SEIZURE DISORDERS

MECHANISM OF SEIZURE TERMINATION

Physiological mechanisms contributing to seizure termination and organized according to membranes, synapses, networks, and circuits are reviewed by researchers from Albert Einstein College of Medicine, and Montefiore Medical Center, Bronx, New York. A better understanding of these mechanisms may lead to novel anticonvulsant therapies. Agents that enhance termination of paroxysmal depolarizing shifts might decrease excitatory amplification in epileptic neurons. Modification of extracellular environment or intracellular ion gradients across membranes may raise seizure threshold and speed seizure termination (Ochoa, 2006). Disrupting gap junction connections between neurons and interneurons may reduce neuronal synchrony. Drugs targeting the GABA receptor to enhance local inhibition without increasing sedation or tachyphylaxis would provide an improvement over benzodiazepines that are of value mainly in acute seizure control. Drugs that alter chloride transporters and gradients might control age-dependent seizure syndromes. (Dzhala et al, 2005). Drugs targeting adenosine kinase, and endocannibanoid and NPY receptors, and altering the hormonal milieu may enhance seizure control and termination. Vagal nerve stimulation (Blount JP et al. 2006), initiated by a patient, will halt seizure activity and may be extended to seizure modifying circuits such as the anterior thalamus, substantia nigra pars reticulata and subthalamic nucleus. Implantable drug infusions systems to regulate seizure onset are a transmeningeal form of therapy under consideration. (Ludvig et al, 2006). (Lado FA, Moshe SL. How do seizures stop? **Epilepsia** Oct 2008;49(10):1651-1664). (Respond: Dr Fred A Lado, EEG Laboratory, Montefiore Medical Center, 111 E 210 St, Bronx, NY 10461. E-mail: flado@montefiore.org).

COMMENT. Factors influencing seizure termination are less well understood than those responsible for seizure initiation, propagation and recurrence. Several factors may be responsible for seizure initiation and termination, and these mechanisms may be modified by age, sex, fever and infection, structural brain injury, and genetics. Mechanisms that operate in the normal brain may be different from those affecting the diseased or epileptic brain. Children with a history of status epilepticus are likely to have status epilepticus with a seizure recurrence. Neuron excitability may be influenced by the extracellular environment, gap junctions, neuromodulators, and circuits. Sites of action of seizure terminating mechanisms include substantia nigra pars reticulata, subthalamic nucleus, superior colliculus, thalamus, and reticular activating system.

CDKL5 MUTATIONS IN BOYS WITH ENCEPHALOPATHY AND EARLY-ONSET INTRACTABLE EPILEPSY

Clinical and EEG data of 3 Italian boys (ages 3, 9, and 13 years) with severe early-onset encephalopathy, mental retardation, facial dysmorphisms, and intractable epilepsy were found to carry missense mutations in the *CDKL5* gene, in a report from Troina, Italy. Seizures were myoclonic, tonic, and partial or spasms, and the EEG abnormalities were multifocal epileptiform discharges while awake and pseudoperiodic bisynchronous

dysrhythmia during sleep. Seizures were resistant to ACTH and antiepileptic drugs. Screening for these mutations is recommended in children with intractable seizures and global developmental delay. (Elia M, Falco M, Ferri R, et al. *CDKL5* mutations in boys with severe encephalopathy and early-onset intractable seizures. **Neurology** Sept 2008;71:997-999). (Respond: Dr Maurizio, Oasi Institute for Research on Mental Retardation and Brain Aging, Via Conte Ruggero 73, 94018 Troina (EN), Italy).

COMMENT. *CDKL5* mutations are reported in girls with X-linked infantile spasms (Weaving LS et al, 2004) and in girls with atypical Rett syndrome (Evans JC et al, 2005). The association of *CDKL5* mutations and seizures is rare in boys (Van Esch H et al, 2007). The recognition of this genetic diagnosis would be helpful in counseling concerning outcome.

The role of genetics in diagnosis and treatment of epilepsy was discussed at the First North American Regional Epilepsy Congress; 60th Annual Meeting of the American Epilepsy Society, Dec 1-5, 2006, San Diego, CA (Bebin M. In: Arnedo V et al. **Rev Neurol Dis** 2007;4(4):217-221). The nocturnal frontal lobe epilepsy gene, autosomal dominant with 75% penetrance, was one of the first identified. The gene mapped to chromosome 20q and the nicotinic receptor opened the door to the channelopathies. Voltage-gated ion channel subunits are involved in GEFS+, Dravet's syndrome, and infantile seizures; potassium channels in neonatal seizures; and potassium and calcium channels in absence epilepsy. *SCN1A* gene controls the sodium channel subunit in Dravet's syndrome, febrile seizures, febrile seizures plus, and myoclonic-astatic epilepsy. SCN1A mutations occur in 79% of severe myoclonic epilepsies of infancy (SMEI) and 69% of borderline cases (Scheffer IE et al. **Brain Dev** 2001;23:732-735; *idem*. In: Arnedo V et al. **Rev Neurol Dis** 2007;4:217-221).

ATTENTION DEFICITS AND ROLANDIC EPILEPSY

Impairment in attention in rolandic epilepsy (RE) was evaluated in 14 studies published between 1990 and 2006, in a study at Columbia University Medical Center and Queens College of the City University of New York, NY. Sample sizes ranged from 9 to 44 subjects. A cross-sectional design was used in 7 studies (6 having active EEG abnormalities and 1 with EEG remission). Longitudinal studies were employed in 7 publications (EEGs were all abnormal and patients were followed until normalized). Twelve studies measured the alerting network, according to the Posner model of attention, 11 studies the orienting network, and 8 the executive network. Impairments in all attention networks were demonstrated by controlled studies but not by uncontrolled studies. At follow-up, when the EEG had normalized, attention impairments had almost completely resolved. The neuroanatomically based model of attention such as Posner's that targets alerting, orienting, and executive functions, is a reliable method of assessment of attention in children with epilepsy. (Kavros PM, Clarke T, Strug LJ, Halperin JM, Dorta NJ, Pal DK. Attention impairment in rolandic epilepsy: systematic review. **Epilepsia** Sept 2008;49(9):1570-1580). (Respond: Deb K Pal MD, PhD, Mailman School of Public Health, 722 West 68th Street, Sixth Floor, New York, NY 10032. E-mail: dkp28@columbia.edu).