GABA (B) and temporal lobe epilepsy

Gambardella et al. report a genetic association between nonlesional temporal lobe epilepsy (TLE) and a missense (G1465A) polymorphism in the GABA (B) receptor gene. Moreover, patients carrying the GABA (B) G1465A polymorphism are also reported to have an increased odds of developing drug refractory TLE.

see page 560

GABA receptors and refractory temporal lobe epilepsy

Commentary from Michael R. Johnson

New antiepileptic drug development will be made possible by better understanding of molecular mechanisms underlying epilepsy. Genetic influences on γ -aminobutyric acid (GABA) are likely to be of importance. The report from Gambardella et al. in this issue of *Neurology* provides novel evidence concerning a GABA receptor and temporal lobe epilepsy. The neuronal response to GABA has two phases. Inotropic (GABA_A) receptors produce a rapid, chloride-mediated postsynaptic membrane hyperpolarization. Metabotropic (GABA_B) receptors generate a long lasting, G-protein-mediated, inhibitory hyperpolarization of postsynaptic membranes as well as inhibition of neurotransmitter release from presynaptic terminals. The GABA_A receptor is a heteromeric complex of subunits including $\alpha 1$ -6, $\beta 1$ -3, $\gamma 1$ -3, δ , ϵ , and π .¹ GABA_B receptors comprise a heterodimer of $\text{GABA}_B\text{R1}$ and $\text{GABA}_B\text{R2}$ subunits, with R1 providing the binding domain and R2 re-

sponsible for second messenger processing.² A central role for GABA_A receptors in epilepsy, long suspected from pharmacologic studies, was firmly established with the identification of mutations in $\gamma 2$ (GABRG2) and $\alpha 1$ (GABRA1) subunits in familial generalized epilepsy.³⁻⁵ Despite a series of pharmacologic studies in animal models suggesting that GABA_B receptors play a critical role in the genesis of spike wave discharges, clear evidence for a role of the GABA_B receptor in human epilepsy has been lacking. The Gambardella et al. report of an association between a polymorphism in the $\text{GABA}_B\text{R1}$ subunit gene (GABBR1) and temporal lobe epilepsy (TLE) is therefore important, not least because the association is, surprisingly, with partial and not generalized epilepsy. In a study population of 141 mostly MRI negative TLE patients (with some patients having MRI evidence for hippocampal sclerosis), a $\text{GABA}_B\text{R1}$ polymorphism was associated with an

impressive risk for TLE. A second intriguing observation was that the polymorphism is associated with a significantly higher risk of drug-refractory epilepsy. These important findings suggest GABA_B -mediated genetic mechanisms contribute increased risk for epilepsy and offer a new insight into genetic mechanisms of poor epilepsy outcome.

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Major fetal malformations in pregnant women with epilepsy

In a prospective follow-up study of 970 pregnancies in women with epilepsy, Kaaja et al. noted major malformations in 3.8% exposed to maternal AEDs and only 0.8% in those not exposed. Carbamazepine, valproate, and oxcarbazepine well as low serum folate concentrations were all associated with major malformation.

see page 575

continued on page 532

Variability of phenytoin in elderly nursing home residents

Birnbaum et al. studied total phenytoin levels obtained while subjects remained on the same phenytoin dose. They followed 56 elderly residents residing in nursing homes across the US and found levels varied as much as two to threefold. This variability suggests that phenytoin levels alone should not be used to guide treatment.

see page 555

The accompanying editorial by Lesser and Sundaram points out that while drug levels are of particular value in detecting noncompliance, there is a large number of defined variables that produce changes in drug levels. However, the two- to threefold variation in the Birnbaum study are unexplained (noncompliance being unlikely in their population). Whatever the reason, the results imply that drug levels are not useful to guide dosage adjustments except in well-defined situations such as pregnancy, where predictable changes are anticipated.

see page 534

Sporadic hemiplegic migraine

Thomsen et al. identified 105 persons with migraine with aura that included motor weakness without a family history. These persons had symptoms identical to familial hemiplegic migraine and different from migraine with typical aura and are classified as a separate entity termed sporadic hemiplegic migraine.

see page 595

The accompanying editorial by Peter Goadsby notes that this large series of patients in whom major motor symptoms proved to be related to migraine provides important data for the clinician confronted with a patient with acute symptoms. Rapid onset and duration <60 minutes point to migraine, but even longer duration symptoms can occur.

see page 536

Dietary factors in AD and PD

In a "Medical Hypothesis" review of studies of human populations and animal models, Mark Mattson notes that high-calorie diets and diets that increase homocysteine levels increase the risk of AD and PD. Low-calorie diets may reduce disease risk by stimulating the production of neurotrophic factors and stress proteins, while dietary folate lowers homocysteine levels and decreases DNA damage in neurons.

see page 690

Randomized controlled trial of pergolide for tics

Gilbert et al. randomized 56 children and adolescents with Tourette's syndrome or chronic motor tics to pergolide or placebo. Pergolide reduced tics and ADHD symptoms without causing weight gain or sedation. These results corroborate those obtained in smaller studies of dopaminergic medications for tic suppression.

see page 606

Pneumonia complicating acute stroke

Katzan et al. found that after adjustment for severity of illness and other patient factors, pneumonia conferred a threefold increase risk of 30-day mortality in patients hospitalized for acute stroke.

see page 620

continued on page 533

Intranasal sumatriptan is effective in cluster headache

In a placebo-controlled, multicenter study, van Vliet et al. demonstrated that sumatriptan 20 mg nasal spray is effective within 30 minutes in the treatment of acute cluster headache. The study adds a further evidence-based option to the treatment of this disabling headache.

see page 630

Neutralizing antibodies (NABs) effect on IFN β bioavailability

Bertolotto et al. studied the effect of NABs on IFN β bioavailability by MxA mRNA quantification. MxA mRNA increases 11-fold from basal level in NAB-negative patients, whereas MxA mRNA was not increased in NAB-positive patients. NABs abolish IFN β bioavailability.

see page 634

Weekly MRI of new brain lesions in relapsing-remitting MS

Cotton et al. performed weekly MRI studies of 113 new enhancing MS lesions. Over 50% enhanced for only 2 weeks or less. Early lesion growth may predict final lesion size. Within-patient heterogeneity of lesion evolution suggests that individual lesions develop independently from each other.

see page 640

Clinical findings of myotonic dystrophy type 2

Myotonic dystrophy type 2 (DM2) results from a CCTG repeat expansion in intron 1 of the zinc finger protein 9 gene. Here, the authors who identified the gene lesion, Day et al., describe the clinical features of 133 families confirmed to have DM2 by an improved molecular diagnostic method. Clinical features mirror adult-onset DM1, with myotonia, muscular dystrophy, cataracts, and endocrine and cardiac involvement.

see page 657

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