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Epileptic Channelopathies and Dysfunctional Excitability - From Gene Mutations to Novel Treatments

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1. Introduction

Epilepsy is not a single disorder, but a collection of disorders that all are characterized by episodic abnormal synchronous electrical activity in the brain. This abnormal activity represents a disturbance of the balance between excitatory and inhibitory neurotransmission. The majority (50%) of epilepsies are cryptogenic, meaning there is a presumptive but no identifiable underlying etiology. Approximately 20% of epilepsies have an identifiable cause (i.e. they are symptomatic) and are usually a result of trauma to the head, stroke, brain tumours, or infections. The remaining 30% are idiopathic, meaning there is no apparent underlying cause (Berg et al., 1999). However, as they are usually associated with a family history of similar seizures, they are mostly considered to be genetic. Mutations in over 70 genes have been found to cause epilepsy (Noebels, 2003). Given the dependence of seizures on synaptic transmission and neuronal excitability, it is not surprising that many of these mutations affect the function of ion channels. Since the identification of the first epilepsy-causing ion channel mutation, scientists have come a long way in the understanding of the pathogenesis of the disease. This chapter deals with some of the main questions that have been asked, and looks at some of the proposed answers to the questions. How do mutations in certain ion channels lead to hyperexcitability and seizures? Why do mutations in one ion channel cause a particular epilepsy syndrome? Why are the seizures often initiated during specific physiological events? And why do most of the childhood epilepsies remit with age? Furthermore, ion channels as targets for antiepileptic drugs will be discussed.

2. Idiopathic epilepsies

In most cases genetic epilepsy syndromes have a complex rather than a simple inheritance pattern. Although the epilepsies described here are thought to be monogenic, not even those considered inherited in a dominant fashion have a penetrance of 100%. Mutations within the same gene can result in clinically distinct phenotypes. Variable expressivity is also a common feature of inherited epilepsy demonstrated by family members with the same mutation that exhibit differences in the clinical severity of the disease (Hayman et al., 1997).

On the other hand, some of the disorders display locus heterogeneity where mutations in distinct genes result in the same syndrome. This indicates that other factors beside the primary mutation influence the clinical manifestation of the epilepsy, e.g. environmental factors, developmental events, or differences in inheritance of genetic susceptibility alleles. The latter is supported by mouse models where differences between the genetic backgrounds of two mouse strains influence the severity of a disease caused by the same sodium channel mutation (Bergren et al., 2005).

Unfortunately, discovery of the responsible gene for an epilepsy syndrome have not led to a prompt understanding of the pathogenesis of the disease. Many of the mutated channels have been characterized in expression systems, but only in some cases have this led to a better understanding of the disease. In other cases this have led to more confusion, as some mutations in a particular channel are found to enhance channel function while others appear to cause a loss of function, even though the clinical manifestation are similar. There are also large discrepancies between results depending on the expression system used to characterize the channels. The mutated channel can e.g. show enhanced function when expressed in *Xenopus laevis* oocytes, while the opposite is shown when expressed in mammalian cells (Meadows et al., 2002). To make it even more difficult, it has been demonstrated that depending on the type of neuron in which a mutated channel is expressed, it can have strikingly different effects on the excitability of the cell (Waxman, 2007). While a mutation can make one type of neuron hyperexcitable, the same mutation can make another neuron hypoexcitable. So changes in neuronal fuction are not necessarily predictable solely from the change in the behaviour of the mutated channel itself, but have to be considered in the cell background in which the mutated channel is expressed. Further, depending on whether a mutated channel mainly is expressed in excitatory or inhibitory neurons, it can have completely opposite effects on the excitability status of the neuronal network (Yu et al., 2006).

The ion channel mutations are bound to cause relative subtle changes in neuronal function. Mutations that cause dramatic changes would likely result in a more severe phenotypes or lethality. The mutations apparently allow normal behaviour under most circumstances, but disturb the equilibrium between excitatory and inhibitory neuronal networks, so that small external perturbations such as fever are sufficient to break the homeostasis and induce seizures.

3. Mutations in sodium channel subunit genes

3.1 Voltage-gated sodium channels

Voltage-gated sodium channels play an essential role in the initiation and propagation of action potentials. These channels open as the membrane depolarizes and inactivate within a few milliseconds of opening. As the membrane polarizes again, the inactivation is removed and a second depolarizing stimulus is able to reopen the channel.

Sodium channels are large, multimeric complexes composed of an α subunit and one or more auxiliary β subunits. The α subunit has four homologous domains, each consisting of six transmembrane helices. The β subunit has one transmembrane segment and an extracellular domain with an immunoglobulin-like fold and belongs to the Ig superfamily of cell adhesion molecules (CAMs) (Catterall, 2000). The association with β subunits modulate cell surface expression and localization, voltage-dependence and kinetics of activation and inactivation, as well as cell adhesion and association with signalling and cytoskeletal

molecules (Patino and Isom, 2010). Nine α subunits ($Na_V1.1$ – $Na_V1.9$ encoded by SCN1A-SCN11A) and four β subunits (encoded by SCN1B-SCN4B) have been characterized so far. In addition, the enigmatic NaX channel, which appears not to be gated by voltage but rather by sodium, is encoded by the SCN7A gene (previously assigned as SCN6A) (Hiyama et al., 2002). $Na_V1.1$, $Na_V1.2$, $Na_V1.3$ and $Na_V1.6$ are the sodium channel α subunits most abundantly expressed in the brain (Yu and Catterall, 2003).

3.2 GEFS+ and SMEI

Febrile seizures, i. e. seizures induced by elevated body temperature, affect approximately 3% of children under 6 years of age and are by far the most common seizure disorder. Generalized Epilepsy with Febrile Seizures Plus (GEFS+) is an autosomal dominant epileptic syndrome where the febrile seizures may persist beyond 6 years of age and which may be associated with afebrile generalized seizures (Scheffer and Berkovic, 1997). The disease has a penetrance of approximately 60%. In 1998, GEFS+ was linked to mutation in SCN1B, the voltage-gated sodium channel β1 subunit gene (Wallace et al., 1998). GEFS+ can also result from mutations in the sodium channel α subunit genes SCN1A (Escayg et al., 2000) and SCN2A (Sugawara et al., 2001), and from mutations in the GABRG2 gene which encodes the γ2 subunit of the $GABA_A$ receptor (Baulac et al., 2001). Heterozygous mutations in SCN1A can also result in Severe Myoclonic Epilepsy of Infancy (SMEI), also known as Dravet syndrome (Claes et al., 2001). This rare form of epilepsy is characterized by generalized tonic, clonic, and tonic-clonic seizures that are initially induced by fever, light, sound, or physical activity and typically begin around 6-9 months of age. Later, SMEI patients also manifest other seizure types including absence, myoclonic, and simple and complex partial seizures. Psychomotor development stagnates around the second year of life and the patients often respond poorly to antiepileptic drugs. The disorder usually occurs in isolated patients as a result of *de novo* mutations (Claes et al., 2003; Ohmori et al., 2002).

3.3 How mutations in sodium channels can cause seizures

As sodium channels are responsible for the upstroke of the action potential one might expect that epilepsy-causing mutations in sodium channel genes increase the activity of the channel, thereby allowing increased influx of sodium ions and consequently neuronal hyperexcitability. Indeed, biophysical analyses of the mutant channels have shown that several of the mutations are gain-of-function mutations that increase sodium currents, e. g. by impairing inactivation or by causing a hyperpolarizing shift in the voltage-dependence of the channel (Lossin et al., 2002; Spampanato et al., 2003; Spampanato et al., 2004). The first identified GEFS+ mutation, a C121W missense mutation that disrupts a conserved disulphide bridge in the extracellular Ig domain of the β1 subunit, causes subtle changes in modulation of sodium channel function and alter the ability of β1 to mediate protein-protein interactions that are critical for channel localization (Meadows et al., 2002; Wallace et al., 1998). Electrophysiological and biochemical studies on the mutant C121W β1 subunit co-expressed with $Na_V1.2$ or $Na_V1.3$ have shown that the C121W mutation causes a reduction in current rundown during high-frequency channel activation and increases the fraction of sodium channels that are available to open at subthreshold membrane potentials (Meadows et al., 2002). The mutation is therefore thought to enhance sodium channel function, thereby increasing neuronal excitability and predisposing to seizures.

On the other hand, many of the characterized sodium channel mutations are found to cause attenuation of sodium current (Barela et al., 2006; Lossin et al., 2003; Sugawara et al., 2001).

While it seems like the mild phenotype of GEFS+ mostly is associated with missense mutations that alter the biophysical properties of the channels, the more severe SMEI phenotype is usually caused by nonsense or frameshift mutations that prevent production of functional channels (Claes et al., 2003; Claes et al., 2001; Nabbout et al., 2003; Ohmori et al., 2002). But how can loss-of-function mutations in a sodium channel cause epilepsy when reduced sodium current should lead to hypoexcitability rather than hyperexcitability? The answer seems to be related to the expression pattern of the channels. $Na_V1.1$ is predominantly found in inhibitory interneurons and is thought to conduct most of the sodium current in these cells, whereas excitatory pyramidal neurons express only negligible levels of $Na_V1.1$ (Ogiwara et al., 2007). Catterall and co-workers showed that haploinsufficiency of $Na_V1.1$ channels in heterozygous knock-out mice led to a phenotype resembling that of SMEI (Oakley et al., 2009; Yu et al., 2006). In these mice, sodium currents in GABAergic interneurons in the hippocampus were substantially reduced, whilst the effect in pyramidal cells was much less severe. Loss of one SCN1A copy led to a reduction in action potential number, frequency and amplitude in the interneurons (Yu et al., 2006). Similarly, studies in several animal models carrying nonsense or missense mutations in SCN1A show impaired interneuron function (Martin et al., 2010; Mashimo et al., 2010; Ogiwara et al., 2007; Tang et al., 2009). These studies indicate that functional loss of one copy of SCN1A reduces the inhibitory function of GABAergic interneurons and enhances the excitability of downstream synaptic targets, thereby predisposing to epileptic seizures.

But if this is true, how does the predicted changed $Na_V1.1$ function in many of the patients lead to hyperexcitability when the consequence should be increased GABA action? One possibility is that enhanced sodium current in the interneurons causes too much inhibition, and that this leads to synchronization of the downstream synaptic targets, as has been suggested in the pathogenesis of autosomal dominant nocturnal frontal lobe epilepsy (ADNFL) (Klaassen et al., 2006) (discussed later). Another possibility is that the functional consequences of the mutations in vivo are different from that predicted after in vitro characterization of the mutant channels, and that all of the mutations actually cause a reduction of sodium current in inhibitory neurons. This is supported by studies on knock-out mice lacking the β1 subunit (Chen et al., 2004). These mice show downregulated $Na_V1.1$ expression, indicating that β1 function might be necessary for normal expression of $Na_V1.1$. As the inhibitory interneurons seem to be most affected by a reduction in $Na_V1.1$, the consequences of the β1 mutations might be reduced sodium current in interneurons rather than, or in addition to, increased $Na_V1.2$ and $Na_V1.3$ function.

As mutations in SCN1A most often are associated with febrile seizures the mutations seem not to be sufficient to cause spontaneous seizure themselves. Why are the seizures triggered by fever? Why are the seizures most prevalent in young children? And what is the reason for the age-specific onset of SMEI? It is known that an increase in body temperature leads to an increase in the rate of respiration, especially in young children (Gadomski et al., 1994). This increased respiration can cause respiratory alkalosis in the immature brain, and alkalosis of brain tissue can lead to enhanced neuronal activity and to epileptoform activity (Lee et al., 1996). Studies on rat pups showed that seizure activity induced by hyperthermia had a well-defined pH threshold and that a rise in brain pH to the threshold level by injection of bicarbonate could provoke seizures (Schuchmann et al., 2006). By suppressing the alkalosis with a moderate elevation of ambient CO_2 to 5%, seizures could be abolished within 20 seconds without affecting body temperature. Bicarbonate-induced pH changes and seizures could also be blocked by elevation of ambient CO_2. In older rats, hyperthermia

only led to a moderate increase in the respiration rate and did not cause respiratory alkalosis and seizures (Schuchmann et al., 2006). Fever and the accompanying elevated pH and enhanced neuronal activity seem therefore to be the drop that makes the barrel overflow and induce the seizures. As several ion channels are sensitive to changes in pH (Jensen et al., 2005; Prole et al., 2003), it will be interesting to see whether some mutations in sodium channel genes render the channels pH-sensitive, which could make the affected individuals specifically susceptible to febrile seizures.

SMEI patients are normal until their first seizure that typically occurs around 6-9 months of age. This age-specificity may to be related to the time-specific expression of sodium channels. $Na_V1.1$ is undetectable during prenatal and early postnatal development, a stage where $Na_V1.3$ is preferentially expressed. $Na_V1.3$ expression declines at the expression of $Na_V1.1$ increases. An animal model of SMEI has shown that loss of inhibition and seizure onset correlates in time with an increase in $Na_V1.1$ levels and decline in $Na_V1.3$ levels (Oakley et al., 2009).

4. Mutations in $GABA_A$ receptor subunit genes

4.1 GABA receptors

GABA is the major inhibitory neurotransmitter in the central nervous system. There are three types of GABA receptors: $GABA_A$, $GABA_B$, and $GABA_C$. $GABA_A$ and $GABA_C$ receptors are ionotropic while $GABA_B$ receptors are G-protein coupled and often act by activating potassium channels. Most of the cortical inhibitory effects of GABA are mediated by $GABA_A$ receptors (Chebib and Johnston, 1999).

The $GABA_A$ receptors are pentameric chloride channels formed by various combinations of different types of α (α1 to α6), β (β1 to β3), γ (γ1 to γ3), δ, ε, π, θ, and ρ (ρ1 to ρ3) subunits, that each have four transmembrane segments, M1 to M4 (Benarroch, 2007). The most prevalent subunit combination consists of α1β2γ2 (McKernan and Whiting, 1996). The subunit composition determines the functional and pharmacological characteristics of the receptors (Meldrum and Rogawski, 2007; Sieghart and Sperk, 2002). Binding of GABA to the receptor triggers opening of the chloride channel, allowing rapid influx of chloride that hyperpolarizes the neuron and thereby decreases the probability of generation of an action potential.

4.2 GEFS+ and ADJME

As mentioned, GEFS+ can also result from mutation in the GABRG2 gene encoding the γ2 subunit of the $GABA_A$ receptor (Baulac et al., 2001). Mutations in the α1 subunit gene (GABRA1) have been linked to Autosomal Dominant Juvenile Myoclonic Epilepsy (ADJME) (Cossette et al., 2002), an idiopathic epilepsy that is not associated with febrile seizures. This disorder typically manifests itself between the ages of 12 and 18 with myoclonic seizures occurring early in the morning and with additional tonic-clonic and absence seizures in some patients.

4.3 How mutant $GABA_A$ receptor subunits can cause seizures

It has been shown that mutations in the γ2 subunit of the $GABA_A$ receptor cause retention of the receptor in the endoplasmatic reticulum (ER) (Harkin et al., 2002; Kang and Macdonald, 2004). Similarly, the A322D mutation in the α1 subunit causes rapid ER associated degradation of the subunit through the ubiquitin-proteasome system (Gallagher et al., 2007).

This reduced cell surface expression would result in decreased inhibitory $GABA_A$ receptor current, and consequently an increase in neuronal excitability and seizure susceptibility. But why are γ2 mutations associated with febrile seizures? And why are mutations in α1 not?
Variations in temperature have effects on most cellular events. For example, synaptic vesicle recycling has been shown to be temperature dependent with increased temperature speeding both endo- and exocytosis, and there is evidence that inhibitory synaptic strength can be modulated within 10 min through recruitment of more functional $GABA_A$ receptors to the postsynaptic plasma membrane (Wan et al., 1997). Studies on cultured hippocamplal neurons showed that while trafficking of wild-type α1β2γ2 receptors is slightly temperature dependent with a small decrease in surface expression after incubation at 40°C for 2h, trafficking of receptors with mutations in the γ2 subunit is highly temperature dependent (Kang et al., 2006). Increases in temperature from 37°C to 40°C impaired trafficking and/or accelerated endocytosis of the mutant receptors within 10 min, suggesting that the febrile seizures may be a result of a temperature-induced reduction in GABA-mediated inhibition. The study also showed that the A322D mutation in the α1 subunit did not cause a temperature-dependent reduction in surface expression, consistent with a resulting epilepsy syndrome not associated with febrile seizures (Kang et al., 2006).

5. Mutations in potassium channel genes

5.1 Kv7 channels and the M-current

The Kv7 family of voltage-gated potassium channels consists of five members, Kv7.1 -5 (also termed KCNQ1-5). All five members share the general structure of voltage-gated potassium channels with four subunits that assemble to form functional tetramers. Each subunit consists of six transmembrane helices, S1-S6, and has a pore forming domain, which is formed by a P-loop between the fifth and the sixth helix. The P-loop contains the GYG (glycine-tyrosine-glycine) sequence, which is highly conserved among potassium channels and confers K^+ selectivity. The fourth helix forms the voltage sensor; it contains several arginine residues and is therefore strongly positive. A S4-S5 linker in one subunit couples the voltage sensor to the intracellular activation gate in S6 of the adjacent subunit (Laine et al., 2003). Although heavily debated, it is believed that when the membrane potential depolarize, the voltage sensor is pushed out leading to bending of the S6 so potassium can enter the channel pore (Long et al., 2005).
All Kv7 channels are strongly inhibited upon activation of muscarinic receptors and are hence called M-channels (Schroeder et al., 2000; Selyanko et al., 2000). The current conducted by these channels, the M-current, was first described in bullfrog sympathetic ganglia as a slowly activating, slowly deactivating, sub-threshold voltage-dependent K^+ current that showed no inactivation (Brown and Adams, 1980). The Kv7 channels have slow activation and deactivation kinetics, and in line with other voltage-gated potassium channels they open upon membrane depolarization. However, the threshold for activation is low compared to most other channels, approximately -60 mV. Since the channels open at voltages that are around or below the threshold for generation of an action potential they allow potassium flow that opposes the depolarization required to generate action potentials, and hence make the neuron less excitable. If the M-channels remain open during excitation of the nerve, the spike frequency is dampened, whiles inhibition of the M-current by activation of muscarinic acetylcholine receptors enables repetitive firing (Hille, 2001).

Kv7 channels are primarily localized at the axon initial segment, the site where synaptic inputs are integrated and action potentials are generated (Pan et al., 2006; Rasmussen et al., 2007). Additionally, immunohistochemical studies have demonstrated a widespread pre-synaptic distribution of some Kv7 channel subunits (Cooper et al., 2000), where they may play a role in depolarization-induced neurotransmitter release (Martire et al., 2004; Martire et al., 2007). Activation of pre-synaptic M-current may hyperpolarize the nerve endings, thus reducing Ca^{2+} influx through voltage-gated Ca^{2+} channels and limiting the amount of neurotransmitter released.

5.2 Benign neonatal familial convulsions

Benign Neonatal Familial Convulsions (BNFC) is a rare autosomal dominant idiopathic form of epilepsy. It is characterized by tonic-clonic seizures that typically begin around three days after birth and remit after 3-4 months. Yet ~16% of patients also experience seizures later in life (Ronen et al., 1993). BNFC is caused by mutations in the genes encoding Kv7.2 (Biervert et al., 1998; Singh et al., 1998) or Kv7.3 (Charlier et al., 1998).

5.3 How mutations in Kv7.2 and Kv7.3 can cause BNFC

All characterized mutations in Kv7.2 and Kv7.3 cause a reduction in M-current, either by changing the channel kinetics (Dedek et al., 2001), by altering the trafficking of the channel to the cell membrane (Schwake et al., 2000), or by decreasing the subunit stability (Soldovieri et al., 2006). The mutations usually cause a reduction in M-current of about 25% (Schroeder et al., 1998). Considering the role of Kv7 channels in controlling neuronal excitability, it is not surprising that a reduction in M-current can cause hyperexcitability and predispose to seizures. Several transgenic strategies have been employed to examine how Kv7.2 and Kv7.3 malfunction lead to BNFC. The traditional knock-out approach resulted in mice that died within a few hours after birth due to pulmonary atelectasis (collapse of the lung) (Watanabe et al., 2000). Even though BNFC often results from Kv7.2 haploinsufficiency, heterozygous $KCNQ2^{+/-}$ mice did not experience neonatal seizures and appeared normal. They did, however, have increased susceptibility to chemically induced seizures (Watanabe et al., 2000). To overcome the postnatal lethality Dirk Isbrandt and colleagues developed mice conditionally expressing dominant-negative Kv7.2 subunits (Kv7.2-G279S) where expression of the transgene could be turned on after birth (Peters et al., 2005). These mice showed spontaneous seizures, exhibited behavioural hyperactivity and had morphological changes in the hippocampus. Mark Leppert and co-workers developed orthologous mouse models carrying disease-causing mutations in the *KCNQ2* (A306T) or *KCNQ3* (G311V) gene (Singh et al., 2008). Mice heterozygous or homozygous for either mutation had reduced seizure threshold, but only mice homozygous for the mutations exhibited spontaneous seizures. The epileptic phenotype was dependent on the specific mutation, the genetic background, sex, and seizure model (Otto et al., 2009). Hence, none of these transgenic strategies have fully recapitulated the human condition but nevertheless provide us with important clues regarding the pathophysiology of BNFC.

It can be questioned why the disease usually only is clinically manifested in neonates when mutations in the channels cause general hyperexcitability. One possible explanation for the age-dependent remission of seizures is related to the expression of Kv7 channels. There is evidence for a developmental upregulation of Kv7 channels (Weber et al., 2006), suggesting that a reduction in M-current of 25% might have a more prominent effect in the fetal brain

and that this reduction is not sufficient to cause seizures later in life when expression levels of Kv7 channels are higher.

Another possible mechanism is related to developmental changes in GABA function. During the first weeks of life, GABA, the main inhibitory neurotransmitter in the adult brain, provides the main excitatory drive to immature hippocampal neurons (Ben-Ari, 2002). Due to delayed expression of a chloride exporter there is a high intracellular concentration of chloride that leads to a negative shift in the reversal potential for chloride ions, so opening of ionotropic GABA receptors leads to an efflux of negative chloride ions and therefore depolarization. When the chloride-extruding system becomes operative, chloride is efficiently transported out of the cell, and GABA begins to exert its conventional inhibitory action (Ben-Ari, 2002). Because of this, the inhibition in neonatal circuits appears mainly to be mediated through presynaptic control of neurotransmitter release. As Kv7 channels are involved in the release of neurotransmitters (Martire et al., 2004; Martire et al., 2007), it was proposed that these channels serve as the main inhibitor in neonates, and that attenuation of M-current due to mutations in Kv7.2 and Kv7.3 causes reduced inhibition that is sufficient to cause epilepsy (Peters et al., 2005). If Kv7 channels are expressed in GABAergic neurons, the reduced M-current would possibly also cause increased GABA release which further would increase excitability at this point of development. It is also important to note that the neonatal brain is particularly prone to seizures (Holmes and Ben-Ari, 1998). As development continues and overall excitability decreases, reduced M-current apparently becomes less problematic and the seizures abate.

Yet, if this is the fact, why do ~16% of the patients experience seizures later in life after GABA has gained its inhibitory function? There is evidence to indicate that suppression of M-current within the first postnatal week can cause developmental defects, and that the resulting morphological changes in the brain, rather than reduced M-current causes the seizures in adulthood (Peters et al., 2005). In other words, it appears to become a symptomatic epilepsy with an idiopathic aetiology.

6. Mutations in nAChR subunit genes

6.1 Nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors (nAChRs) consist of five subunits that assemble to form functional pentamers. Each subunit consists of a long extracellular N-terminal domain, four transmembrane helices (TM1-TM4), and a short extracellular C-terminal end. The second transmembrane segment (TM2) from each subunit lines the channel pore. The amino acids that compose the TM2 are arranged in such a way that three rings of negatively charged amino acids are oriented toward the central pore of the channel. These provide a selectivity filter that ensures that only cations can pass through the pore. Brief exposure to high concentrations of Ach causes opening of the water-filled pore and permits an influx of Na^+ and Ca^{2+} and an efflux of K^+ (Waxham, 2003). After a few milliseconds, the receptor closes to a nonconducting state. Prolonged exposure to agonist causes desensitization of the channel, which stabilizes the receptor in an unresponsive, closed state (Dani and Bertrand, 2007).

The neuronal nAChRs can be either homomeric, consisting of five α subunits, or heteromeric with two α subunits and three β subunits. So far, 12 nAChR subunits expressed

in the brain have been identified (α2-α10 and β2-β4). The most widely distributed nAChRs in the human brain are the homomeric α7 and the heteromeric α4β2. The biochemical, pharmacological and biophysical characteristic of the channels are dependent on the subunit composition (Dani and Bertrand, 2007).

6.2 Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE) is a focal epilepsy characterized by clusters of brief nocturnal motor seizures with hyperkinetic or tonic manifestations. Seizures typically occur very soon after falling asleep or during the early morning hours, initiated during stage 2 non-rapid-eye-movement (NREM) sleep. Onset usually occurs around age 10 and the seizures often persist through adult life. However, in most patients the seizures tend to peter out in adulthood.

In 1995, a missense mutation (S248F) in the nAChR α4 subunit gene (CHRNA4) was found to underlie ADNFLE (Steinlein et al., 1995). Additional disease causing mutations in this gene (Hirose et al., 1999; Steinlein et al., 1997), and mutations in the β2 subunit gene (CHRNB2) (Phillips et al., 2001) have later been identified. Because α4 and β2 subunits combine, it is not strange that mutations in either subunit produce comparable epileptic symptoms. Almost every known mutation is found in the TM2 region of the two subunits. A common finding among the mutations is that the sensitivity to ACh is increased (Bertrand et al., 2002).

6.3 How mutations in nAChRs can cause ADNFLE

Stage 2 NREM sleep is characterized by the appearance of sleep spindles and slow waves, transient physiological rhythmic oscillations that are produced by synchronized synaptic potentials in cortical neurons. It appears that the seizure often arise from a sleep spindle that transforms into epileptic discharges (Picard et al., 2007). Thalamocortical circuits are thought to play a role in the generation of these sleep spindles.

Thalamic relay neurons are reciprocally connected to cortical neurons by excitatory synapses. Both thalamic and cortical neurons also excite GABAergic interneurons of the nucleus reticularis, which in turn inhibit thalamic relay neurons thus forming a feedback-loop (Kandel et al., 2000). The thalamic relay neurons have two different modes of signalling activity: a transmission mode during wakefulness and rapid eye movement (REM) sleep and a burst mode during NREM sleep. In the transmission mode, the resting membrane potential of the thalamic relay neurons is near the firing threshold and incoming excitatory synaptic potentials drive the neuron to fire in a pattern that reflects the sensory stimuli. During the burst mode the thalamic relay neurons are hyperpolarized and respond to brief depolarization with a burst of action potentials, which indicates that the thalamus is unable to relay sensory information to the cortex (Kandel et al., 2000). The thalamic relay neurons can be in different modes because they possess special Ca^{2+} channels named T-type channels. These channels are inactivated at the resting membrane potential but become available for activation when the cell is hyperpolarized, and can then be transiently opened by depolarization (Contreras, 2006). The interneurons of the nucleus reticularis that form synapses at the relay neurons hyperpolarize the relay neurons upon activation of $GABA_A$ receptors, thus removing the inactivation of the T-type Ca^{2+} channels. Incoming excitatory synaptic potentials can then trigger transient opening of the T-type Ca^{2+} channels and the

resulting influx of Ca^{2+} brings the neuron's membrane potential above threshold. The cell now fires a burst of action potentials that produces the synchronized postsynaptic potentials in cortical neurons that cause the spindle waves seen on the electroencephalogram. When sufficient Ca^{2+} has entered the cell a Ca^{2+}-activated K^+ current is triggered that hyperpolarizes the relay neurons and terminate the spindle (Contreras, 2006). Because of the feedback loops from the relay neurons and cortical neurons that innervate the interneurons of the nucleus reticularis, these are again activated, which allows for another round of burst firing.

There is a high expression of the α4β2 nAChR subtype in the thalamus and the subtype can be found diffusely distributed onto pyramidal cells and GABAergic interneurons in the cortex. The thalamic relay neurons and the nucleus reticularis receive input from two groups of cholinergic neurons in the upper brain stem: the pedunculopontine and laterodorsal tegmental nuclei (LDT). These are critical for keeping the thalamic relay neurons in transmission mode during wakefulness and REM sleep. The LDT releases Ach during NREM sleep at the time of an arousal that interrupts the sleep spindle oscillations through depolarization of thalamic relay neurons (Lee and McCormick, 1997). The cortex receives cholinergic input from neurons in the nucleus basalis of Meynert that enhance cortical response to incoming sensory stimuli (Kandel et al., 2000).

After studying transgenic ADNFLE mice with heterozygous expression of an ADNFLE mutation ($Chrna4^{S252F}$ or $Chrna4^{+264}$), Boulter and colleagues suggested that an Ach-dependent sudden increase in the response of GABAergic cortical interneurons contributes to the epileptogenesis in ADNFLE patients (Klaassen et al., 2006). They showed that asynchronously firing cortical pyramidal cells got synchronized when relived from a large GABAergic inhibition triggered by cholinergic over-activation of mutant nAChRs in the cortical interneurons.

Dani and Bertrand suggested that this, together with an increased positive response of cortical pyramidal cells through cholinergic stimulation of their hypersensitive α4β2 nAChRs, contributes to induction of the seizures (Dani and Bertrand, 2007). As the cortical pyramidal cells project back to the thalamus, excitatory stimuli will be boosted on to the interneurons of the nucleus reticularis and the relay neurons and induce synchronous activity and seizures (Dani and Bertrand, 2007).

In addition, PET studies using a high affinity α4β2 agonist have showed a clear difference in the pattern of the nAChR density in the brains of ADNFLE patients compared to control subjects (Picard et al., 2006). The studies showed that patients had increased α4β2 density in the epithalamus, the interpeduncular nucleus (IPN) of the ventral mesencephalon and in the cerebellum, while the density in the right dorsolateral prefrontal region was decreased. As the IPN projects to the LDT, the authors proposed that prolonged depolarizations in IPN neurons, because of both increased density of α4β2 and hypersensitive receptors, could result in over-activation of the LDT and consequently the thalamic relay neurons (Picard et al., 2006). At the time of arousals, ACh acting on sensitized thalamic relay neurons could prevent the normal arousal-induced interruption of the sleep spindle oscillations and transform them into pathological Thalamocortical oscillations, triggering epileptic seizures (Picard et al., 2006).

Neither of these mechanisms excludes the others. In fact, they might work together yielding even stronger possibilities for induction of seizures.

7. Ion channel modulators as antiepileptic drugs

Many of the antiepileptic drugs on the market today exert strong effects on ionic currents. Sodium channel blockers were used in the treatment of epilepsy as early as in 1940, and since then several other sodium channel blockers have been developed. Carbamazepine, first introduced in 1968, stabilizes the inactive conformation of sodium channels and is widely used in the treatment of partial and generalized tonic-clonic seizures. Lamotrigine blocks sodium channels in a voltage- and use-dependent manner and is efficient for partial, absence, myoclonic and tonic-clonic seizures (Kwan et al., 2001). Drugs that potentiate GABA receptor function, such as benzodiazepines, have also been used as anticonvulsants for several years. These act by binding to the interface between the α and γ subunits of the $GABA_A$ receptor, resulting in allosteric activation of the receptor (Kwan et al., 2001). Several established and novel antiepileptic drugs have been reported to act on various K^+ currents, but none of them exert their main effect on potassium channels (Meldrum and Rogawski, 2007). Carbamazepine also exerts an effect on nAChRs by blocking the open conformation of the channel and is very effective in treatment of patients with ADNFLE. This effect might be related to the fact that several of the disease causing mutations in CHRNA4 and CHRNA2 increase the sensitivity to the drug (Ortells and Barrantes, 2002).

The knowledge of how mutations in ion channels cause neuronal hyperexcitability and epilepsy has led to new therapeutic strategies for prevention of seizures. The mutated proteins serve as mechanistic proof of concept that pharmacological antagonization of the epilepsy causing mechanisms could have desirable effects on neuronal excitability. These mechanisms are not necessarily targeted for treatment of the respective epilepsy syndrome, but as they are showed to cause hyperexcitability in the affected patients, antagonizing drugs may reduce excitability in patients with other types of epilepsy. An excellent example of this is Retigabine (other names are Trobalt, Potiga, or Ezogabine), which was approved by both the European Medicines Agency and the U.S. Food and Drug Administration in 2011 as adjunctive treatment for partial onset seizures. It was originally synthesized as a GABA modulator, but it was later shown that its main molecular target is the neuronal Kv7 channels (Main et al., 2000; Rundfeldt and Netzer, 2000; Wickenden et al., 2000). Retigabine induces a large hyperpolarizing shift in the voltage-dependence of activation of Kv7 channels, accelerates the activation kinetics and slows deactivation kinetics. Enhancement of M-current would clearly be effective in prevention of seizures in BNFC patients, but mutations in the Kv7 channels might render them insensitive to such drugs, which hampers the use of Kv7 channel openers in the treatment of BNFC. The hypothesis of reduced $Na_V1.1$ current in the pathogenesis of GEFS+ and SMEI, together with its primary expression in inhibitory interneurons, indicates that this sodium channel subtype plays a role in reducing neuronal excitability (Ogiwara et al., 2007; Yu et al., 2006). This opens the intriguing possibility that selective $Na_V1.1$ openers can function as anticonvulsants, even though sodium channel openers generally are known as epileptogenic substances.

An understanding of the etiology of the epilepsy syndromes and the causal factors in individual patients are also critical for selection of the right medication. Sodium channel blockers, which normally would exhibit anticonvulsant properties, would clearly not be the right choice to treat patients with SMEI, where a lack of sodium current seems to be the underlying cause. Similarly, as too much inhibition seems to play a role in the pathogenesis

of ADNFLE, GABA receptor agonist might have a negative effect in these patients. In fact, Boulter and co-workers showed that the $GABA_A$ receptor antagonist picrotoxin, which normally exhibits convulsive properties, was efficient in preventing seizures in the ADNFLE mice (Klaassen et al., 2006).

8. Conclusion

As about 30% of all patients with epilepsy respond poorly to antiepileptic drugs, there is clearly a need for development of new therapies. The growing understanding of the epileptic channelopathies and the structural and functional characterization of the mutated channels provide several opportunities for creation of novel and improved drugs.

9. References

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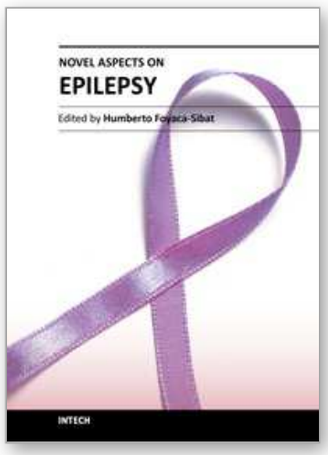

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This book covers novel aspects of epilepsy without ignoring its foundation and therefore, apart from the classic issues that cannot be missing in any book about epilepsy, we introduced novel aspects related with epilepsy and neurocysticercosis as a leading cause of epilepsy in developing countries. We are looking forward with confidence and pride in the vital role that this book has to play for a new vision and mission. Therefore, we introduce novel aspects of epilepsy related to its impact on reproductive functions, oral health and epilepsy secondary to tuberous sclerosis, mithocondrial disorders and lisosomal storage disorders.

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