Cord-Michael Becker
Institut für Biochemie (Emil-Fischer-Zentrum), Universität Erlangen-Nürnberg,
Fahrstraße 17, D-91054 Erlangen

Ion channel alterations in epilepsy and hyperekplexia

The physiological function of the CNS relies on a balance of excitatory and inhibitory impulses mediated by voltage and ligand gated ion channels. Various forms of epilepsy correlate with mutations of genes coding for voltage dependent sodium (e.g., benign familial neonatal seizures), potassium (e.g., benign familial neonatal convulsions), and calcium (e.g., juvenile myoclonic epilepsy) channels. Mice carrying mutations in the orthologous ion channel genes serve as models of corresponding human disorders. From these studies, it has become apparent that ion conducting as well as accessory subunits of these channel types may be affected. The mouse mutant *entla* develops an absence epilepsy characterized by EEG activities at 2 and 4 Hz, in addition to ataxia and paroxysmal dyskinesia. The underlying mutation on mouse Chr 9 was identified as an allele of the *Cacna2d2* gene. This gene encodes the accessory $\alpha 2\delta$ 2 subunit of P/Q type calcium channels, a target of the antiepileptic drug gabapentin. The *entla* allele harbors an exon duplication that interferes with post-translational processing, i.e. the formation of a disulfide linkage. This results in a dramatic reduction of both, calcium currents and [^{3}H]gabapentin binding. The *entla* mouse thus represents a model of genetically alteratered protein processing producing a complex absence epilepsy syndrome.

At the postsynaptic face, the neurotransmitter signal is converted to excitatory or inhibitory currents by binding to ligand gated ion channels. Mutations of the nicotinic receptor $\alpha 4$ subunit gene *(CHNRA4)* cause autosomal dominant nocturnal frontal lobe epilepsy. In contrast, mutations of the glycine subunit genes α *(GLRA1)* and β *(GLRB)* result in *hyperekplexia* (startle disease, stiff baby syndrome), a non-epileptic neurological condition. Upon recombinant expression, mutant acetylcholine and glycine receptor subunits frequently display altered transmitter binding and ion conductance. Taken together, hereditary forms of epilepsy may be attributed to molecular alterations of both, protein maturation and single channel physiology.