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INSIDE

Will Prevention of Aβ Prevent Neurofibrillary Tangle Generation in Alzheimer's Disease?

ABSTRACT AND COMMENTARY

Synopsis: *These findings provide compelling evidence in favor of the amyloid cascade hypothesis, which suggests that Aβ leads to the development of hyperphosphorylated tau aggregates within neurons.*

Source: Oddo, et al. Aβ Immunotherapy Leads to Clearance of Early, But Not Late, Hyperphosphorylated Tau Aggregates Via the Proteasome. *Neuron.* 2004:43,321-332.

AMYLOID BETA (Aβ) PLAQUES AND NEUROFIBRILLARY TANGLES are the histologic hallmarks of the neuropathology of Alzheimer's Disease (AD). The relationship of Aβ deposition to the development of neurofibrillary tangles however, has been unclear. Recently, a triple transgenic mouse model of AD, which has both Aβ deposits, as well as tau pathology, has been developed. These mice have mutations in the amyloid precursor protein, a mutated gene for presenilin 1, and a mutant form of the tau gene. The rodents develop plaques and tangles in the cortex, amygdala, and hippocampus, just as people with AD do. The plaques precede the tangles, consistent with the idea that Aβ build up is the initiating factor.

In the present study, Oddo and colleagues have generated direct evidence that Aβ contributes to the generation of neurofibrillary tangles, which are composed of hyperphosphorylated tau aggregates. Oddo et al injected their triple transgenic mice with anti-Aβ antibodies administered into the hippocampus. Oddo et al showed that there was a reduction in the extracellular Aβ deposits, as well as intracellular Aβ, which occurs rapidly, and that this also reduces early tau pathology. The Aβ deposits were cleared within 3 days, and the tau lesions required a slightly longer timepoint and were not reduced until 5 days postinjection. The Aβ, therefore, cleared first followed by the clearance of tau localized in the somatodendritic compartment of the neurons. At 30 days after the injections, the Aβ deposits had reemerged. In a second group of animals, the antibodies erased

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plaques in 6-month and 12-month old animals. They also cleared pretangle tau aggregates in the 6-month old animals, but had no effect in the 1-year old mice, in which the tau had become hyperphosphorylated. Oddo et al also used an alternative approach in which they administered an inhibitor of g-secretase, which leads to similar results. This once again will reduce the generation of Aβ. These findings, therefore, provide compelling evidence in favor of the amyloid cascade hypothesis, which suggests that Aβ leads to the development of hyperphosphorylated tau aggregates within neurons. The clearance of these aggregates was dependent on the proteasome, since it was blocked by proteasome inhibitors.

COMMENTARY

The present results show that clearance of Aβ early in the disease process prevents the development of hyperphosphorylated tau aggregates, which contributes to the generation of neurofibrillary tangles. This is the most direct evidence to date linking Aβ to the generation of neurofibrillary tangles. It is consistent with recent neuropathologic studies of patients treated with Aβ immunization. This clinical trial had been halted due to an excess of brain inflammation. Several of these patients who came to autopsy, however, showed a clearance of Aβ, yet persistent neurofibrillary tangles. The results indicate that Aβ targeted therapies may be useful for clearing both Aβ plaques and the neurofibrillary tangles of AD, provided that the intervention occurs early in the course of the illness. — **M. FLINT BEAL**

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Will CT or MR Angiography Become the Standard for Evaluation of Carotid Stenosis?

ABSTRACTS AND COMMENTARY

Synopsis: *CT angiography has high sensitivity and high negative predictive value for carotid disease.*

Sources: Josephson, et al. Evaluation of Carotid Stenosis Using CT Angiography in the Initial Evaluation of Stroke and TIA. *Neurology.* 2004;63:457-460.; Marie, et al. Measuring Carotid Stenosis on Contrast-Enhanced Magnetic Resonance Angiography. *Stroke.* 2004;35:2083-2088.

IMAGING OF THE CAROTID ARTERIES IS A RECOMMENDED part of the diagnostic evaluation of patients with ischemic stroke or TIA. It has been demonstrated in several studies that carotid endarterectomy will benefit patients, particularly those with high-grade stenosis. The accepted gold standard for evaluation of carotid artery stenosis is catheter angiography. This however, has substantial risk and is expensive. Alternatives include MR angiography and CT angiography. These have the advantage of being non-invasive. In the present study to evaluate the accuracy of CTA, Josephson and colleagues compared the degree of stenosis found using CTA with digital subtraction angiography (DSA), in consecutive patients during a 3-year period. This was done from April 2000 to November 2002 at the University of California, San Francisco. Eight-one vessels were studied. The stenosis on the CTA of the internal carotid artery was measured in the axial plane at the point of maximum stenosis, and referenced to the distal cervical internal carotid by 2 blinded readers. Similarly, 2 blinded readers measured stenosis with the digital subtraction angiography studies. Josephson et al found that using a 70% cutoff value for stenosis CTA and DSA were in agreement in 78 of 81 vessels (96%). CTA was 100% sensitive, and the negative predictive value of

a CTA demonstrating < 70% stenosis was 100%. Josephson et al conclude that CT angiography has high sensitivity and high negative predictive value for carotid disease.

A recent study has also compared DSA to contrast-enhanced magnetic resonance angiography (CEMRA). One hundred and sixty-seven symptomatic patients scheduled for DSA were prospectively recruited to undergo CEMRA. Josephson et al determined the severity of stenosis using 3 different methodologies, adopted by their North American Symptomatic Trial (NASCET) collaborators, the European Carotid Surgery Trial (ECST), and the common carotid (CC) methods. Measurements were each made in 284 vessels of the 142 included patients. Both the CEMRA and the DSA were analyzed in a blinded and randomized manner by 3 independent attending neuroradiologists. Josephson et al found that the NASCET method was the most predictive in measuring severe stenosis. The 3 different methods of examining stenosis however, did show reasonable intermodality correlation and agreement. With CEMRA however, Josephson et al determined a lower sensitivity for detection of severe stenosis with ECST, as compared to NASCET using DSA as the reference standard. The sensitivity for determining severe stenosis with CEMRA, with the NASCET analysis, was 93%. Overall, the diagnostic accuracy CEMRA for detection of severe stenosis as measured by NASCET was 93% sensitivity and 88% specificity. The positive predictive value was 72.5%, and negative predictive value 97.4%. The sensitivity in specificity therefore, appears to be less than that determined in the prior CTA study above.

COMMENTARY

CTA and CEMRA have major advantages over DSA in that they do not have the routine complication rate and high expense associated with DSA. The issue has been whether they have adequate sensitivity and negative predictive value. The present study suggests that this is the case with CTA. CEMRA was less sensitive and specific. Multi-detector CT scanners are continually improving in their sensitivity. General Electric has recently released a 64-slice scanner, which will have a considerable improvement in its overall ability to image the carotid artery. Even more sensitive CT scanners are under development. It is, therefore, highly likely that CTA will become the method of choice in evaluating carotid stenosis in the future. — **M. FLINT BEAL**

Homocysteine, Vitamins, and Cerebral Veins

ABSTRACT & COMMENTARY

Synopsis: *In this population, deficient nutritional status may contribute to its relatively high incidence of CVT.*

Sources: Cantu C, et al. Hyperhomocysteinemia, Low Folate and Vit B12 Concentrations, and Methylene Tetrahydrofolate Reductase Mutation in Cerebral Venous Thrombosis. *Stroke*. 2004;35:1790-1794.; Hankey GJ, et al. Vitamin Therapy to Prevent Stroke. The Jury is Still Out. *Stroke*. 2004;35: 1995-1998.

Hyperhomocysteinemia or elevation of plasma total homocysteine (Hyper-tHcy) is an independent risk factor for cardiovascular disease and stroke.[1] A recent meta-analysis of data from 12 prospective studies found that a 25% elevation in tHcy was associated with a 10% higher risk of cardiovascular disease, and a 20% greater risk of stroke.[2] Nevertheless, the recent Vitamins in Stroke Prevention (VISP) TRIAL[3] did not find a significant treatment effect of lowering tHcy by therapy with folic acid, vitamin B12, vitamin B6, and riboflavin on recurrent stroke, coronary event, or death. Hyper-tHcy also has been implicated as a risk factor for AD[4] and cerebral vein thrombosis (CVT)[5].

Although CVT is an uncommon diagnosis in American and European stroke registries, CVT comprised 8% of more than 2000 cerebrovascular disease cases in a Mexico City Hospital stroke registry.[6] Cantu and colleagues sought to explain this discrepancy by studying 45 Mexican patients with CVT and 90 control subjects. (*see table*) They measured plasma levels of tHcy, folate, and vitamin B12, and performed genotyping of the methylene tetrahydro-folate reductase (MTHFR) gene.

The most common predisposing factor for CVT was puerperium in 51%. Other predisposing factors included: anticardiolipin antibodies in 11 patients, protein S or protein C deficiency in 6, prothrombin gene mutation in 4, Factor V Leidin mutation in 2, use of oral contraceptives in 2, pregnancy in 1, and SLE in 1. Twenty-five patients (55%) were anemic.

Most patients presented clinically with headaches (96%), focal neurological deficits (69%), seizures (62%), impaired consciousness (44%), and intracranial hypertension (40%).

The most commonly affected venous sinuses were the superior sagittal (82%) and lateral sinuses (47%).

Table

CVT Patients Compared With Controls

Variable	Patients N=45	Controls N=90	*P*
Age in yrs.*	28 (14-55)	28 (16-53)	NS
Sex %			
Female	84	74	NS
Male	16	26	NS
Baseline tHcy µ mol/L*	9 (3-42)	7 (2-29)	0.01
Postload tHcy µ mol/L*	27 (10-77)	21 (4-50)	0.006
Folate nmol/L*	6 (3-12)	9 (2-16)	< 0.0001
B12 pmol/L*	330 (97-1515)	431 (157-2177)	0.07

* (median + range)

Venous infarction was present on neuroimaging studies in 76%, and was hemorrhagic in 49%.

Prognosis was good: most patients made a total recovery (60%), or had only minor neurological deficits (36%).

The adjusted Odds Ratio (OR) for CVT associated with high (> 90th percentile) fasting levels of tHcy was 4.6. The adjusted OR for low plasma folate values or low B12 levels (< 10th percentile) and the presence of CVT was 3.5 and 5.1, respectively. There was a higher frequency of MTHFR mutation in patients with CVT (22% vs 10%), but it was not statistically significant. Patients with MTHFR mutation and low folate levels presented the highest tHcy levels. Cantu et al concluded that in this population, deficient nutritional status may contribute to its relatively high incidence of CVT.

COMMENTARY

Cantu et al confirmed the previously noted[5] association between Hyper-tHcy and CVT. Their results add to a large body of epidemiological and laboratory evidence that indicates that increased plasma concentrations of tHcy are thrombogenic. Additionally, they found that a low folate and vitamin B12 state was independently associated with an increased risk of CVT in a nutritionally deficient population. This latter result is consonant with the Health Professional Follow UP Study[7] findings, namely that stroke risk was lower in healthy men whose folate intake was in the highest quintile, compared with those in the lowest quintile. In contrast, the VISP Trial[3] found no significant difference in the 2-year cumulative incidence of recurrent cerebral infarction between patients allocated to high-dose multivitamins and those taking low-dose multivitamins. As pointed out by Hankey and colleagues in an editorial, VISP enrolled patients primarily from North America, and did not have the statistical power to exclude a modest, but clinically important, therapeutic effect of folic acid-based multivitamin therapy. Physicians in the United States, Canada, and Europe are justified in concluding that insufficient evidence exists to recommend routine screening and treatment of Hyper-tHcy with folate and other vitamins to prevent thrombotic vascular disease. In selected high risk individuals or populations for whom the potential benefits are great, however, clinicians should recommend folic-acid-based, multivitamin therapy in high doses. — **JOHN J. CARONNA**

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Treatment for Painful Diabetic Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *Pregabalin appears to be a safe and effective alternative for the treatment of painful diabetic polyneuropathy.*

Source: Rosenstock J, et al. Pregabalin for the Treatment of Painful Diabetic Neuropathy: A Double-Blind, Placebo-Controlled Trial. *Pain.* 2004:110:628-638.

Consequent to being the most common form of neuropathy in the Western Hemisphere, diabetic polyneuropathy (DPN) treatment is pursued with determined relentlessness. Tricyclic antidepressants and anticonvulsants are the major classes of medication used, and greater numbers of drugs in each category are reported as beneficial. Pregabalin, a gamma-aminobutyric acid (GABA)

analog with analgesic, anxiolytic, and anticonvulsant activity, is among the most recent additions to the list.

One hundred forty-six DPN patients, with 1-5 years of pain, were enrolled in a randomized, double-blind placebo-controlled, multicenter 8 week trial to determine the efficacy of pregabalin (300 mg/d) in providing relief of painful neuropathy. Pain had to measure at least 40 on the Short-Form McGill Pain Questionnaire (SF-MPQ) visual analog scale, and at least 4 on the average daily pain score (scale 0-10, from no pain to worst possible pain). Patients were at least 18 years of age, male or female, not pregnant or lactating, and otherwise free of psychiatric disorders, renal insufficiency, or other confounding conditions. Analgesic medications, other than aspirin, tylenol, or serotonin reuptake inhibitors, were prohibited during the trial. Mean pain score at end point was the primary efficacy parameter, defined as the mean of the last 7 daily diary entries by the patient, scored on a 0-10 scale. Six secondary end point measures were employed, including the SF-MPQ, daily sleep interference score, patient global impression of change, physician global impression of change, Short Form (SF-36) Health Survey, and profile of mood states. Statistical analysis was achieved by using an analysis of covariance model.

Mean pain scores, mean sleep interference scores, SF-MPQ scores, SF-36 Bodily Pain subscale, and Total Mood Disturbance and Tension-Anxiety components of profile of mood states significantly improved with pregabalin compared to placebo. Dizziness, somnolence, infection (colds or upper respiratory infections, likely due to the winter season of the study period, rather than medication), and peripheral edema were more common in pregabalin treated patients, but were mild or moderate. Eleven percent (n = 8) of pregabalin patients discontinued treatment due to adverse effects, compared to 3% (n = 2) in the placebo group. Diabetic control was unchanged. Pregabalin appears to be a safe and effective alternative for the treatment of painful diabetic polyneuropathy.

COMMENTARY

Another recent addition to the therapeutic armamentarium for painful diabetic neuropathy (PDN) is the serotonin-norepinephrine reuptake inhibitor venlafaxine (Effexor). Two hundred forty-four PDN patients were randomized in a 6-week, double-blind placebo-controlled trial to study the safety and efficacy of venlafaxine extended-release (V-ER), in doses up to 225 mg/d. Pain had to measure greater than 40 on the Visual Analog Scale-Pain Intensity (VAS-PI) for entry into the trial, and patients had to have at least a 3 month history of moderate severity diabetic neuropathy pain. Exclusionary criteria included depression, drug or alcohol abuse, renal or hepatic disease, and seizure disorder. Primary efficacy measures included VAS-PI and VAS-PR (Visual Analog Scale-Pain Relief), and secondary efficacy measures encompassed Clinical Global Impressions-Severity of Illness, Clinical Global Impressions-Improvement, and Patient Global Rating of Pain Relief. Statistical analysis comprised parametric analysis of covariance, pairwise Fisher protected F-test, and t-test.

Higher dose V-ER (150-225 mg/d) provided significantly more pain relief than either the lower dose of V-ER or placebo, as measured by VAS-PI and VAS-PR. Lower dose V-ER was no more efficacious than placebo. Secondary outcome measures were similarly improved on the higher, but not lower dose V-ER or placebo. Somnolence (15%), nausea, dyspepsia, insomnia, sweating (10% each), and flatulence and myalgia (7% each) were the most common reported adverse events on the higher dose V-ER and occurred more than twice as frequently compared to placebo. In the higher dose V-ER group, 6% (n = 7) demonstrated noteworthy EKG changes, including 10 A-V block, ventricular extrasystoles, and atrial fibrillation. Of these, 3 withdrew from the study. Venlafaxine extended-release in doses of 150-225 mg/d is safe and effective for the relief of painful diabetic neuropathy, comparable to gabapentin or tricyclic antidepressants. — **MICHAEL RUBIN**

The Diagnostic Yield of a Standardized Approach to Idiopathic Sensory-Predominant Neuropathy.

ABSTRACT & COMMENTARY

Synopsis: *Patients with sensory-predominant neuropathy should be tested for glucose tolerance and vitamin B^{12} concentration.*

Source: Smith AG, et al. *Arch of Intern Med*. 2004;164: 1021-1025.

Smith and colleagues report that 61% of patients with idiopathic neuropathy, referred to a tertiary medical center for further evaluation, had an abnormal glucose tolerance test (GTT), with normal HgbA1c or fasting blood glucose in most cases.

Of interest, 30% of the patients had normal electrophysiologic studies, although several had skin biopsy showing reduced density of intraepidermal nerve fibers, confirming the diagnosis. Twenty-five percent of patients reported having at least 1 first-degree relative with symptoms of neuropathy, suggesting direct inheritance or familial predisposition, as may be seen in such conditions as celiac

disease or diabetes.

B^{12} deficiency was found in 2 of 87 patients tested. The diagnostic yield of other tests was low, so that they were not recommended. In 31% of patients, no known cause could be identified despite extensive testing.

COMMENTARY

The paper emphasizes the importance of testing for glucose intolerance in otherwise unexplained neuropathy. The yield for other tests may have been confounded by referral bias. Most of the patients were evaluated elsewhere first, so that only those with negative tests would have been referred for further evaluation. Glucose intolerance was obviously missed, probably because its link to neuropathy is still not widely appreciated. More meaningful recommendations for testing would have to come from studies of newly diagnosed patients, or non-selected neuropathy populations. The fact that approximately one third of patients remained undiagnosed, is a reflection of the abysmal state of the field, and the need for more research. — **NORMAN LATOV**

Dr. Norman Latov is the Director of the Peripheral Neuropathy Center and the Professor of Neurology and Neuroscience at Weill Medical College at Cornell University.

Understanding Immune Regulation in Multiple Sclerosis

ABSTRACT & COMMENTARY

Synopsis: *NK cells may regulate activation of autoimmune memory T cells in an antigen non-specific fashion to maintain the clinical remission in 'CD95(+) NK-high' multiple sclerosis patients.*

Sources: Takahashi K, et al. The Regulatory Role of Natural Killer Cells in Multiple Sclerosis. *Brain*. 2004;127:1917-1927.;Viglietta V, et al. Loss of Functional Suppression By CD4+CD25+ Regulatory T Cells in Patients With Multiple Sclerosis. *J Exp Med*. 2004;199:971-979.; Antel J, et al. Multiple Sclerosis and Immune Regulatory Cells. *Brain*. 2004;127:1915-1916.; Putheti P, et al. Circulating CD4+CD25+T Regulatory Cells Are Not Altered in Multiple Sclerosis and Unaffected By Disease-Modulating Drugs. *J Clin Immunol*. 2004;24:155-161.

TAKAHASHI AND COLLEAGUES FOUND THAT IN A majority of multiple sclerosis patients, in stable clinical remission, a subset of lymphocytes known as natural killer (NK) cells demonstrate a high frequency of CD95 (Fas) receptors on their surface, and express high levels of down regulatory Th2 cytokines, such as IL-5. By depleting these "CD95+NK-high" lymphocytes, they were able to induce a high number of myelin basic protein (MBP)-reactive CD4+ T cells secreting Th1 cytokines, such as interferon-gamma.

Putheti and colleagues had examined the potential role of an important regulatory T cell subset (CD4+CD25+), which appears to be important in the development of self-tolerance, and whose deletion leads to the development of multiple autoimmune disorders in animal models of disease including experimental allergic encephalomyelitis (EAE). They were unable to show any difference in absolute quantitative numbers of CD4+CD25+ in multiple sclerosis compared to normal controls, or show a change in numbers with disease-modifying drugs. However, in another study by Viglietta and colleagues, this subset of T cells, defined by the CD4+CD25+ phenotype, was shown to have impaired effector function in multiple sclerosis, leading to reduced T cell suppressor activity.

COMMENTARY

While the primary etiology of multiple sclerosis is unknown, the leading concept of a relapsing multifocal inflammatory brain pathology from myelin-reactive T cells remains a central dogma. As our understanding of basic cellular immunology has advanced, so has our appreciation of the complex network of regulatory lymphocytes controlling immune responses. The above studies define some of the advances in the field.

In the study by Takahashi et al, NK cells appear to have suppressor capabilities for MBP-reactive T cells, and maintain clinical remission in an antigen non-specific fashion. NK cells lack the standard receptor diversity of T cells, and although they can distinguish self from non-self, they can exert cytotoxic effects to cells lacking self-MHC expression. By contrast, in the report by Viglietta et al, they have identified a dysfunction of CD4+CD25+ suppressor T cells that appear to act by antigen-specific cell-cell MHC dependent mechanisms. It will be helpful to understand how current multiple sclerosis therapies interact with these immune regulatory cell subsets, and whether future strategies may utilize natural endogenous mechanisms of immune regulation by cultivating disease-T suppressor cells. — **BRIAN R. APATOFF, MD, PHD**

Lumbar Synovial Cysts

ABSTRACT & COMMENTARY

Synopsis: *Those patients undergoing decompression alone may postoperatively develop progression or the new appearance of olisthy, while those primarily fused rarely show further increase or a new onset of slip.*

Source: Epstein NE. Lumbar Synovial Cysts. A Review of Diagnosis, Surgical Management, and Outcome Assessment. *J Spinal Disord Tech.* 2004;17:321-325.

TYPICALLY LOCATED AT L4-5 OR L5-S1, LESS OFTEN AT L3-4 or L2-3, lumbar synovial cysts originate from facet joint arthrosis, and are present in 0.6% of computerized tomography (CT) or magnetic resonance imaging (MRI) studies of the lumbar spine. Cervical and thoracic synovial cysts occur much less frequently, approximately 50-fold. Men are affected twice as often as women. The average age of patients being 65 years, spanning a range from 28-94 years.

Radiculopathy is the typical mode of presentation in 55-97% of cases, with neurogenic claudication due to spinal stenosis affecting 25-44%. However, clinical signs are only seen in 18%, and include motor or sensory deficits (approximately 40% each), deep tendon reflex alteration (57%), or cauda equina syndrome (13%). Diagnosis is made by imaging where cysts may be seen to be periarticular, posterolateral, or epidural in location. Facet joint deterioration is seen in up to 90%, with spondylolisthesis in 32%. Cysts are hypo- or isointense on T1-weighted MRI scans, hyperintense centrally on T2 images, and demonstrate capsular enhancement around their periphery with gadolinium. MRI is more sensitive than CT study in diagnosing synovial cysts, 77% vs 56%, respectively. Myelography will reveal the cyst in only 42%.

Steroid facet-joint injection will benefit one third of patients, whereas the need for decompressive laminectomy surgery, with or without cyst resection, will be determined by the degree of spondylostenosis. Overall, surgical series report good/excellent response in 91%, and fair/poor outcome in 9%, with postoperative complications including cerebrospinal fluid fistula, discitis, epidural hematoma, phlebitis, and death. Combining primary fusion with laminectomy does not improve outcome.

COMMENTARY

Microsurgical resection of lumbar synovial cysts appears equally efficacious (*Neurosurgery.* 2004;54;107-111). Among 17 patients with magnetic resonance imaging (MRI) evidence of synovial cysts, 47% of whom demonstrated grade 1 spondylolisthesis, microsurgical resection resulted in good/excellent results in 94%, with a mean operating time of only 97 minutes, and an average blood loss of only 35 cc. One patient experienced a dural tear, but this did not involve the arachnoid membrane, and no treatment was necessary. Endoscopic or microscopic synovial cyst resection is safe and effective, and absent laminectomy, minimizes the need for fusion. — **MICHAEL RUBIN**

Hyperexcitability of the Dendritic Arbor as a Basis for Epileptogenesis

ABSTRACTS & COMMENTARY

Synopsis: *Such acquired channelopathy is likely to amplify neuronal activity and may contribute to the initiation and/or propagation of seizures in TLE.*

Sources: Bernard, C., et al. Acquired Dendritic Channelopathy in Temporal Lobe Epilepsy. *Science.* 2004;305:532-532.; Staley K. Epileptic Neurons Go Wireless [editorial]. *Science.* 2004;305 482-483.

INCREASES IN NEURONAL EXCITABILITY AND/OR decreases in inhibition are broadly thought to be the basis of epileptogensis. As Bernard and colleagues put it, there is "an augmented neuronal input-output relation" leading to hyperexcitability. Bernard et al have found mechanisms by which changes in the expression and post-translational modification of ion channels in the dendritic tree can affect neuronal excitability.

While dendrites serve as a main integrator for synaptic input, this function has previously been thought to be relatively passive. One effect that has not received much attention is back-propagating action potentials (b-APs). B-APs can produce an echo in the dendritic tree that could theoretically affect the magnitude, or other properties (such as burst firing), of the forward AP propagating down the axon. Normally, A-type potassium (K+) chan-

nels in the dendrite serve to modulate (ie decrease) the magnitude of b-APs.

Pilocarpine-treated rats have been used as a model of human temporal lobe epilepsy. Using whole-cell dendritic recording in hippocampal CA1 pyramidal cells from such rats, Bernard et al discovered that b-AP amplitudes were significantly larger in these rats vs sham-treated animals. They further found that the increase in b-AP amplitude was due to both 1) decreases in the transcriptional expression of A-type K+ channels and 2) phosphorylation of these channels. B-AP amplitude could be reduced in both pilocarpine and sham-treated rats by inhibiting phosphorylation.

COMMENTARY

Animal models of epileptogenesis, in particular the kindling paradigm, have emphasized potential changes in neuronal network properties. Under this model, rodents begin to have spontaneous seizures after repetitive electrical stimulation of the brain; a major pathological feature of this model is new axonal sprouting in the hippocampus. On the other hand, less experimental data is available providing insight into intrinsic neuronal factors modifying excitability, including: ion channel type, number, and distribution; biochemical modification of receptors; activation of second-messenger systems (eg via metabotropic receptors); and modulation of gene expression (eg, for ion channels and receptor proteins).

Bernard et al have made a significant contribution to understanding the molecular and cellular pathophysiology of epileptogenesis by describing how changes in the expression and function of A-type K+ channels could lead to augmented b-APs and burst firing in the pilocarpine model of temporal lobe epilepsy. Some currently marketed antiepileptic drugs (eg, topirimate) do act in part via modulation of K+ channels, but it is not known whether these agents work specifically through A-type K+ channels on dendrites. Alert looks forward to clinical applications that exploit the fact that, as Bernard et al point out, "Dendrites contain a very high density of ion channels that can be targeted by antiepileptic drugs." — **ANDY DEAN**

CME Questions

12. In the study of Cantu et al, all of the following were associated with an increased risk of CVT *except*:

a. hyper-tHcy.
b. low plasma folate level.
c. low plasma B^{12}.
d. MTHFR gene mutation and low folate levels.
e. MTHFR gene mutation and normal folate levels.

13. Relief of painful diabetic neuropathy may be obtained with

a. venlafaxine extended-release 25 mg/d.
b. venlafaxine extended-release 50 mg/d.
c. venlafaxine extended-release 75 mg/d.
d. venlafaxine extended-release 100 mg/d.
e. venlafaxine extended-release 150-225 mg/d.

14. Lumbar synovial cysts may be treated by

a. steroid injection.
b. endoscopic synovial cyst resection.
c. microscopic synovial cyst resection.
d. decompressive laminectomy surgery, with or without cyst resection.
e. All the above.

Answers: 12. (e); 13. (e); 14. (e)

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In Future Issues:

Phantom Sensations from Congenitally Absent Limbs

PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Linking COX-2 Inhibitors and Cardiovascular Event Risk

A new, and as of yet unpublished study, has raised increased concern about the relationship between rofecoxib (Vioxx), Merck's blockbuster COX-2 inhibitor, and cardiovascular events. The study, which was presented at a meeting in Bordeaux France, was financed by the FDA in collaboration with California's HMO giant Kaiser Permanente. The study was designed to determine if celecoxib, rofecoxib, ibuprofen, naproxen, or other NSAIDs increase the risk of acute myocardial infarction (AMI) or sudden cardiac death (SCD). Utilizing the 6-million member California database for Kaiser Permanente, all patients ages 18-84 who had taken a COX-2 inhibitor or nonselective NSAIDs between January 1999 and December 2001 were entered into the cohort. Controls were a risk-set match 4:1 on event date, birth year, gender, and health plan region. There were 8199 acute cardiac events within the study cohort (6675 AMI, 1524 SCD). The data revealed that rofecoxib use at > 25 mg per day increased the risk of acute cardiac events 3.15 fold (OR, 3.15 [1.14-8.75]). Rofecoxib at a dose < 25 mg resulted in an odds ratio of 1.29 (0.93-1.79), which was not statistically significant. When comparing low-dose rofecoxib to celecoxib (Celebrex), the risk of AMI and SCD was higher with rofecoxib (P= 0.04). Other NSAIDs, including naproxen, indomethacin, and possibly diclofenac, also increased the risk of AMI and SCD. These data will be presented in this country in October at the American College of Rheumatology. Concern about the relationship between rofecoxib and cardiac events was first raised with the publication of the VIGOR trial (*N Engl J Med.* 2000;343:1520-1528) which showed a relative risk of cardiac events associated with rofecoxib of 2.38 (95% CI, 1.39-4.00; P= .002). Dr. Eric Topol and colleagues from the Cleveland clinic subsequently reevaluated these data along with data from other studies and raised the concern of prothrombotic potential of COX-2 inhibitors, especially rofecoxib (*JAMA.* 2001;286:954-959). Their concern centered on the tendency for COX-2 inhibitors to block production of prostacyclin—thus blocking antiaggregatory and vasodilatory effects, while having no effect on thromboxane, which is responsible for platelet aggregation. Blockage of thomboxane is a COX-1 effect and accounts for the majority of the cardioprotective effects of aspirin and other NSAIDs. Rofecoxib, the most COX-2 specific of the drugs tested, may unbalance thromboxane and prostacycline accounting for the cardiovascular risk.

Some have considered a strategy of adding aspirin to a COX-2 inhibitor, but a new study suggests that aspirin negates the GI benefits of the COX-2 inhibitor, the primary benefit of COX-2 inhibitors over nonselective NSAIDs.

Researchers from USC performed a double-blind trial of rofecoxib, rofecoxib plus low-dose

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aspirin, ibuprofen, or placebo in patients without ulcers or erosive esophagitis. Endoscopies were performed at baseline, 6 weeks, and 12 weeks. At 12 weeks, the cumulative index of ulcers was placebo 5.8%, aspirin 7.3%, rofecoxib plus aspirin 16.1%, and ibuprofen 17.1% ($P < 0.001$ for rofecoxib plus aspirin and for ibuprofen vs each of placebo and aspirin). Over the same time, rofecoxib plus aspirin and ibuprofen both significantly increased the number of erosions (both $P < 0.001$ vs aspirin and placebo). The authors conclude that low-dose aspirin does not significantly increase ulcer recurrence, but that the addition of a COX-2 inhibitor with aspirin increases the rate of ulceration to a rate that is similar to a nonselective NSAIDs (*Gastroenterology.* 2004;127:395-402).

Viagra: Maximum Capacity at High-Altitudes?

High-altitude hikers may soon be requesting sildenafil (Viagra) prescriptions based on the results of a new study. The drug, which is a phosphodiesterase-5 inhibitor, is known to cause pulmonary vasodilation. German researchers postulated that such an effect may increase exercise capacity during induced hypoxemia at low altitudes and at Mount Everest base camp. Fourteen healthy mountaineers and trekkers were assessed with measurements of systolic pulmonary artery pressure, cardiac output, and peripheral arterial oxygen saturation at rest and during assessment of maximal exercise capacity on cycle ergometry while breathing a hypoxic gas mixture at low altitude, and retested at high-altitude at the Mount Everest base camp. Sildenafil 50 mg significantly increased arterial oxygen saturation during exercise ($P = 0.005$), reduced systolic pulmonary artery pressure at rest ($P < 0.001$), and during exercise ($P = 0.031$). Sildenafil also increased maximum workload and maximum cardiac output compared with placebo. At high-altitude, the drug had no effect on arterial oxygen saturation at rest nor during exercise compared with placebo, however, the sildenafil reduced systolic pulmonary artery pressure at rest ($P = 0.003$), during exercise ($P = 0.021$), increased maximum workload ($P = 0.002$), and cardiac output ($P= 0.015$). Two patients noted worsening headache at high-altitude with the drug. The authors conclude that sildenafil is the first drug to increase exercise capacity during severe hypoxia both at sea level and at high-altitude (*Ann Intern Med.* 2004;141:169-177). An accompanying editorial suggests that sildenafil is not a substitute for acclimatization to high-altitude and suggests that the findings of the study are compelling and that further research into a phosphodiesterase inhibitors in the treatment of pulmonary vascular disease is needed (*Ann Intern Med.* 2004;141:233-235).

FDA Actions

Eli Lilly has received FDA approval to market duloxetine (Cymbalta) for the treatment of major depression. The drug is a serotonin and norepinephrine reuptake inhibitor (SNRI), similar to venlafaxine (Effexor-Wyeth). The drug is also being studied for the treatment of stress urinary incontinence and diabetic neuropathic pain. Lilly, and the drug approval process for duloxetine, came under scrutiny earlier this year when a 19-year-old female volunteer committed suicide after discontinuing the drug during clinical trials. The patient had no history of depression prior to the study.

Shire Pharmaceuticals has received expanded indication for its mixed amphetamine product Adderall XR for the treatment of adults with attention deficit hyperactivity disorder (ADHD). The drug is a one-a-day preparation that has been widely used in children since 2001.

The FDA and Genentech have issued a warning to physicians regarding the risk of serious arterial thromboembolic events associated with bevacizumab (Avastin). The drug is an angiogenesis inhibitor, a novel antineoplastic used to treat metastatic colon cancer and other solid tumors. Reports of cerebral infarctions, myocardial infarctions, transient ischemic attacks, and angina have all been associated with use of the drug.

The FDA has approved an orally disintegrating form of carbidopa/levodopa for the treatment of Parkinson's disease. The preparation dissolves rapidly in the mouth without the need for water, allowing for dosing even when patients are rigid or suffering from "off periods," when producing can be problematic. It will be marketed under the trade name Parcopa and will be available in 10/100 tabs, 25/100 tabs, and 25/250 tabs, similar to brand name Sinemet levodopa/carbadopa.