. PCNA immunoreactivity was increased, paralleling the BrdU increase, which suggests in situ proliferation rather than migration. Systemic, as opposed to intraventricular administration, produced uniform staining throughout the striatum. Also, BrdU labelling was increased after only 3 days of D3 stimulation, arguably, not giving the cells enough time to have migrated from the SVZ. Importantly, the majority of the newborn cells in both the RMS and the striatum co-expressed neuronal markers, indicating the new cells were new neurones. Some even expressed TH (i.e. were likely dopaminergic neurones). GFAP (astrocytic) labelling was not increased.

So, D3 stimulation increases neurogenesis in the striatum (and, in unpublished observations, in the substantia nigra). As mentioned, D3 has mitogenic properties via the MAPK system; but also through tyrosine kinase activation. TK activation is normally mediated via neurotrophins,

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and indeed there is evidence for cross talk between D3 and BDNF (brain derived neurotrophic factor). BDNF also increases neurogenesis. Perhaps D3 activation could be harnessed to produce new neurones to replace those lost in neurodegenerative diseases like PD and HD. Perhaps this action may underlie some of the disease modifying properties of drugs such as pramipexole.

Identification of a substrate for neurogenesis in the striatum and substantia nigra offers potential for a therapeutic target for brain repair in conditions that affect these regions. -WAR

Van Kampen JM, Hagg T, Robertson HA.

Induction of neurogenesis in the adult rat subventricular zone and neostriatum following D3 receptor stimulation.

EUROPEAN JOURNAL OF NEUROSCIENCE

2004; 19; 2377-2387

EPILEPSY: Religiosity and the hippocampus

I clearly recall one patient coming to clinic with page upon page of closely written and perseverative text, concerning the Isle of Innisfree and its religious significance. The Geschwind syndrome triad of hypergraphia, religiosity and hyposexuality may be useful qualifications for a life in cloisters but is also thought to represent a behavioural syndrome in some patients with temporal lobe epilepsy. In this study 33 residents of the Chalfont centre with refractory epilepsy were included and underwent volumetric MRI. They were assessed on the validated and widely used neurobehavioural inventory (NBI) and divided into three groups; high or low religiosity, high or low sexuality and high or low writing behaviour. The only behaviour that was correlated with an MRI abnormality was hyper-religiosity, patients had significantly smaller right hippocampal but not amygdala volumes. The authors refer to a study of Kumagata Minakata, apparently a Japanese genius with the Geschwind triad whose post-mortem MRI showed right hippocampal atrophy. The mechanism of these associations is unknown. -MM

Wuerfel J,

Krishnamoorthy

ES, Brown RJ,

Lemieux L,

Koepf M,

Tebartz van Elst

L, Trimble MR.



Religiosity is

associated with hippocampal but not amygdala volumes in patients with refractory epilepsy.

JOURNAL OF NEUROLOGY NEUROSURGERY PSYCHIATRY

2004;75:640-642.



Joan of Arc

ANATOMY: the oddest thing

Silas Weir Mitchell, one of America's greatest neurologists, learnt his trade – as many have done since – on the battlefield. Amongst the nerve injuries he described were several examples of the curious phenomenon of a unilateral injury leading to bilateral deficits. This paper from the Nerve Injury Unit at the Massachusetts General Hospital, explores this curious business further. In 6 rats, the left common peroneal and tibial nerves were ligated, leaving the sural intact. Then various sensory stimuli (von Frey hairs, pinprick, acetone) were applied to the rat paws. The result was long-lasting allodynia and hyperalgesia in ipsilateral sural-innervated territory only, because of unexplained mechanisms. Then the density of neurites was measured in punch skin biopsies from different nerve-innervated skin. One week later, on the lesioned side, there was 90% reduced neurite density in tibia-innervated skin, and increased neurite sprouting in the neighbouring sural area.

The remarkable finding was that there was a 50% reduction in the neurite density of the contralateral tibial-innervated skin, suggesting some anatomical connection between homologous nerves across the midline. Yet none is known to exist. In this study, there was no accompanying contralateral limb deficit, but as Weir Mitchell's cases illustrate, the same mechanism may lead to real problems in humans with unilateral

injury. All very curious. -AJC

Oaklander AL, Brown JM.

Unilateral nerve injury produces bilateral loss of distal innervation.

ANNALS OF NEUROLOGY

Weir Mitchell

2004;55:639-44.



EPILEPSY: ictal autopsychy

Hands up those who went into neurology because they were fascinated by the insights that neuroscience can give into the workings of the human mind. I number myself among these although sadly I can now rarely understand the titles of articles in cognitive neuroscience journals, let alone their content. One of the most tantalising symptoms is autopsychy – the pathological perception of one's body or face image from an internal or external (out-of-body experience) viewpoint. The authors describe three patients with ictal autopsychy, one of whom also had other unusual ictal sensations including palinopsia, and macroasomatognosia, (feeling body parts were enlarged). This patient underwent video-EEG-telemetry and three seizures were recorded, each beginning with a right parietocentral discharge. She had evidence of right parietal cortical dysplasia on MRI and the other two patients, with no ictal recordings, had right parieto-occipital oligodendroglioma and scarring following a right posterior haemorrhage. Right parietal, especially inferior parietal involvement seems to be crucial for the expression of this experience.

Maillard L, Vignal JP, Anxionnat R, Taillander L, Vespignani. -MM

Semiologic value of ictal autopsychy.

EPILEPSIA

2004; 45:391-394

HUNTINGTON'S DISEASE: Modification of huntingtin fragments increases toxicity

Huntington's disease is caused by an autosomal dominantly inherited expanded CAG repeat in the IT15 gene on chromosome 4. The gene normally encodes for a protein of unknown function called huntingtin (htt), but in disease the protein contains an expanded glutamine (Q) stretch, encoded by the expanded CAG repeat. Fragments of the polyQ htt are believed to confer more toxicity to the cell than full-length mutant htt.

Steffan and colleagues have used cell lines transfected with a toxic fragment of htt to show that small ubiquitin-like modifier (SUMO) and ubiquitin can modify the fragment. It is known that both SUMO and ubiquitin bind to lysine residues in the fragment. The authors manipulated the fragment and transfected fragments with or without a long proline stretch, and with or without lysine mutations (thereby removing the binding site for SUMO and ubiquitin). Western blotting revealed that fragments were only modified (and thus their size altered) when lysine residues were intact, indicating that these sites were required for SUMOylation and ubiquitination. Also, fragments were only ubiquitinated if they lacked the proline stretch. When SUMO was fused to the N terminus of the fragment, it accumulated and stabilised. Moreover, SUMOylation (and, independently, removal of the proline stretch) reduced aggregate formation. This may be because SUMO competes for the ubiquitin binding site (and ubiquitin is known to increase aggregation formation). Importantly, SUMO may be increasing the amount of pre-aggregation toxic oligomers.

SUMO, when co-expressed with the htt fragment in striatal cells, represses certain gene promoters. The first 17 amino acids of htt can target proteins to the cytosol. The SUMO modification is targeted to these amino acids. The authors postulate that this cytosolic signal is reduced by SUMO, thus increasing htt nuclear localisation, such that it can influence transcription.

Mutant htt fragments were next transfected into Drosophila. Flies expressing the mutant fragment display a loss of photoreceptors. Those with a mutation in SUMO have much less photoreceptor loss; and flies with mutant ubiquitin have slightly more photoreceptor loss. Thus, SUMO contributes to neurodegeneration and ubiquitin confers slight protection.

In summary, htt can be SUMOylated; this increases htt accumulation but reduces aggregation (possibly increasing toxic oligomers), possibly

masks a cytosolic signal, represses transcription, and increases neurodegeneration in a fly model. Inhibition of SUMOylation (e.g. inhibition of E3-ligase, which normally allows SUMO to attach to htt) may be potentially therapeutic in HD. SUMO has also been implicated in the pathogenesis of other neurodegenerative diseases including SCA-1, DRPLA and Alzheimer's disease. Thus the potential therapeutic avenues may stretch far. - WAR

Steffan J, Agrawal N, Pallps J, Rockabrand E, Trotman LC, Slepko N, Illes K, Lukacovich T, Zhu Y, Cattaneo E, Pandolfi P, Thompson L, Marsh J. *SUMO Modification of Huntingtin and Huntington's Disease Pathology*. SCIENCE 2004, 304, 100-104

HUNTINGTON'S DISEASE: HD mouse models are protected from excitotoxicity

Excitotoxicity, as a cause or consequence of neurodegeneration, has long been explored. Mice transgenic for the expanded HD gene have a complex response to excitotoxic injury, with different strains and different ages of mice having different levels of susceptibility to excitotoxins. Taking all these studies together, it seems that transgenic mice which express huntingtin fragments, as opposed to the full length protein, are less susceptible to excitotoxic injury. Furthermore, this effect increases as the mouse ages. Jarabek and colleagues explore this phenomenon, and possible mechanisms in the N171-82Q mouse. This is a transgenic model, with the N-terminal fragment of huntingtin inserted into the mouse genome under the prion promoter.

These mice become symptomatic between 9 and 14 weeks. Mice at 7, 15 and around 20 weeks were chosen as representing pre-symptomatic, symptomatic and hypokinetic advanced disease. When quinolinic acid was injected into the striatum, the 15 week transgenic mice showed less neuronal death than their wild type littermates. 7-week-old mice showed no difference, but, strangely, hypokinetic mice were not tested. Only in hypokinetic mice was the number of NMDA receptors reduced (NR1 subtype). So, there must be another mechanism accounting for neuroprotection in the 15 week old mice. Since phosphorylation of the NR1 subunit has been associated with increases in the NMDA receptor current, the authors conducted Western blots and quantified the protein level of phosphorylated NR1 in the two mouse groups at different ages. They demonstrated a progressive decrease in phosphorylation at serine 897 in the transgenic mice. Phosphorylation at this site is protein kinase A dependent. As dopaminergic D1 receptors increase PKA levels, they were next quantified. A progressive decrease in D1 receptors was found from 15 weeks in the transgenic mice. So, the authors postulate that reduced D1 leads to reduced PKA dependent NR1 phosphorylation thus less excitotoxicity. They do, however, point out that other pathways are likely to be involved in phosphorylation, as D1 receptors were not reduced in 7 week old mice although phosphorylated NR1 was. Another effect of reduced D1 receptors is an increase in the anti-apoptotic protein, P13 kinase, which was found only in the hypokinetic mice.

nNOS is activated by NMDA mediated calcium influxes, and contributes to neurodegeneration. There was a progressive decrease in membrane associated nNOS from 15 weeks in the transgenic mice. This was not due to translocation from the cytoplasm as nNOS was not reduced in this fraction. So, presumably nNOS is being upregulated (although no mRNA was measured).

PSD-95 is a scaffolding protein, supporting both the NMDA receptor and the nNOS receptor; it is found in progressively lower levels from 7 weeks in the transgenic mouse. Citron is another protein that is supported by PSD-95, and is involved in dendritic spine formation. It too, is reduced in the transgenic mouse; fewer spines mediate less glutamatergic input and thus less excitotoxicity (dendritic spines are known to be reduced in transgenic mice).

This study has confirmed that another transgenic model is resistant to excitotoxicity and proposed some mechanisms for this (although causality has not been proven). These include reduced D1 receptor so less phosphorylation of NMDA receptors; reduced scaffolding for NMDA and nNOS; increased anti-apoptotic proteins, and reduced dendritic spine forming proteins. These protective changes may represent a protective response to chronic low-level excitotoxicity in those mice that express huntingtin fragments. It has been suggested that mice, which express full-length huntingtin, represent a much earlier stage of the disease and therefore such protective mechanisms are not yet in place. It has long been thought that neuronal dysfunction

rather than cell death is the more important, certainly for fragment-expressing transgenic mice, and intriguingly such 'protective' changes may in fact be detrimental, causing or contributing to a disorder in functional neurotransmission, and so disease phenotype. -WAR

Jarabek B.R., Yasuda R.P., Wolfe B.B.

Regulation of proteins affecting NMDA receptor-induced excitotoxicity in a Huntington's mouse model.

BRAIN

2004: 127, 505-516

PARKINSON'S DISEASE: Placebo effects

The origins of placebo effects have always been controversial, and of late there has been interest in this effect in Parkinson's disease (PD) and the role of dopamine. However, a brief communication in Nature Neuroscience suggests that this placebo activated dopamine effect in PD is associated with decreased activity in the neurons of the subthalamic nucleus (STN). In this study, 11 patients undergoing surgery for PD were given placebo injections of subcutaneous saline (having previously been given apomorphine via this route) and the efficacy of this treatment correlated with a significant decrease in discharge in about 100 neurons recorded in the STN. Only 6 patients reported a placebo effect, whilst 5 did not, and this enabled the effect to be seen although does beg questions as to why some patients can produce this effect whilst others do not. Nevertheless this demonstration at the single unit level in the STN of the effects of placebo in PD, is of interest and once more highlights the importance of placebo in the treatment of this condition – which must be considered in any novel therapeutic trials in this condition. -RAB

Benedetti F, Calloca L, Torre E, Lanotte M, Melcarne A, Pesare M, Bergamasco B, Lopiano L.

Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus.

NATURE NEUROSCIENCE

2004:7:587-588.

The Migraine Trust

Monday 20th September – Thursday 23rd September 2004
The Conference Centre, Kensington Town Hall, London, UK.

15th Migraine Trust International Symposium
PROGRESS THROUGH RESEARCH

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