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Review article

Pathophysiology of epilepsy

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Abstract

This work reviews the current knowledge on epileptogenesis and pathophysiology of epilepsy. Recently, gene defects underlying four monogenic epilepsies (generalized epilepsy with febrile seizures, autosomal dominant nocturnal frontal lobe epilepsy, benign familial neonatal convulsions and episodic ataxia type 1 with partial seizures) have been identified, shedding new light on the pathophysiology of epilepsy as these diseases are caused by ion channel mutations. Although epileptic syndromes differ pathophysiologically, common ictogenesis-related characteristics as increased neuronal excitability and synchronicity are shared as well as mechanisms involved in interictal-ictal transition. Emerging insights point to alterations of synaptic functions and intrinsic properties of neurons as common mechanisms underlying hyperexcitability. This work also reviews the neurochemical mechanisms of epilepsy. An imbalance between glutamate and γ-aminobutyric acid neurotransmitter systems can lead to hyperexcitability but catecholaminergic neurotransmitter systems and opioid peptides were shown to play a role in epileptogenesis as well. An overview of currently available anti-epileptic drugs and their presumed mechanisms of action is given as an illustration of the neurochemistry of epileptogenesis. Most anti-epileptic drugs exert their anti-epileptic properties through only a few neurochemical mechanisms that are meanwhile basic pathophysiological mechanisms thought to cause seizures.

Key words : Epilepsy ; pathophysiology ; epileptogenesis ; ictogenesis ; neurochemistry ; anti-epileptic drugs.

1. Introduction

Several decades have been devoted to the study of the pathophysiology of epilepsy. Increasing knowledge in the field only contributed to a partial understanding of the underlying mechanisms. Nevertheless, insight in the pathophysiology of epilepsy and its underlying histological and neurochemical alterations has contributed to rational development strategies of new anti-epileptic drugs (AEDs).

Although various epileptic syndromes were shown to differ pathophysiologically, they apparently share common ictogenesis-related characteristics such as increased neuronal excitability and synchronicity. Emerging insights point to alterations of synaptic functions and intrinsic properties of neurons as common mechanisms underlying hyperexcitability. Progress in the field of molecular genetics revealed arguments in favor of this hypothesis as mutations of genes encoding ion channels were recently discovered in some forms of human epilepsy.

This work reviews the current knowledge on the pathophysiology of epilepsy with special emphasis on ictogenesis, mechanisms of interictal-ictal transition and neurochemical mechanisms underlying epilepsy. Where possible, examples concerning pathophysiological mechanisms underlying distinct epileptic syndromes will be given.

2. Pathophysiology of epilepsy

Epileptic seizures arise from an excessively synchronous and sustained discharge of a group of neurons. The single feature of all epileptic syndromes is a persistent increase of neuronal excitability. Abnormal cellular discharges may be associated with a variety of causative factors such as trauma, oxygen deprivation, tumors, infection, and metabolic derangements. However, no specific causative factors are found in about half of the patients suffering from epilepsy.

Underlying causes and pathophysiological mechanisms are (partially) understood for some forms of epilepsy, e.g. epilepsies caused by disorders of neuronal migration and monogenic epilepsies. For several other types of epilepsy, current knowledge is only fragmentary.

2.1. DISORDERS OF NEURONAL MIGRATION

The major developmental disorders giving rise to epilepsy are disorders of neuronal migration that may have genetic or intrauterine causes (Meldrum, 1994). Abnormal patterns of neuronal migration lead to various forms of agyria or pachygyria whereas lesser degrees of failure of neuronal

migration induce neuronal heterotopia in the subcortical white matter. Recent experimental data suggest that cortical malformations can both form epileptogenic foci and alter brain development in a manner that diffuse hyperexcitability of the cortical network occurs (Chevassus au Louis *et al.*, 1999). Other studies revealed increases in postsynaptic glutamate receptors and decreases in γ-aminobutyric acid (GABA) (A) receptors in microgyric cortex which could promote epileptogenesis (Jacobs *et al.*, 1999).

Tuberous sclerosis is a developmental disorder with autosomal dominant inheritance in which disordered neuronal migration and epilepsy are commonly found. Periventricular heterotopia is an X-linked dominant disorder of cerebral cortical development. Fox *et al.* (1998) showed that mutations in the filamin 1 gene prevent migration of cerebral cortical neurons causing periventricular heterotopia. Affected females present with epilepsy whereas affected males die embryonically. Recently, however, a male patient with bilateral periventricular and subcortical heterotopia was described which raises the possibility of a novel gene involved in brain formation (Sisodiya *et al.*, 2000). X-linked lissencephaly and double cortex syndrome is another disorder of neuronal migration. Double cortex or subcortical band heterotopia often occurs in females whereas more severe lissencephaly is found in affected males. A causal mutation in a gene called doublecortin was recently identified (Gleeson *et al.*, 1998). It was suggested that doublecortin acts as an intracellular signaling molecule critical for the migration of developing neurons (Allen and Walsh, 1999).

Although these disorders are relatively rare, studying the underlying pathophysiological mechanisms may shed light on the pathophysiology of more common epileptic syndromes.

2.2. Genetics of human epilepsy

Epilepsies with complex inheritance

About 40% of patients suffering from epilepsy have a genetic background that contributes to the aetiology of epilepsy (Gardiner, 2000). Most familial epilepsies like juvenile myoclonic epilepsy, childhood absence epilepsy, and benign childhood epilepsy with centrotemporal spikes have a complex mode of inheritance resulting from the interaction of several loci together with environmental factors (McNamara, 1999).

In patients with absence seizures (and their first degree relatives), biochemical changes (e.g. increased plasma glutamate levels) have been identified which can be related to a generalized increase in cortical excitability (Van Gelder *et al.*, 1980). Probably, the genetic predisposition of absence epilepsy is based on a gene-dependent biochemical derangement leading to increased cortical excitability. Genetic data generated by studies on animal models of absence epilepsy show a relative simple inheritance factor of one gene that determines being epileptic or not while other genes determine number and duration of epileptic fits (Renier and Coenen, 2000).

Monogenic epilepsies

Monogenic epileptic disorders are rare, accounting for no more than 1% of patients. Recent advances in the genetics and molecular biology of these diseases unravelled the underlying pathophysiology of some of these epileptic syndromes.

In 1996, Berkovic *et al.* described a new epileptic syndrome : familial temporal lobe epilepsy. Simple partial seizures with psychic or autonomic symptoms are frequently occurring seizure types whereas complex partial fits are infrequent. Pedigree analysis suggested autosomal dominant inheritance with age-dependent penetrance (Berkovic *et al.*, 1996). Linkage to chromosome 10q has been reported in one family but the genetic defect remains to be elucidated (Berkovic and Scheffer, 1997a).

Autosomal dominant partial epilepsy with auditory features is characterized by auditory hallucinations, although other sensory symptoms have been reported as well (Winamer *et al.*, 2000). Clinical semiology points to a lateral temporal localization which is supported by electroencephalogram (EEG)-data that revealed inconstant focal abnormalities over both temporal regions (Michelucci *et al.*, 2000). In a single case, brain Magnetic Resonance Imaging (MRI) showed atrophy with an increased T2 signal in the lateral portion of the right temporal lobe (Michelucci *et al.*, 2000). This epileptic syndrome was found to be linked to chromosome 10q22-24 (Winamer *et al.*, 2000).

Gene defects underlying four other monogenic epilepsies (generalized epilepsy with febrile seizures, autosomal dominant nocturnal frontal lobe epilepsy, benign familial neonatal convulsions and episodic ataxia type 1 with partial seizures) have recently been identified, shedding new light on the pathophysiology of epilepsy as these diseases are caused by ion channel mutations (Steinlein, 1998 ; Zuberi *et al.*, 1999).

Generalized epilepsy with febrile seizures type I is an autosomal dominant epileptic syndrome that is caused by a point mutation in the b_1-subunit of a voltage-gated Na^+ channel (Wallace *et al.*, 1998) whereas type II is caused by a point mutation in the a_1-subunit of a voltage-gated Na^+ channel (Escayg *et al.*, 2000). These mutations cause distinct types of epilepsy in different members of the same family, which may result from inheritance of the mutant gene in the context of other susceptibility genes or environmental factors (McNamara, 1999).

Benign familial neonatal convulsions is a syndrome that is inherited in an autosomal dominant pattern. Mutations of two distinct but related voltage-gated K^+ channel genes have been identified (Biervert *et al.*, 1998). Although both genes (KCNQ2 and KCNQ3) are located on different chromosomes (20q and 8q respectively), their co-expression explains how these 2 different mutations cause an identical disease phenotype.

In some families, autosomal dominant nocturnal frontal lobe epilepsy is caused by a point mutation in a gene on chromosome 20q (CHRNA4), encoding the a_4 subunit of the neuronal nicotinic acetylcholine (ACh) receptor (Steinlein *et al.*, 1995). At least some ACh receptors are located presynaptically, thus promoting the release of neurotransmitters as GABA. The mutant receptor causes a reduction of ACh-mediated Ca^{2+} flux, which results in a decrease of GABA released from presynaptic terminals leading to synaptic disinhibition (McNamara, 1999). However, the majority of the families with autosomal dominant nocturnal frontal-lobe epilepsy are not linked to CHRNA4, indicating the presence of genetic heterogeneity (Gardiner, 2000).

Episodic ataxia type 1 is a rare autosomal dominant disorder, characterized by brief episodes of ataxia associated with myokymia (Zuberi *et al.*, 1999). The patients suffering from this syndrome also show partial epileptic fits. The syndrome is associated with point mutations in the human voltage-gated potassium channel gene on chromosome 12p13 (Zuberi *et al.*, 1999). As potassium channels determine the excitability of neurons, it is suggested that this mutation is pathogenic (Zuberi *et al.*, 1999).

These recent discoveries illustrate that ion channel dysfunctions can play a crucial role in the pathophysiology of epilepsy. As several AEDs act on ion channels, these findings are relevant to other epileptic syndromes in man.

2.3. Pathophysiology of distinct types of epilepsy

Mesial temporal lobe epilepsy

Mesial temporal lobe epilepsy is characterized by recurrent complex partial seizures and hippocampal sclerosis. Ipsilateral to the epileptogenic focus, hippocampal neuronal loss results in significantly reduced hippocampal volumes as measured by means of MRI (Jokeit *et al.*, 1999). Besides hippocampal volumetry, MR proton spectroscopy was shown to be a valuable tool to correctly lateralize patients with mesial temporal lobe epilepsy (Kuzniecky *et al.*, 1998). In patients with intractable temporal lobe epilepsy, interictal Positron Emission Tomography (PET) studies found decreased [^{11}C]flumazenil (FMZ) binding (benzodiazepine receptor binding) and glucose metabolism at the medial thalamic nucleus (Juhász *et al.*, 1999). These findings are common and have strong lateralization value for the seizure focus in human temporal lobe epilepsy. The decreased benzodiazepine receptor binding possibly reflects neuronal loss but may also indicate decreased benzodiazepine receptor density in the medial thalamic nucleus which remains to be elucidated. This structure may indeed play an important role in temporal lobe epilepsy as the nucleus medialis thamali has strong reciprocal connections with other parts of the limbic system (Engelborghs *et al.*, 1998b ; Juhász *et al.*, 1999). Interictal PET studies revealed increased glucose metabolism and FMZ binding in the lateral thalamus of patients with temporal lobe epilepsy, possibly reflecting an upregulation of GABA-mediated inhibitory circuits (Juhász *et al.*, 1999).

A recent study investigated expression and distribution of GABA(A)-receptors in the hippocampus of pilocarpine-treated rats (Fritschy *et al.*, 1999). A loss of a critical number of interneurons in the gyrus dentatus was noticed, which might play a role in seizure initiation (Fritschy *et al.*, 1999). Meanwhile, long-lasting upregulation of GABA(A)-receptors in granule cells was found, which might represent a compensatory response to seizure activity (Fritschy *et al.*, 1999). Central benzodiazepine receptor density in the CA1 region was shown to be significantly reduced by means of autoradiography in post-mortem samples of patients with hippocampal sclerosis (Hand *et al.*, 1997). On the other hand, affinity for FM2 was increased in subiculum and gyrus dentatus (Hand *et al.*, 1997). Other publications suggest that enhanced sensitivity to glutamate may be an important element in the pathophysiology of temporal lobe epilepsy as a quantitative autoradiographic analysis of ionotropic glutamate receptor subtypes revealed an upregulation in the reorganized human epileptogenic hippocampus (Brines *et al.*, 1997).

Gelastic epilepsy

Gelastic seizures are frequently caused by hypothalamic hamartomas (Engelborghs *et al.*, 2000). In a series of 9 patients with gelastic seizures, 4 had hypothalamic hamartoma (Striano *et al.*, 1999). Hypothalamic hamartomas are rare congenital malformations and often present as a clinical syndrome, characterized by pubertas praecox, mental retardation, and gelastic seizures. Later, refractory epilepsy with multiple seizure types develops. Patients with hypothalamic hamartoma may as well have focal epileptiform discharges in the anterior temporal or frontal lobe on ictal electrocorticographic recordings but focal cortical resection was shown not to affect seizure frequency (Cascino *et al.*, 1993). According to depth electrode data showing ictal onset from the lesion, seizures seem to

begin in the intrinsically epileptogenic hamartoma (Munari *et al.*, 1995 ; Kuzniecky *et al.*, 1997). Ictal single-photon emission computed tomography performed during typical gelastic seizures demonstrated hyperperfusion in the hamartoma and the hypothalamic region (Kuzniecky *et al.*, 1997). Moreover, complete surgical extirpation or a gamma knife radiosurgical treatment of the hypothalamic hamartoma results in seizure remission (Kuzniecky *et al.*, 1997 ; Georgakoulias *et al.*, 1998 ; Unger *et al.*, 2000). It therefore seems probable that epileptic discharges arise in the hypothalamus and spread via hypothalamic-amygdala connections to produce focal temporal lobe ictal discharges (Saper, 1990 ; Berkovic *et al.*, 1997b).

Rasmussen encephalitis

Rasmussen encephalitis is a rare, progressive, neurodegenerative illness of unknown cause that typically affects children in the first decade of life (Rasmussen *et al.*, 1958). Severe seizures that are refractory to anti-epileptic medication, hemispheric atrophy, and dementia are cardinal features of this disease. Rabbits immunized with glutamate receptor subunit 3 (GluR3) protein developed epilepsy and cerebral histopathological changes characteristic of Rasmussen encephalitis (Rogers *et al.*, 1994). This led to the discovery of anti-GluR3 antibodies in serum of patients with Rasmussen encephalitis (Rogers *et al.*, 1994). Effectiveness of plasma exchanges or intravenous immunoglobin therapy as treatment of Rasmussen encephalitis was demonstrated in a series of patients (Andrews *et al.*, 1996 ; Topcu *et al.*, 1999), which further proves the auto-immune pathogenesis of Rasmussen encephalitis.

Insights gained from the study of Rasmussen encephalitis may help to increase our knowledge about more common forms of epilepsy. Some patients undergoing temporal lobectomy for refractory epilepsy show localized inflammatory histopathological changes and increased auto-antibodies in serum (Dambinova *et al.*, 1997 ; Peltola *et al.*, 2000) ; whether or not this is caused by an autoimmune pathogenesis remains to be elucidated (McNamara, 1999).

3. Kindling and epileptogenesis

Goddard (1967) was the first to describe that periodic stimulation of neural pathways progressively leads to recurrent behavioral and electrographic seizures. Kindling procedures have provided a substrate for the study of the role of enhanced synaptic efficacy in seizure disorders. It is now considered to be a first choice experimental procedure in the study of the potential mechanisms of epileptogenesis. The phenomenon can be evoked in various brain regions, but amygdala kindling is most frequently used in epilepsy research as a model for complex partial seizures (Fisher, 1989). Although kindling has been shown to be phenomenologically different from other types of plastic changes in the central nervous system (Sutula, 1991), there are many points of similarity between kindling and the process of long-term potentiation. Kindling has been shown to depend upon functional as well as structural changes in glutamatergic synapses. The anticonvulsant effects of glutamate receptor blocking agents like NMDA antagonists seem to be at least partly due to their inhibitory effects on in vitro kindling.

4. Ictogenesis

Excitability is a key feature of ictogenesis that may originate from individual neurons, neuronal environment or a population of neurons (Traub *et al.*, 1996). Excitability arising from single neurons may be caused by alterations in membrane or metabolic properties of individual neurons. When regulation of environmental, extracellular concentrations of ions or neurotransmitters is suboptimal, the resulting imbalance might enhance neuronal excitation. Collective anatomic or physiologic neuronal alterations may convert neurons into a hyperexcitable neuronal population. In reality, these three theoretical mechanisms are thought to interact during specific ictal episodes. Each epileptic focus is unique as the differential contribution of these three concepts leading to ictal events is thought to differ from focus to focus.

4.1. Excitability arising from individual neurons

Functional and perhaps structural changes occur in the postsynaptic membrane, thus altering the character of receptor protein - conductance channels, thereby favoring development of paroxysmal depolarizing shift (PDS) and enhanced excitability. Epileptic neurons appear to have increased Ca^{2+} conductance. It may be that latent Ca^{2+} channels are used, that the efficacy of Ca^{2+} channels is increased or that the number of Ca^{2+} channels is chronically elevated. However, development of burst activity depends on the net inward current and not on the absolute magnitude of the inward current. When extracellular K^+ concentrations are increased (as during seizure activity), the K^+ equilibrium across the neuronal membrane is reduced, resulting in reduced outward K^+ currents. The net current will become inward, depolarizing the neuron to the extent that Ca^{2+} currents will be triggered. This results in a PDS and a burst of spikes (Fig. 1) (Dichter, 1997).

4.2. Excitability arising from neuronal microenvironment

Both functional and structural alterations occur in epileptic foci. The functional changes involve

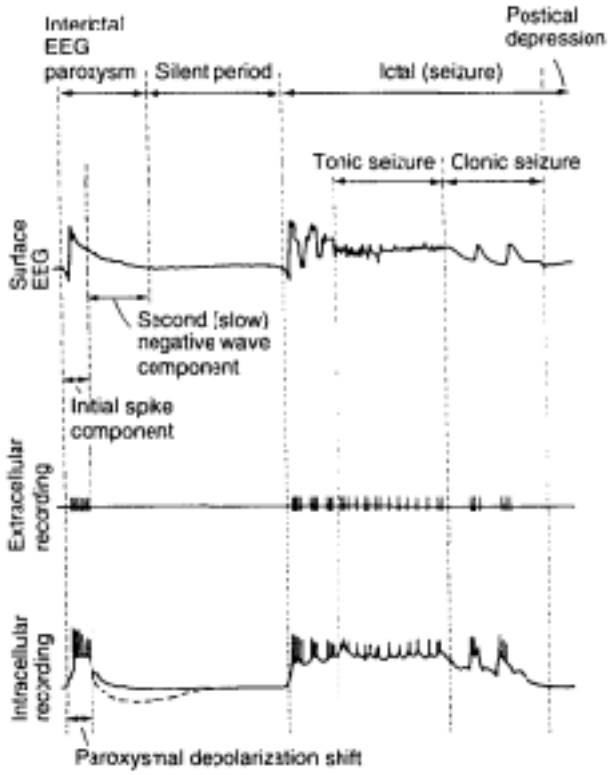

FIG. 1. — The hallmark of a discharge is the paroxysmal depolarization shift. The ability to record such events at the scalp suggests that numerous neurons are firing in synchrony (From : Browne T.R., Feldman R.G., eds. Epilepsy : Diagnosis and Management. Boston : Little, Brown and Company, 1983, p.12).

concentrations of cations and anions, metabolic alterations, and changes in neurotransmitter levels. The structural changes involve both neurons and glia. Excessive extracellular K^+ depolarizes neurons and leads to spike discharge. During seizures, changes in extracellular Ca^{2+} (a decrease of 85%) precede those of K^+ by milliseconds and Ca^{2+} levels return to normal more quickly than K^+.

Glia are able to clear neurotransmitters from the extracellular space and to buffer K^+ thus correcting the increased extracellular K^+ concentrations that occur during seizures. Epileptic foci may show proliferation of glia that differ however in morphological and physiological properties (Bordey and Sontheimer, 1998). Gliosis will affect glial K^+ buffering capacity and hence may contribute to seizure generation (Grisar *et al.*, 1999).

4.3. The epileptic cell population

Collective anatomic or physiologic neuronal alterations might produce progressive, network-dependent facilitation of excitability, perhaps coupled with a decrease of inhibitory influences, e.g. due to selective loss of inhibitory neurons. Mossy fiber sprouting (MFS) is an example of neuronal alterations leading to increased excitability (Cavazos *et al.*, 1991).

MFS was demonstrated in patients with refractory temporal lobe epilepsy with hippocampal sclerosis on neuroimaging as well as in numerous animal models of temporal lobe epilepsy (Sutula *et al.*, 1988 ; Sutula *et al.*, 1989). In normal conditions, the dentate granule cells limit seizure propagation through the hippocampal network. However, the formation of recurrent excitatory synapses between dentate granule cells, as is thought to occur after MFS, may transform the dentate granule cells into an epileptogenic population of neurons (Figure 2) (McNamara *et al.*, 1999). Possibly, a vicious circle develops : seizures cause neuronal death which results in MFS which in turn increases seizure frequency.

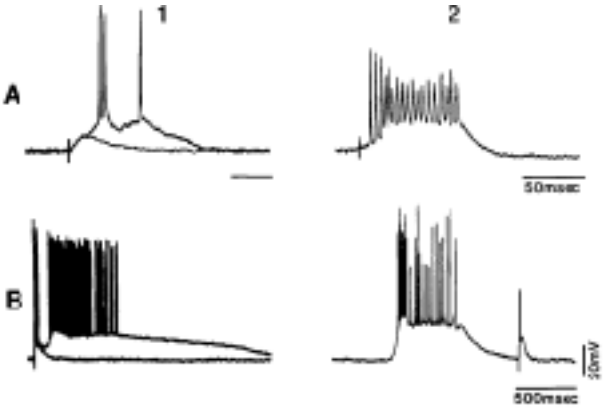

FIG. 2. — Many central neurons burst, but rarely in a prolonged manner (panel A). In an epileptic focus, neurons burst spontaneously and for prolonged periods (note the paroxysmal depolarization shift) (panel B).

5. Mechanisms of interictal-ictal transition

Mechanisms producing signal amplification, synchronicity, and spread of activity are likely to be involved in interictal-ictal transitions. Different theoretical mechanisms of interictal-ictal transition are summarized in table 1 and discussed in the following section. In vivo, interictal-ictal transition can seldom be attributed to one theoretical mechanism, but often results from the interaction of different mechanisms.

5.1. Nonsynaptic mechanisms

Alterations in ionic microenvironment

Repetitive ictal and interictal activity causes increases in extracellular K^+ leading to increased neuronal excitability (Moody *et al.*, 1974). Some neurons are very sensitive to changes in membrane K^+ currents, e.g. pyramidal cells in the CA1 region of the hippocampus (Rutecki *et al.*, 1985).

Table 1

Summary of mechanisms of interictal-ictal transition

Nonsynaptic mechanisms
1. Alterations in ionic microenvironment ; e.g. increased extracellular K^+, decreased extracellular Ca^{++}
2. Decreases in size of extracellular space
3. Failure of ion transport : Na^+-K^+ pump or Cl^--K^+ co-transport
4. Presynaptic terminal bursting
5. Ephaptic interactions
Synaptic mechanisms
1. Depression of GABA-ergic inhibition
2. NMDA receptor activation ; voltage-dependent EPSPs
3. Frequency potentiation of EPSPs
4. Actions of modulators

Active ion transport

Activation of the Na^+-K^+ pump is important for regulation of neuronal excitability during excessive neuronal discharges (Ayala *et al.*, 1970). Substances like ouabain that block the Na^+-K^+ pump can induce epileptogenesis in animal models. Hypoxia or ischemia can result in Na^+-K^+ pump failure thus promoting interictal-ictal transition.

A Cl^--K^+ co-transport mechanism controls the intracellular Cl^- concentration and the Cl^- gradient across the cell membrane which regulates effectiveness of GABA-activated inhibitory Cl^- currents. Interference with this process could cause a progressive decrease in the effectiveness of GABA-ergic inhibition leading to increased excitability (Prince, 1988).

Presynaptic terminal bursting

The amount of transmitter released is related to depolarization of presynaptic terminals. Changes in axon terminal excitability will have effects on synaptic excitation (Prince, 1988).

Abnormal bursts of action potentials occur in the axonal arborizations of thalamocortical relay cells during epileptogenesis. Since one thalamocortical relay cell ends on a large number of cortical neurons, synchronization can occur which might play an important role in interictal-ictal transition (Engelborghs *et al.*, 1998b).

Ephaptic interaction

Ephaptic interactions are produced when currents from activated neurons excite adjacent neurons in the absence of synaptic connections. Ephaptic effects are strongly dependent on the size of the extracellular space. When extracellular space is small, ephaptic interactions are promoted (Traub *et al.*, 1985).

5.2. Synaptic mechanisms

Two theoretical mechanisms can occur : decreased effectiveness of inhibitory synaptic mechanisms or facilitation of excitatory synaptic events. Both mechanisms will be discussed in the following section.

6. Neurochemical mechanisms underlying epilepsy

6.1. GABA

The GABA hypothesis of epilepsy implies that a reduction of GABA-ergic inhibition results in epilepsy whereas an enhancement of GABA-ergic inhibition results in an anti-epileptic effect (De Deyn *et al.*, 1990). Inhibitory postsynaptic potentials (IPSPs) gradually decrease in amplitude during repetitive activation of cortical circuits. This phenomenon might be caused by decreases in GABA release from terminals, desensitization of GABA receptors that are coupled to increases in Cl^- conductance or alterations in the ionic gradient because of intracellular accumulation of Cl^- (Wong and Watkins, 1982). In case of intracellular accumulation of Cl^-, passive redistribution is ineffective. Moreover, Cl^--K^+ co-transport becomes less effective during seizures as it depends on the K^+ gradient. As Cl^--K^+ co-transport depends on metabolic processes, its effectiveness may be affected by hypoxia or ischemia as well. These mechanisms may play a critical role in ictogenesis and interictal-ictal transition.

Several studies have shown that GABA is involved in pathophysiology of epilepsy in both animal models and patients suffering from epilepsy. GABA levels and glutamic acid decarboxylase (GAD) activity were shown to be reduced in epileptic foci surgically excised from patients with intractable epilepsy and in CSF of patients with certain types of epilepsy (De Deyn *et al.*, 1990). In stiff-man syndrome, a disease associated with epilepsy and diabetes mellitus, auto-antibodies to GAD were demonstrated (Solimena *et al.*, 1988). A reduction of ^{3}H-GABA binding has been reported in human brain tissue from epileptic patients whereas PET studies demonstrated reduced benzodiazepine receptor binding in human epileptic foci (Savic *et al.*, 1996). The degree of benzodiazepine receptor reduction showed a positive correlation with seizure frequency.

The GABA receptor complex is involved in various animal models of epilepsy as well. Low CSF levels of GABA were revealed in dogs with epilepsy (Löscher and Swartz-Porsche, 1986). Reduced GAD levels were revealed in the substantia nigra of amygdala-kindled rats (Löscher and Schwark, 1985). Significant alterations in GABA and benzodiazepine binding have been shown in

the substantia nigra of genetically seizure-prone gerbils (Olsen *et al.*, 1985). Mice with a genetic susceptibility to audiogenic seizures have a lower number of GABA receptors than animals of the same strain that are not seizure prone (Horton *et al.*, 1982).

Several endogenous (guanidino compounds) and exogenous (e.g. bicuculline, picrotoxin, penicillin, pilocarpine, pentylenetetrazol) convulsants inhibit GABAergic transmission through inhibition of GABA synthesis or through interaction with distinct sites at the postsynaptic GABA(A) receptor (De Deyn and Macdonald, 1990 ; De Deyn *et al.*, 1992 ; D'Hooge *et al.* 1999). Convulsant agents that block synaptic GABA-mediated inhibition, amplify the dendritic spike-generating mechanism that involves Ca^{2+} (Dichter and Ayala, 1987 ; Fisher, 1989). Synaptic inputs are thought to trigger and synchronize this process throughout a population of cells which then might result in an epileptic fit.

Several AEDs are GABA analogues, block GABA metabolism (e.g. vigabatrin, tiagabine, valproate) or facilitate postsynaptic effects of GABA. However, a study evaluating dose-dependent behavioral effects of single doses of vigabatrin in audiogenic sensitive rats, suggests that the anti-epileptic properties of vigabatrin not only depend on GABA-ergic neurotransmission but might also be explained by decreased central nervous system levels of excitatory amino acids or increased glycine concentrations (Engelborghs *et al.*, 1998a).

6.2. Glutamate

Glutamatergic synapses play a critical role in all epileptic phenomena. Activation of both ionotropic and metabotropic postsynaptic glutamate receptors is proconvulsant. Antagonists of N-methyl-D-aspartate (NMDA) receptors are powerful anti-convulsants in many animal models of epilepsy. Several genetic alterations have been shown to be epileptogenic in animal models but no specific mutation relating to glutamatergic function has yet been linked to a human epilepsy syndrome. Nevertheless, there is evidence for altered NMDA receptor function in acquired epilepsy in animal models and in men. An increased sensitivity to the action of glutamate at NMDA receptors is seen in hippocampal slices from kindled rats and in cortical slices from cortical foci in human epilepsy (Hwa and Avoli, 1992). This results in an enhanced entry of Ca^{2+} into neurons during synaptic activity (Louvel and Pumain, 1992). Changes in metabotropic glutamate receptor function may also play a key role in epileptogenesis (Chapman, 1998).

Epileptic seizures and epilepsy form frequent complications of uremia. As a possible underlying mechanism, we have demonstrated the accumulation of a series of uremic guanidino compounds which were shown to inhibit GABA-ergic neurotransmission (De Deyn and Macdonald, 1990). One of these endogenous agents was in addition shown to be an agonist at the excitatory NMDA receptor (D'Hooge *et al.*, 1996 ; De Deyn *et al.*, in press (a)).

In patients with absence seizures, plasma glutamate levels were found to be significantly increased (Van Gelder *et al.*, 1980). Neuronal membranes are exposed to increased amounts of extracellular glutamate thus increasing neuronal excitability. A recent study on a genetic rat model of epilepsy (WAG/RIJ rats ; spontaneous spike-wave (SW) discharges accompanied by behavioral abnormalities) provides evidence for an interaction of glutamatergic and serotonergic mechanisms in the triggering and maintenance of epilepsy (Filakovszky *et al.*, 1999). Intracerebroventricular injection of 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), a 5HT1A receptor agonist, caused marked increase of the cumulative duration and number of SW discharges whereas dizocilpine (MK-801), a NMDA receptor antagonist, decreases SW discharges (Gerber *et al.*, 1998). Both substances opposed each other's effects in this rat model of epilepsy.

6.3. Catecholamines

Abnormalities of CNS catecholamines have been reported in several genetic models of epilepsy. In spontaneous epileptic rat, dopamine was decreased in the nucleus caudatus whereas noradrenaline was increased in midbrain and brainstem (Hara *et al.*, 1993). Decreased levels of dopamine have been found in epileptic foci of epilepsy patients (Mori *et al.*, 1987). In animal models of absence epilepsy, seizures are exacerbated by dopamine antagonists while fits are alleviated by dopamine agonists (Snead, 1995). These results suggest that decreased dopamine facilitates appearance of seizures by lowering the threshold triggering such seizures.

Tottering mice have an absence-like syndrome that is characterized by episodes of behavioral arrest associated with 6 to 7 Hz cortical SW EEG discharges. Selective destruction of the ascending noradrenergic system at birth prevents the onset of the syndrome. Therefore, it has been suggested that the syndrome is caused by a noradrenergic hyperinnervation of the forebrain (Meldrum, 1994).

Recent data indicate that the serotonergic system regulates epileptiform activity in a genetic rat model of absence epilepsy as intraperitoneal or intracerebroventricular administration of 8-OH-DPAT caused marked and dose-dependent increases in number and duration of SW discharges (Gerber *et al.*, 1998).

6.4. Opioid peptides

In experimental studies, opioids and opioid peptides had both convulsant and anticonvulsant properties (Meldrum, 1994). Kappa agonists suppress SW discharges in an animal model of abscence epilepsy (Przewlocka *et al.*, 1995). Peptides with a m agonist action induce hippocampal or limbic seizures when administered intraventricularly possibly due to inhibition of inhibiting interneurons. In patients with complex partial seizures, PET studies pointed out that m receptor density is increased in the temporal cortex (Mayberg *et al.*, 1991).

7. Pathophysiology of epilepsy and mechanisms of action of AEDs

(Levy *et al.*, 1995 ; Macdonald and Kelly, 1995 ; Thomas, 1999)

Most of the presently used AEDs were discovered by screening without a rationale as to the mechanism of action. As knowledge on the pathophysiology of epilepsy increases and the mechanisms of action of most AEDs are at least partially unravelled, it becomes clear that most AEDs exert their anti-epileptic properties through only a few neurochemical mechanisms that are meanwhile basic pathophysiological mechanisms thought to cause epileptic fits (table 2). Thanks to increased use of animal models of epilepsy, a better insight in the pathophysiology of epilepsy and improved knowledge on mechanisms of action of AEDs, several new more rationally designed AEDs were developed and marketed during the past decade (De Deyn *et al.*, in press (b)).

Established AEDs decrease neuronal membrane excitability by interacting with ion channels or neurotransmitter receptor complexes. AEDs that decrease membrane excitability through interaction with ion channels act on sodium and calcium channels. Most AEDs that interact with neurotransmitter complexes promote inhibitory GABA-ergic neurotransmission although some more recently developed drugs act through inhibition of excitatory neurotransmission as well. The most frequently used AEDs and their (presumed) mechanisms of action are summarized in table 3.

Numerous AEDs interfere with ion channel functioning. Both ethosuximide and valproate block voltage-dependent Ca^{++} channels of the T-type which explains their anti-epileptic efficacy in generalized absence epilepsy (Stefani *et al.*, 1997). Carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate and zonisamide are known to reduce voltage-dependent Na^{+} currents.

Several established AEDs promote inhibitory neurotransmission. Vigabatrin is an enzyme-activated irreversible inhibitor of GABA-transaminase and has a weaker GABA uptake inhibitory effect whereas tiagabine is a pure GABA uptake inhibitor. Both AEDs thus increase the functional pool of GABA. Benzodiazepines enhance GABA-ergic inhibition through interaction with the GABA (A) receptor. Till present, progabide is the only AED exerting GABA agonistic effects at both type A and B sites. Several other AEDs have (weaker) GABA-ergic properties but act on other mechanisms as well. The main mechanism underlying phenobarbital's anti-epileptic effects is attributed to

Table 2

Correlation between mechanisms of epileptogenesis and mechanisms of action of AEDs

	Mechanisms of epileptogenesis	Mechanisms of actions of AEDs
GABA	• Reduced GABA in microgyric cortex • Reduced benzodiazepine receptor binding in medial thalamic nucleus (*mesial temporal lobe epilepsy*) • Reduced benzodiazepine receptor density in CA1 region (*hippocampal sclerosis*) • Reduced GABA levels and GAD activity (*epileptic foci*) • Auto-antibodies to GAD (*Stiff-man syndrome*)	• Increased functional pool of GABA (*vigabatrin, tiagabine*) • Enhanced GABA-ergic inhibition (*benzodiazepines*) • GABA agonistic effects (*progabide*) • (Weaker) GABA-ergic properties (*phenobarbital, gabapentin, topiramate, valproate, zonisamide*)
Glu	• Upregulation of hippocampal ionotropic glutamate receptors (*temporal lobe epilepsy*) • Anti-gluR3 antibodies (*Rasmussen encephalitis*) • Increased plasma glutamate levels (*absence seizures*)	• Inhibition of glutamate release (*lamotrigine*) • Block of glycine site at NMDA receptor (*felbamate*)
Na^{+}	• Mutation voltage-gated Na^{+} channel (*generalized epilepsy with febrile seizures*)	• Reduction of voltage-gated Na^{+} currents (*carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, topiramate, valproate, zonisamide*)
K^{+}	• Mutation voltage-gated K^{+} channel (*benign familial neonatal convulsions*)	
Ca^{++}	• Reduced ACh-mediated Ca flux (*nocturnal frontal lobe epilepsy*)	• Reduction of T-type Ca^{++} currents (*ethosuximide, valproate*)
	→ Increased membrane excitability	→ Decreased membrane excitability

Table 3

Mechanisms of actions of anti-epileptic agents

Anti-epileptic agent	Mechanism(s) of action
Benzodiazepines	Enhances GABA action Reduces sustained repetitive firing
Carbamazepine	Blocks voltage-dependent Na^+ channels Limitation of sustained repetitive firing
Ethosuximide	Reducing T-type Ca^{++} currents Blocking synchronized thalamic firing
Felbamate	Inhibition of glutamatergic neurotransmission (reduces NMDA action, blocks glycine-site on NMDA receptor) GABA potentiation Blocks voltage-dependent Na^+ channels Blocks L-type Ca^{++} channels
Gabapentin	GABA analog but does not bind to GABA receptors Increases synaptic GABA : activation of Glutamic Acid Decarboxylase ? May block amino acid transporter Binds to voltage-dependent Ca^{++}channels Æ reduced intraneuronal concentration of Ca^{++} Possibly : inactivation of Na^+ channels
Lamotrigine	Reduces glutamate release Inhibits voltage-activated Ca^{++} currents, blocks voltage-dependent Na^+ channels
Levetiracetam	Unknown mechanism of action Increases seizure threshold and inhibits seizure spread in kindled rats
Oxcarbazepine	Inhibition of voltage-dependent Na^+ channels Inhibition of voltage-activated Ca^{++} currents
Phenobarbital	Enhances GABA action Reduces sustained repetitive firing Reduces voltage-dependent Ca^{++} currents
Phenytoin	Blocks voltage-gated Na^+ channels Reduces Ca^{++} currents
Primidone	Reduces sustained repetitive firing - blocks voltage-dependent Na^+ currents
Progabide	GABA agonist at A and B sites
Remacemide	NMDA receptor antagonist Inactivation of Na^+ channels
Tiagabine	Neuronal and glial GABA-uptake inhibitor
Topiramate	Na^+ channel block Reduction of L-type Ca^{++} currents Potentiation of GABA at the GABA(A) receptor : enhancement of Cl^- flux Inhibition of glutamatergic neurotransmission : weak block of AMPA/kainate receptors Inhibition of carbonic anhydrase
Valproate	Increases CNS GABA levels by increased synthesis and reduced catabolism Blocks T-type Ca^{++} currents Enhances Na^+ channel inactivation
Vigabatrin	GABA-Transaminase inhibitor Inhibits GABA uptake
Zonisamide	Blocks Na^+ channels Blocks T-type Ca^{++} channels Enhances GABA action Inhibition of carbonic anhydrase

the reduction of voltage-dependent Ca^{++} currents although this drug enhances GABA-ergic neurotransmission as well. Gabapentin, topiramate, valproate and zonisamide are other examples of drugs that have amongst others GABA-ergic properties.

Lamotrigine is currently the best example of a drug acting through excitatory neurotransmission as it inhibits the release excitatory amino acids, especially glutamate. Although lamotrigine also blocks ion channels, its effect on glutamate release is thought to be primarily responsible for anti-epileptic properties. Felbamate blocks the glycine site at the NMDA receptor which is at least partially related to its anti-epileptic effects. Besides ion channel inhibition and potentiation of GABA-ergic neurotransmission, topiramate interferes with excitatory neurotransmission as it weakly blocks amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors.

A link between from one side the preclinical profile and mechanisms of action of AEDs and from the other side clinical profile can be made. In general, AEDs exerting anti-epileptic properties through interaction with one single mechanism of action, have a narrow clinical profile (e.g. ethosuximide). However, most AEDs interfere with a combination of basic mechanisms of anti-epileptic action such as inhibitory neurotransmission and Na

and/or Ca channel functioning (e.g. valproate). The relative importance of basic mechanisms of anti-epileptic action involved (partially) determines the clinical profile of AEDs. Drugs effective against myoclonic seizures generally enhance GABA-ergic inhibition. Drugs effective against generalized tonic-clonic and partial seizures appear to reduce sustained high-frequency repetitive firing by delaying recovery of Na^+ channels from activation (e.g. carbamazepine, valproate). It has been suggested that T-type Ca^{++} channels of thalamic relay neurons play a critical role in the generation of 3 Hz spike-and-wave discharges that characterize generalized absence epilepsy. Indeed, drugs that block T-type Ca^{++} currents are effective against generalized absence seizures (ethosuximide, valproate).

Conclusions

Although different epileptic syndromes differ pathophysiologically, ictogenesis-related mechanisms are often shared. The study of rare epileptic syndromes as monogenic epilepsies shed new light on ictogenesis and consequently substantially increased our knowledge and understanding of the pathophysiology of epilepsy. It now is generally accepted that ictogenesis mainly results from neuronal membrane hyperexcitability. Both neurotransmitter systems and ion channels play a crucial role in neuronal excitability.

Most of the presently used AEDs were discovered by screening without a rationale as to the mechanism of action. As our knowledge on the pathophysiology of epilepsy increases and the mechanisms of action of most AEDs are at least partially unravelled, it becomes clear that most AEDs exert their anti-epileptic properties through only a few neurochemical mechanisms leading to decreased neuronal membrane excitability. At this point, pathophysiological mechanisms of ictogenesis meet with mechanisms of action of AEDs. This knowledge allowed linking preclinical mechanisms of action with clinical profiles of AEDs. A more detailed understanding of the pathophysiology of epilepsy and epileptogenesis will thus further contribute to still more specific and efficacious pharmacological interactions in this field of clinical neurology.

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