Past, present and future of epilepsy

Passado, presente e futuro da epilesia

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ABSTRACT

Epilepsy is a complex brain disorder with diverse clinical features. Moreover, epilepsy is one of the most common serious neurological disorders worldwide with no age, racial, social class, national or geographic boundaries. This disease causes recurring seizures that happen when clusters of neurons in the brain send out wrong signals. A common way to explain seizures is that a disruption has ocurred in the normal balance of excitation and inhibition. Using different experimental models, it is clear that genes, developmental mechanisms, and neural plasticity play major roles in creating a state of underlying hyperexitability. Epilepsy patients may have strange sensations and emotions or behave strangely before a seizure occurs. Different features of epileptic seizures have been reported, where the patients may have violent muscle spasms or lose consciousness. This is a disorder with many possible causes, making mechanistic predictions a challenge. Anything that disturbs the normal pattern of neuron activity - from illness to brain damage to abnormal brain development - can lead to epilepsy. Several experimental models have been developed with the objective to gain insight into the mechanisms of disruption involved in epilepsy. Nonetheless, the target and/or mechanism of action of many of drugs used to control epilepsy remains unclear. Their elucidation should improve diagnosis and may provide new targets for the development of specific prophylactic therapies for epilepsy.

Key words

epilepsy, seizures, mechanims, treatment.

RESUMO

A epilepsia é desordem cerebral complexa com diversas manifestações clínicas. Além disso, a epilepsia é uma das doenças neurológicas mais comuns ao longo do planeta, sem barreiras geográficas para idade, raça, sexo ou nacionalidade. A doença causa convulsões recorrentes que ocorrem quando grupos de neurônios cerebrais sinalizam erroneamente. Um modo comum de explicar as convulsões é a de que houve uma falha do balanço normal de excitação e inibição. Através do uso de diferentes modelos experimentais está claro que genes, mecanismos de desenvolvimento e plasticidade neural têm um papel importante em criar o estado de hiperexcitabilidade. Pacientes com epilepsia podem ter sensações estranhas e se comportar de forma estranha antes de uma convulsão. Diferentes formas de convulsões epilépticas são docu-

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mentadas, onde os pacientes podem ter violentos espasmos musculares ou perda de consciência. Esta é uma doença com várias causas possíveis, fazendo com que a previsão dos mecanismos seja um desafio. Qualquer modificação no padrão normal de atividade neuronal, desde doenças, dano cerebral até desenvolvimento cerebral anormal, pode levar a epilepsia. Diversos modelos experimentais têm sido desenvolvidos com o objetivo de entender os mecanismos envolvidos na epilepsia. Entretanto, o alvo ou o mecanismo de ação de muitos dos fármacos utilizados no controle da epilepsia permanecem obscuros. A sua elucidação deverá melhorar o diagnóstico e providenciar novos alvos para o desenvolvimento de terapias profiláticas para a epilepsia.

Palavras-chave
epilepsia, convulsões, mecanismos, tratamento.

1. GENERAL FEATURES

Epilepsy is a brain disorder characterized predominantly by recurrent and unpredictable interruptions of normal brain function, called epileptic seizures. Epilepsy is not a singular disease entity but a variety of disorders reflecting underlying brain dysfunction that may result from many different causes (FISHER et al., 2005). This disorder is one of the most common neurologic problems worldwide. Approximately 2 million persons in the United States have epilepsy, and 3 percent of persons in the general population will have epilepsy at some point in their lives (ANNEGERS, 2001). In recent years, important advances have been made in the diagnosis and treatment of seizure disorders. However, the cellular and molecular mechanisms by which epilepsy develops, called epileptogenesis, is still unknown (SCHACHTER, 2001; CHANG and LOWESTEIN, 2003).

In patients with epilepsy, the normal pattern of neuronal activity becomes disturbed, causing strange sensations, emotions, behavior or sometimes convulsions, muscle spasms, and loss of consciousness. Anything that disturbs the normal pattern of neuron activity can lead to seizures. Despite advances in the sensitivity of diagnostic tests less than half of the patients with this disorder have an identifiable cause, such as congenital brain malformations, inborn errors of metabolism, brain trauma, brain tumors, stoke, intracranial infection, vascular malformation, cerebal degeneration, withdraw states, and iatrogenic drug reactions (SCHACHTER, 1998; SCHACHTER, 2004). Cerebral disease, cerebral degeneration and brain tumors are more common causes in elderly patients than in younger patients (SCHOLD et al., 1977).

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Seizures can last from a few seconds to a few minutes. They can have many symptoms, from convulsions and loss of consciousness to blank staring, lip smacking, or jerking movements of arms and legs (FISHER et al., 2005). This is a clinical event; therefore, detailed specification of these clinical phenomena during an epileptic seizure is difficult, because of the wide range of possible manifestations. Seizure presentation depends on location of onset in the brain, patterns of propagation, maturity of the brain, confounding disease processes, sleep–wake cycle, medications, and a variety of other factors. Seizures can affect sensory, motor, and autonomic function; consciousness; emotional state; memory; cognition; or behavior. Not all seizures affect all of these factors, but all influence at least one. In this context, sensory manifestations are taken to include somatosensory, auditory, visual, olfactory, gustatory, and vestibular senses, and also more complex internal sensations consisting of complex perceptual distortions (Commission on epidemiology and prognosis, International League Against Epilepsy, 1993; BROWNE, 1999, WHO, 2006).

According to the 2001 ILAE Glossary of Descriptive Terminology for Ictal Semiology (BLUME et al., 2001), cognitive deficits during seizures can appear as problems with perception, attention, emotion, memory, execution, praxis, or speech. Memory distortions can be either negative or positive, in the sense of interruption of memory formation or retrieval as a negative symptom, or intrusion of inappropriate memories as a positive symptom. Positive memory symptoms give rise to "d´ej`a vu" and other forced memories during seizures. Some of the distorted memories previously were classified as psychic symptoms, which is a potentially ambiguous term. Emotional state is difficult to specify but must be considered in the definition, because some seizures manifest as fear, elation, satisfaction, anxiety, or other subjective sensations that cannot be ascribed to the primary senses (FISHER et al., 2005).

Epilepsy is among the disorders that are strongly associated with significant psychological and social consequences for everyday living (BAKER, 2002). People with hidden disabilities such as epilepsy are among the most vulnerable in any society. While their vulnerability may be partly attributed to the disorder itself, the particular stigma associated with epilepsy brings a susceptibility of its own. Stigmatization leads to discrimination, and people with epilepsy experience prejudicial and discriminatory behaviour in many spheres of life and across many cultures (PAHL and BOER, 2005). People with epilepsy experience violations and restrictions of both their civil and human rights. Civil rights violations, such as unequal access to health and

life insurance or prejudicial weighting of health insurance provisions, withholding of the right to obtain a driving licence, limitations to the right to enter particular occupations and the right to enter into certain legal agreements, in some parts of the world even marriage, are severely aggravated by epilepsy. Discrimination against people with epilepsy in the workplace and in respect of access to education is not uncommon for many people affected by the condition (WHO, 2006).

2. SEIZURE TYPES

There are many classifications of epilepsy. A full classification would be extremely complicated. In general, epilepsy syndromes types are based on the specific biologic mechanisms involved in the seizure and parts of the anatomy where the seizure is located. The seizure type usually is established from the description of the behaviors that occure before, during and after the seizure. The two main seizure types are generalized and partial seizures. Generalized seizures affect both sides of the brain simultaneosly and usually are not associated with cerebral pathology. Partial seizures (also called focal or localized) affect a restricted area of the brain and indiacte the possibility of an underlying lesion. In some cases, partial seizures can spread to wide regions of the brain (SCHACHTER, 2004; WHO, 2006).

Although specific seizures can be classified according to their clinical features, e.g., partial and generalized seizures (Commission on Classification and Terminology of the International League against Epilepsy, 1981), epilepsy syndromes can also be classified according to the type of seizure (Table 1), the presence

Table 1 - Epilepsy Seizures

PARTIAL		GENERALIZED
Focal	**Local**	Absence
Simple		Myoclonic
Complex		Clonic
Partial		Tonic
evolving to secondarily		Tonic-clonic
Generalized		Atonic

Table 1. Classification of epileptic seizures. Seizures are mainly divided into partial and generalized. Partial seizures are charachterized by clinical or EEG evidence that suggest a localization of the attacks in the brain, while generalized seizure lack localization.

or absence of neurologic or developmental abnormalities, and electroencephalographic (EEG) findings (Commission on Classification and Terminology of the International League against Epilepsy, 1989; LÖSCHER, 1993).

2.1. Partial seizures

This is the more common type of epilepsy and is generally defined as a disorder of the neurons that starts on one side of the brain. It is currently subcategorized as "simple", "complex partial" and "secondarily generalised" seizures. The term "partial" however, implies that such seizures affect only small or specific locations in the brain. In reality, they almost always involve diffuse and even widespread problems. (i) *Simple Partial Seizures*. A person with a simple partial seizure does not lose consciousness but may experience confusion, jerking movements, tingling, or odd mental and emotional events. Such events may include "d´ej`a vu", mild hallucinations, or extreme responses to smell and taste. After the seizure, the patient usually has temporary weakness in certain muscles. (ii) *Complex Partial Seizures*. Slightly over half of the seizures in adults are complex partial types, and about 80% of these seizures originate in the temporal lobe, the part of the brain located close to the ear. Disturbances there can result in loss of judgment, involuntary or uncontrolled behavior, and a loss of consciousness. About 20% of these patients have seizures that start in the brain's frontal lobes. Prior to the actual seizure, people sometimes experience a warning sign, known as an aura, which can be an odd odor, a feeling of warmth, or a visual or auditory hallucination. They then may lose consciousness briefly and appear to others as motionless with a vacant stare. Emotions can be exaggerated; some sufferers even appear to be drunk. After a few seconds, some may begin to perform repetitive movements, such as chewing or smacking of lips. Episodes usually last no more than two minutes, and people can have them infrequently or as often as every day or more. A throbbing headache may follow a complex partial seizure. (iii) *Partial seizures becoming secondarily generalised*. In these, partial seizures end with the person having a motor convulsion (MOSEWICK and SO, 1996; BROWNE and HOLMES, 1999; SCHACHTNER, 2004; ENGEL, 2006; SEINO, 2006).

2. 2. Generalized seizures

This type of seizure is caused by nerve cell disturbances that occur in more diffuse areas of the brain than do partial seizures. Therefore, they have a more serious effect on the patient. They are further subcategorized as tonic–clonic (or grand mal) or absence (petit mal) seizures. (i) *Tonic–Clonic (Grand Mal) Seizures*. The first stage of a grand mal seizure is called the tonic phase, in which the flexor and extensor muscles suddenly contract, causing the patient to fall and lie rigidly for about 10 to 30 seconds. Some people experience a premonition or aura before a grand mal seizure; most, however, lose consciousness without warning. If the throat or larynx is affected, there may be a high–pitched musical sound called *stridor* when the patient inhales. Spasms occur for about 30 seconds to a minute as the seizure enters the clonic phase, when the muscles begin to alternate between relaxation and rigidity. After this phase, the patient may lose bowel or urinary control. The seizure usually lasts a total of two to three minutes, after which the patient remains unconscious for a while and then awakens to confusion and extreme fatigue. A severe throbbing headache similar to migraine may also follow the tonic–clonic phases. (ii) *Absence (Petit Mal) Seizures*. Petit mal or absence seizures are brief (three to 30 seconds) with losses of consciousness and may consist of only a short cessation of physical movement and loss of attention. Such seizures may pass unnoticed by others. Small children may simply appear to be staring or walking distractedly. Petit mal may be confused with simple or complex partial seizures or even with attention deficit disorder. In petit mal, however, a person may experience attacks as often as 50 to 100 times a day. About 25% of patients with petit mal develop grand mal seizures. An EEG test that shows a specific brain wave pattern can usually identify these patients (MOSEWICK and SO, 1996; BERKOVIC, 1997; BROWNE and HOLMES, 1999; SCHACHTNER, 2004; ENGEL, 2006; SEINO, 2006).

3. CELLULAR AND MOLECULAR MECHANISMS

3.1. Voltage-gated ion channels

The discovery of genetically determined epileptic syndromes associated with specific mutations of genes codifying for subunits of voltage or ligand-activated ion channels highlights the role of ion channels in epileptogenesis. Furthermore some forms of epilepsy might be caused by alterations in ion channels that lead to a reduced repolarization reserve or that increase or prolong excitation. Voltage-gated ion channels clearly are involved in the pathogenesis of epilepsy, with evidence implicating derangement of sodium (Na^+), potassium (K^+), and calcium ($Ca2^+$) voltage-gated channels, in both inherited and acquired forms of epilepsy (STEINLEIN and NOEBELS, 2001).

Neuronal firing is controlled by numerous ionic conductances that interact to produce a wide array of threshold and subthreshold behaviors. The foundation of the understanding of neuronal firing comes from the pioneering work of Hodgkin and Huxley, who showed that the action potential upstroke is due to the rapid influx of sodium ions (Na^+). Na^+ influx through specific ion channels in the neuronal membrane causes a depolarizing inward current. Once open, Na^+ channels inactivate and cannot pass further current until they recover from inactivation. Na^+ channel inactivation, in conjunction with outward current through potassium (K^+) channels, allows the membrane potential to repolarize to the resting level. Alterations of Na^+ currents can lead to abnormal neuronal activity, such as occurs in epilepsy. The transient voltage-gated Na^+ current mediates the upstroke of the action potential. A small fraction of Na^+ current, termed the persistent Na^+current , fails to inactivate significantly, even with prolonged depolarization (STAFSTRON, 2007). Furthermore, the generalized epilepsy with febrile seizures plus (GEFS+) has been associated with mutations in the Na^+ channel β-subunit gene, *SCN1B* (GEFS+1), and the Na^+ channel α-subunit gene *SCN1A* (GEFS+2). These mutations might decrease the rate of Na^+ channel inactivation, resulting in different epilepsies (SINGH, et al., 1999, ESCAYG, et. al., 2000).

Potassium channels are important regulators of electrical signaling and are implicated in the pathology of epilepsy (for a review see ROGAWSKI, 2000). There have been described two proteins related to the benign familial neonatal convulsions (BFNC), a generalized epilepsy syndrome. Generalized epilepsies often have a strong genetic component. In 1998 two homologous voltage-activated K^+ channels designated *KCNQ2* (*KvEBN1*) and *KCNQ3* (*KvEBN2*) were

identified as the disease genes in BFNC (BIERVERT et al., 1998; SINGH et al., 1998, CHARLIER et al., 1998). *KCNQ2* and *KCNQ3* encode proteins with sequence homology to members of the six-transmembrane domain K^+ channel gene superfamily. Although KCNQ2 and KCNQ3 can each form functional voltage-dependent K^+ channels by themselves, evidence indicates that the two subunits coassemble to form heteromers. Schroeder and colleagues predicted a 25% loss of heteromeric KCNQ2/KCNQ3-channel function is sufficient to cause electrical hyperexcitability in BFNC (SCHROEDER, et al., 1998). Besides KCNQ2 and KCNQ3 are expressed in an overlapping distribution in brain, with high levels in critical areas for seizures, including the hippocampus, neocortex and thalamus, but are not expressed in most other tissues. Even more, the co-injection of *KCNQ2* and *KCNQ3* subunit cRNAs in *Xenopus* oocytes yields currents that are much larger in amplitude (> tenfold) than those obtained with either of the subunits alone the (SCHROEDER et al., 1998; TINEL et al., 1998; YANG et al., 1998).

The voltage-gated Ca^{2+} channels play essential roles in the nervous system as they are involved in neurotransmitter release, gene expression, in the generation of absence seizures, and their mutations are a substrate for juvenile myoclonic epilepsy (ARMIJO et al., 2005, CARAFOLI, 2002, WEST et al., 2001). Moreover Schumacher et al. (1998) showed that modulation of postsynaptic Ca^{2+} channels can contribute to the anticonvulsant action of phenytoin in human hippocampal granule cells.

Insight into the structure and function of these brain specific Na^+, K^+ and Ca^{2+} channels will improve diagnosis and may provide new targets for the development of specific prophylactic therapy for episodic cerebral disorders such as epilepsy, and may also be important for the study of (neuronal) cell death.

3.2. Neurotransmitters

Epilepsy may also develop because of an abnormality in brain wiring, an imbalance of nerve signaling chemicals called neurotransmitters, or some combination of these factors. The two main neurotransmitters that play a key role in the development and maintenance of epilepsy are γ-amino butyric acid (GABA) and glutamate (Glu). During neurotransmission both amino acid regulate strength and duration of the communication between neurons. Glu "turns on" while GABA "turns off" neurotransmission. Besides, neurochemical and pharmacological data support the notion that Glutamatergic and GABAergic systems are related to the beginning, maintenance and end of many types of epilepsy (BRADFORD, 1995).

GABA is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS) (ROBERTS, 1976). The development of selective agents has led to the identification of at least two distinct classes of GABA receptors, $GABA_A$ and $GABA_B$. They differ in their pharmacological, electrophysiological and biochemical properties (OLSEN and TOBIN, 1990; TILLAKARATNE et al., 1995). In $GABA_A$ receptors the GABA-binding site is directly responsible of opening the Cl^- channel. This in turn potentially can excite the cell to fire or to activate Ca^{2+} entry via voltage-gated channels and has been proposed as a physiologically relevant event (OLSEN and DELOREY, 1999). $GABA_B$ receptors are coupled indirectly to K^+ channels. When activated, these receptors can decrease Ca^{+2} conductance and inhibit cAMP production via intracellular mechanisms mediated by G proteins. Activation of $GABA_A$ receptors result in an increased inhibition of the postsynaptic neuron while $GABA_B$ receptors can mediate both postsynaptic and presynaptic inhibition (VELISEK and MARES, 1995). Presynaptic inhibition may occur as a result of $GABA_B$ receptors on nerve terminals causing a decrease in the influx of Ca^{2+}, thereby reducing the release of neurotransmitters (OLSEN and DELOREY, 1999).

GABA exerts its primary (fast) effects through chloride currents associated with $GABA_A$ receptors, it either depolarizes or hyperpolarizes the postsynaptic neuron, depending on chloride's electrochemical gradient across the neuronal membrane. There are evidences in the literature that acute and chronic changes in chloride transporter expression, by reducing or even reversing the inhibitory influence of GABA, underlie the generation of seizures acutely or the process of epileptogenesis (DZHALA et al, 2005; STAFSTROM, 2006).

Another aspect of the changing perspective on GABA concerns the key role it plays in the develop-

ment of neuronal circuits. It is a major excitatory neurotransmitter in the immature brain at a time when glutamatergic synaptic connections are beginning to mature (Ben Ari, 2002). In the early postnatal period in rats, the pairing of depolarizing GABA-mediated responses with glutamate release at immature excitatory synapses that contain only *N*-methyl-D-aspartate (NMDA) receptors relieves their voltage-dependent block by magnesium ions. The resulting NMDAreceptor-mediated calcium influx provides the signal required for insertion of AMPA-type glutamate receptors into the postsynaptic membrane and, therefore, leads to their maturation into active synapses. Given this crucial role in the development of excitatory synapses, it is likely that the depolarizing action of GABA contributes to the particular vulnerability of neonates to seizures and epilepsy. This developmental process appears to be analogous to the insertion of AMPA receptors that occurs during induction of long-term potentiation in more mature brain circuits, when glutamate provides the depolarizing signal. Considering the importance of long-term potentiation in learning and memory functions, disruption of these analogous signaling patterns by seizures may have long-lasting consequences in patients at a vulnerable age (MATHEWS, 2007).

The $GABA_A$ receptor is of prime importance in the pathogenesis of absence epilepsy because of its apparent role in the synchronization and desynchronization of thalamocortical circuitry. Perturbation of this process leads to the generation of absence seizures. The oscillatory burst firing of thalamocortical circuitry is attributed to the ability of neurons located in the nucleus reticularis thalami (nRT) to impose their own oscillatory behavior on thalamocortical relay neurons located in the ventral basalis (VB) of the thalamus. The ability of the nRT to switch between oscillatory and burst firing dictates electroencephelographic (EEG) synchronization and desynchronization. The nRT consists of GABAergic neurons that project to the VB, providing inhibitory input. Also, GABAergic nRT neurons project onto one another providing intra-nRT inhibition, which decreases input to the VB. The nRT GABAergic neurons receive glutamatergic inputs from thalamocortical VB fibers and also from corticothalamic fibers projecting back from layer VI of the cerebral cortex (YEM, 1985; STERIADE at al, 1993; MCCORMICK and BAL, 1997; GUIN-TING WONG and CARTER SNEAD III, 2001).

The amino acid Glu is considered to be the main excitatory neurotransmitter in the mammalian CNS. Glu is involved in synaptic plasticity, being essential for normal brain function, including memory and learning (FONUM, 1984; OTTERSEN and STORM-MATHISEN, 1984; COLLINGRIDGE and LESTER, 1989; HEADLEY and GRILLNER, 1990; OZAWA et al., 1998). Glu also plays a major role in crucial steps of CNS development, participating in synapse induction and elimination, cell migration, and differentiation (DANBOLT, 2001). Glu exerts its signaling role by acting on glutamate receptors (GluRs) located on the neural cell surface in such a way that Glu concentration in the surrounding extracellular fluid usually determines the extent of receptor stimulation (OZAWA et al., 1998). GluRs are divided in ionotropic and metabotropic type. The first ones, as their name indicates, are ion permeable receptors (to Na^+ and Ca^{++}) and metabotropic receptors are coupled to G proteins and second messenger signaling (WATKINS and EVANS, 1981).

The amount of Glu in the synaptic cleft depends on the balance between its release by presynaptic neurons and its uptake that occurs fundamentally through system localized in the astrocyte membrane and also in the presynaptic neuronal terminal because no extracellular enzyme capable of significantly metabolizing glutamate is known (NICHOLLS, 1993; MARAGASKIS and ROTHSTEIN, 2001). When present at high concentrations in the synaptic cleft, Glu may lead to excitotoxicity, a process corresponding to overstimulation of Glu receptors leading subsequently to neuronal damage (ANDERSON and SWANSON, 2000; MELDRUM, 2000; DANBOLT, 2001; MARAGAKIS and ROTHSTEIN, 2001). Glu toxicity has been related to neuronal death in ischemia, hypoxia, hypoglycemia and trauma (CHOI, 1988; IKONOMIDOU et al., 1989) and with many chronic neurodegenerative disorders of the CNS, including Huntington's and Alzheimer's, and *status epilepticus* (BREWER, 2000; DANBOLT, 2001; MARAGAKIS and ROTHSTEIN, 2001).

Glu uptake is the process responsible for the maintenance of extracellular glutamate concentrations be-

low neurotoxic levels. This uptake is mainly accomplished by Na-dependent high-affinity systems mediated by a family of proteins known as amino acid transporters (KANNER, 1993; AMARA and FONTANA, 2002; BEART and O'SHEA, 2007). The different Glu transporters subtypes are expressed regionally in distinct patterns, with glial and neuronal transporter expression appearing in a coordinated manner during CNS development (DANBOLT, 1994, 2001). There are 5 types of excitatory amino acid transporters (EAAT): EAAT1 (GLAST), EAAT2 (GLT-1), EAAT3 (EAAC), EAAT4 and EAAT5 (for a review see DANBOLT, 1994 and 2001).

In the last decade, Glu transporters and receptors dysfunction has been associated with epilepsy, since reuptake impediment increases Glu extracellular concentration and the consequent neuron population loss (for a review see MELDRUM et.al., 1999). In these terms, glial cells play a mayor role in the correct maintenance of synaptic activity, since this cell type is specialized in the Glu uptake. Besides, glial cells transform Glu to glutamine (by glutamine synthetase) and returns to neurons completing the neurotransmission cycle (SCHOUSBOE, 1981). Glu transporters are expressed in neurons and glial cells. Nevertheless, Glu uptake carried out by astrocytes seems to have a more major role than neurons (MCLENNAN, 1976; ROTHSTEIN et al., 1996; TANAKA et al., 1997). Glu removal by astrocytes occurs through the Na^+ dependent transporters GLAST and GLT-1 (HAUGETO et al., 1996), being the only EAATs expressed by astrocytes in mammalian brain, and associating uptake and protection against neurotoxicity to this cell type.

Although human studies have not proven a direct role of defective Glu uptake in epilepsy, a reduced expression of glutamate transporters was found to produce or to be associated with seizure activity in several animal models. For example, mice lacking the astroglial-type GLT-1 develop spontaneous seizures (TANAKA et al., 1997), and a decreased expression of Glu transporters GLAST, GLT-1, and EAAC1 was found in a rat model of absence epilepsy (DUTUIT et al., 2002). Rothstein et al. previously showed that antisense treatments that knock down expression of GLAST, GLT-1, or EAAC1 have differential effects. Whereas impairment of the expression of the glial subtypes (GLAST and GLT-1) caused massive excitotoxicity and neurodegeneration, a deficit in the neuronal subtype (EACC1) was responsible for only mild neurotoxicity and epilepsy.

Moreover, glial cells, although long considered to be merely supporting cells in the central nervous system, may also have another important role (ZHU and HOPER, 2000). Glia performs key buffering functions that help to maintain the uptake of potassium and Glu and other aspects of the extracellular milieu of neurons. Theoretically, disruption of these glial functions could cause neuronal hyperexcitability, since increased levels of extracellular potassium decrease the threshold for neuronal firing and increased levels of glutamate could increase neuronal activation (CHANG and LOWESTEIN, 2003). Thus, a change in the neuronal microenvironment may be another mechanism of epileptogenesis.

Recent advances in the technology of live-cell imaging and light-excitation, however, have revealed that astrocytes, while lacking membranes that are excitable in classic terms, can generate oscillatory intracellular calcium waves, which can propagate through the astrocytic network (CORNELL-BELL et al., 1990) and release neuroactive transmitters, such as Glu (BEZZI et al., 1998), even by means of Ca^{2+-} mediated exocytosis (BEZZI et al., 2004). It has been shown that astrocytic Ca^{2+} waves propagate via the extrusion of ATP into the extracellular space. ATP then acts in a paracrine fashion, binding purinergic receptors expressed on nearby astrocytes (COTRINA et al., 1998; GUTHRIE, et al., 1999). Therefore, the development of live-cell imaging technology has now revealed the existence of the astrocytic "excitable cytoplasm," similarly to the venerable demonstration of the axonal excitable membrane by Hodgkin, Huxley, in the 1930s. The discovery of excitable astrocytes begged the question of whether these cells could actively drive the abnormal neuronal changes underlying epilepsy. Indeed, astrocytic calcium waves have properties that could facilitate seizures. They can propagate spatially and result in long-range changes in excitation of synaptically unconnected neurons (NEWMAN and ZAHS, 1998). In addition, astrocytic Ca^{2+} waves have a propagation velocity comparable to that of spreading depression, and it was found that Ca^{2+} waves often

precede spreading depression, although a cause–effect relationship between the two phenomena was not demonstrated (KUNKLER and KRAIG, 1998; BASARSKI et al., 1999; MARTINS-FERREIA et al., 2000).

4. TREATMENT

The primary focus of care for patients with epilepsy is the prevention of further seizures, which may, after all, lead to morbidity or even mortality (LAUTENSCHLAGER et al., 2003). The goal of treatment should be the maintenance of a normal lifestyle, preferably free of seizures and with minimal side-effects of the medication. Up to 70% of people with epilepsy could become seizure free with drug treatment. In 25–30% of people with epilepsy the seizures cannot be controlled with drugs. Epilepsy surgery is a safe and effective alternative treatment in selected cases (WHO, 2006). Attention to the psychosocial, cognitive, educational and vocational aspects is an important part of comprehensive epilepsy care (TOUT, 1999).

Drug therapy is approached to symptom control, i.e., suppression of seizures. Therefore drugs used for the treatment of epileptic patients should be referred to as anticonvulsive drugs and not as antiepileptic drugs, since they do not cure epilepsy. The mechanisms of action by which they act are not well understood but it involves an alteration of the balance between neuronal inhibition and excitation (WHITE, 1999). There are three recognized basic mechanisms of action at a cellular level: modulation of voltage-gated ion channels (Na^+, $Ca2^+$, K^+), enhancement of GABA mediated inhibitory neurotransmission and attenuation of Glu mediated excitatory transmission (KWAN et al., 2001).

4.1. Voltage-gated ion channels

Voltage-gated ion channels regulate the flow of ions across cell membranes. Upon depolarization, Na^+ channels activate leading to ion flux into the cell and thus propagate the action potential. Then the channel enters to an inactivated state. In this state the channel cannot re-activate. Repolatization occurs when the neuronal membrane can convert the channel back to the resting state from which it can re–convert to an open state (CATTERALL, 1992; RASDALE and AVOLI, 1998). Neuronal Na^+ channels can cycle through these conformational states in only a few milliseconds. This process is crucial to maintain normal brain functions but at the same time is implicated in generating epileptic discharges. Neuronal Na^+ channels are one of the most important targets for anticonvulsive drugs (UPTON, 1994; MACDONALD and KELLY, 1995; MELDRUM, 1996; WHITE, 1999).

Most of the anticonvulsive drugs used in the treatment of epilepsy bind to the inactivated state of sodium channels and thus produce a voltage- and frequency-dependent reduction in channel conductance. This in turn limits the repetitive neuronal firing but has no effect on the generation of single action potentials (KWAN et al., 2001).

Voltage–sensitive calcium channels are often recruited in response to initial sodium-dependent action potential generation and therefore are also implicated in depolarization. Calcium channels can be classified into high and low threshold, according to the membrane potential at which they are activated (HOFMANN et al., 1994). Several anticonvulsive drugs have been reported to target voltage-sensitive Ca^{2+} channels in a subtype-specific manner (STEFANI et al., 1997).

Potassium channels are implicated in excitability at a neuronal level. They are involved in the repolarization of the plasma membranes after Na^+ channel activation (PONGS, 1999) and hence limiting action potential firing (PORTER and ROGAWSKI, 1992). Consequently, K^+ channel blockers precipitate seizures (YAMAGUCHI and ROGAWSKI, 1999), whereas K^+ channel activators have anticonvulsivant effects in some experimental seizure models (GANDOLFO et al., 1989; ROSTOCK et al., 1996).

4. 2. GABA mediated inhibition

GABA is the primary inhibitory neurotransmitter. In neurons there are 2 types of GABA receptors; receptors "A" which open chloride channels and hyper polarize cells, and "B" which open K^+ and Ca^{++} channels. The GABA A receptor has provided an excellent target for the development of drugs with an anticonvulsant action. Impairment of GABA function is known to provoke seizures (LÖSCHER, 1999). By modifying GABA level, one can modify seizure expression. De-

creased GABA synthesis can lower seizure threshold. On the other hand, increasing GABA raises seizure threshold. Several anticonvulsive drugs exert their action by modulating the GABAergic-system either by increasing GABA synthesis, increasing release or allosteric receptor facilitation. For example, some drugs elevate brain GABA levels by inhibiting the enzyme GABA transaminase, which is responsible for intracellular GABA catabolism. Others, elevate synaptic GABA levels by inhibiting the GABA uptake transporter, GAT1, and prevent the uptake of GABA into neurons and glia. Some of these anticonvulsive drugs act by enhancing GABA synthesis and also by decreasing neuronal calcium influx via a specific subunit of voltage-dependent calcium channels. The GABA system also represents one of the most successful targets for the rational design of new anticonvulsive drugs (LÖSCHER, 1998).

4.3. Glutamate mediated excitatory transmission

Glu is one of the principal excitatory neurotransmitters in the mammalian brain (MELDRUM, 2000). However none of the commonly used anticonvulsants exerts their pharmacological action by solely modulating the glutamate system. Nevertheless it has been reported that blockage of ionotropic glutamate receptors and reduction of Glu release is the way some anticonvulsive drugs act although the latter effect may be more indicative of their actions on Ca^{2+} channels than a direct effect on the glutamate system (KWAN et al., 2001). Furtheremore Hassel et al. showed an increase in glutamate transport under chronic valproate (VPA) treatments in hippocampal preparations (HASSEL et al., 2001). Recently, Aguirre et al. defined GLAST up-regulation by VPA at different levels in Bergman glial cells (Aguirre personal comunication). These data also highlight the astrocytes key role normal neurotransmission, as well as their potential involvement in the etiology or correction of varied epilepsy conditions (ROGAWSKI, 2005).

5. CONCLUDING REMARKS

With the exception of migraine, the epilepsies are the most common episodic neurological disorders. Epilepsy can be defined by a group of disorders that leads to recurrent and unpredictable interruptions of normal brain function. However, the understanding of cellular and molecular bases of human seizure susceptibility remained unclear. It now appears that some forms of idiopathic epilepsy are the result of specific defects in channel function. The discovery of ion channel mutations in rare genetic forms of epilepsy, such as BFNC, raises the possibility that genetically-determined alterations in ion channel structure, expression or regulation might play a role in susceptibility to the more common sporadic epilepsies. The characterization of such ion channel alterations, GABAergic and Glutamatergic proteins (receptors and transporters) regulation with their functional consequences lays the basis for the development of targeted, genotype-specific therapies.

Therefore it is not surprising that the current drugs used to treat epilepsy have such a diverse range of pharmacological actions. Identifying the complete and diverse mechanisms by which these drugs act is the immediate challenge. Worldwide, the proportion of patients with epilepsy who at any given time remain untreated is large, and is greater than 80% in most low income countries (SANDER, 1991; DREIFUSS, 1997). The size of this treatment gap reflects either a failure to identify cases or a failure to deliver treatment. In most situations, however, both factors will apply. Inadequate case-finding and treatment have various causes, some of which are specific to low income countries. They include people's attitudes and beliefs, government health policies and priorities (or the lack of them), treatment costs and drug availability, as well as the attitude, knowledge and practice of health workers. In addition, there is clear scarcity of epilepsy-trained health workers in many low income countries. The lack of trained personnel and a proper health delivery infrastructure are major problems, which contribute to the overall burden of epilepsy (WHO, 2006).

We believe that one of the researchers goals should be to inform the general public about these disease, and in the future clarify the diferent mechanisms that undely this illness and try to find a real cure. Not only one that prevents the syntomatology but one that can prevent future generations from this disease.

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