Arrest of neuronal migration between 9 and 13 weeks causes reduction in the number of gyri and the phenotype of a region of smooth surface. Cortex is thickened with enlarged ventricles and hypoplasia of the corpus callosum. Cortical layers are poorly organized, displaying 4 cortical layers and the presence of diffuse neuronal heterotopia [109]. The Miller-Dieker syndrome and isolated Lissencephaly sequence has a mutation in the LIS1 gene encoding a non-catalytic subunit of platelet activating factor (PAF) acetylhydrolase, a heterotrimeric enzyme that inactivates PAF [110, 111]. How this altered enzyme causes altered neuronal migration is unknown.

X-linked Lissencephaly and double cortex. X-linked Lissencephaly and double cortex, classical Lissencephaly, occurs in hemizygous males with milder effects in heterozygotic females where some neurons migrate abnormally to subcortical white matter causing a subcortical band heterotopia [112]. The mutated gene codes for DCX or doublecortin [113, 114]. Analysis of mutations of DCX have shown missense mutations, frameshift mutations and splice site mutation [110, 114, 115]. DCX is expressed in frontal lobes in adults but widely expressed in fetal brain [110, 114, 115]. Function of DCX is unknown at this time.

Periventricular heterotopia are formed of neurons in regions that fail to migrate and are found as nodules along the walls of ventricles. This X-linked dominant disorder is lethal to males while females have seizures and other systemic signs but with normal IQ [116, 117]. Locus is mapped to Xq28 with a regional gene FLN1 that encodes an actin-binding protein filamin1 [118]. Patients have shown point mutation and a frameshift mutation with resultant truncation of the FLN1 protein.

Progressive Myoclonus Epilepsies

This heterogeneous group of debilitating, sometimes fatal epileptic encephalopathies cause segmental arrhythmic myoclonus, massive myoclonus, GTCS or clonic seizures with or without absence, dementia, and progressive neurological deficits especially of cerebellar origin.

Unverricht-Lundborg (Baltic-Mediterranean PME). This disorder has been described worldwide, not just in the Baltic regions [119]. Clinical patterns tend to be uniform, with debilitating, slowly progressive, stimulus sensitive myoclonus. Onset is between 6–18 years. Generalized clonic and GTC seizures may appear on awakening. Valproic acid delays progression. Mild ataxia is present, and mild intellectual deterioration and dementia occur late in disease with patients becoming incapacitated in about 5 years [120]. Inheritance is autosomal-recessive with variable progression; 21q22.3 linkage in 12 Finnish families with 68 members and 26 affected. LOD was 10.08 [121].

Mapping located several highly polymorphic microsatellite markers with a critical region of ~175 Kb. Several cDNA fragments were isolated that encode cystatin B, a cysteine protease inhibitor. Southern blots revealed an unstable region of DNA in the noncoding region upstream of the transcription start site of the cystatin B. This region contains an expansion of a polymorphic dodecamer (5"cccgccccgcg-3'). This expansion of a dodecamer is the first example of instability of a repeat unit other than trinucleotides and accounts for about 92% of patients. Range of the expansion varies from 30 copies up to 75 copies [96, 122–125].

Lafora's Disease. This fatal progressive myoclonic syndrome has a pattern of autosomal recessive inheritance, with seizures beginning in early adolescence but they may start as late as 18 years. Patients commonly die within 5–10 years after first symptoms. Symptoms begin with GTCS, absence or drop attacks with subtle irregular or asymmetric myoclonus. With progression the myoclonus becomes almost constant. Photic induced high-voltage, spike waves and polyspikes interrupt the slow background of the EEG. Dementia, dyspraxis, and visual loss lead to vegetative state. Cytoplasmic inclusions in brain, muscle, liver, and skin are periodic acid-Schiff positive and contain polyglycosans. In 38 families with 16 containing consanguinity, localization was found to 6q24 [126] where the gene EPM2A codes for a protein tyrosine phosphatase called Laforin [127–129].

Mitochondrial Disorders. Mitochondrial disorders commonly present with seizures [130]. Mitochondrial encephalopathy is associated with segmental or generalized myoclonus. MERRF syndrome (Myoclonic epilepsy and ragged red fiber syndrome) has a clinical constellation of myopathy, ataxia, deafness and dementia with progressive myoclonic epilepsy [126]. Most common pathogenic mutation is A to G transition at position 8344 in tRNA-lys [131]. This heteroplasmic mutation has varied proportion of mutated DNA in families. This mutation results in premature termination of translation of mitrochondrial mRNAs with resultant reduced polypeptide synthesis [132–134].

Molecular Neuropharmacology

Knowledge of fundamentals of the molecular biology of epilepsy should lead to another level of drug development. For example, valproate reduces excitatory synaptic transmission responsible for synchronization of cell firing that leads to epileptic bursting [135–137]. Valproate interferes with excitatory synaptic processes and suppresses depolarization induced by NMDA. However, VPA has a molecular effect as well with resulting up-regulation of glutamate transporter protein production resulting in the inactivation of the effect of glutamate by termination of action following enhanced transport from the synaptic cleft [138]. In addition, Ueda *et al.* [138] demonstrated that valproate down-regulates the production of GABA transporter proteins, an effect that should result in prolongation of the inhibitory effect on intrasynaptic GABA. Future work should raise questions about the details of ion channelopathy that may be specific to epilepsy and how drugs can be designed to affect highly specified seizure disorders.

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