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Pathophysiology of epilepsy: An updated review

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Abstract
The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizures originate from the grey matter of any cortical or subcortical area. Cytokines and other inflammatory mediators play an important role in epileptogenesis. Inflammations in human epileptic brain have been evidenced. Cytokines are important factors to cause neuronal excitability. Neurochemical changes are the main mechanisms underlying in epilepsy. These include GABA, catecholamine, alterations of ionic environment viz. potassium channels, sodium channels and calcium channels. Thus, the involvement of oxidative stress in epileptogenesis is well reported.

Keywords: Cytokines, GABA, sodium channels, calcium channels

Introduction

Pathophysiology of epilepsy

Seizures are paroxysmal manifestations of the cerebral cortex. A seizure results when a sudden imbalance occurs between the excitatory and inhibitory forces within the network of cortical neurons. The basic physiology of a seizure episode is detected to in an unstable cell membrane or its surrounding/adjacent supportive cells. The seizure originates from the grey matter of any cortical or subcortical area (Hirtz *et al.*, 2007) [1]. Initially a small number of neurons fire abnormally. Normal membrane conductance and inhibitory synaptic current breakdown and excess excitability spread either locally to produce a focal seizure or more widely to produce a generalized seizure. This onset propagates by physiologic pathways to involve adjacent to remote areas. As abnormality of potassium conductance, a defect in the voltage activated ion channels, or a deficiency in the membrane ATPase linked to ion transport may cause neuronal membrane unstable and cause a seizure. Certain neurotransmitters (e.g. glutamate, aspartate, acetyl choline, norepinephrine, histamine, corticotrophin releasing factor, purines, peptides, cytokines and steroid hormones) enhance the excitability and propagation of neuronal activity, whereas a-amino butyric acid (GABA) and dopamine inhibit neuronal activity and propagation. During a seizure, the demand for blood flow to the brain increases to carry off CO_2 and to bring substrate for metabolic activity of the neurons, as the seizure prolongs, the brain suffers more from ischemia that may result in neuronal destruction and brain damage. Mutation in several genes may be linked to some types of epilepsy. Genes that code for protein subunits of voltage-sensitive and ligand-activated ion channels have been associated with the generalized epilepsy and infantile seizure syndromes. One speculated mechanism for some forms of inherited epilepsy are mutation of the genes which code for sodium channel proteins these defective sodium channels remain open for long time and causing the neurons hyper excitable as a result glutamate an excitatory neurotransmitter may be released in large amount form the neurons which by binding with nearby glutamatergic neurons triggers excessive calcium (Ca^{2+}) release in the post synaptic cells 16 which may be neurotoxin to the affected cells (Meisler *et al.*, 2005) [2].

Inflammation has been implicated in the progressive nature of neurodegenerative diseases, and inflammatory processes are now considered key contributors to acute and chronic neurodegenerative disorders, such as ischemic stroke and Alzheimer's disease. In the last decade, experimental and clinical findings support a crucial role of inflammatory processes in epilepsy, in particular in the mechanisms underlying the generation of seizures. Since inflammation represents a homeostatic response to brain injury or pathological threats, its involvement in epilepsy should be envisaged when the extent or duration of inflammatory processes in brain tissue is exceeding the homeostatic threshold.

Sources and Targets of Cytokines and Inflammatory Mediators in Epileptic Tissue

Experimental evidence in rodents demonstrates that seizures induce high levels of inflammatory mediators in brain regions involved in the generation and propagation of epileptic activity. In particular, a rapid-onset inflammatory response is triggered in glia by seizures induced by chemo convulsant or electrical stimulation (Medel-Matus *et al*, 2014) [3]. Prototypic inflammatory cytokines such as interleukin (II)-1b, IL-6 and TNF-α are upregulated in activated microglia and astrocytes, and then trigger a cascade of downstream inflammatory events that also involves neurons and endothelial cells of the blood-brain harrier (BBB) (i.e., activation of NFkB, COX-2, complement system, chemokines, acute phase proteins) (Vezzani *et al.*, 2011) [4]. The rapid release of high-mobility-group box 1 (HMGB1) from neurons, microglia. and astrocytes following pro-convulsant injuries, and its activation of Toll-like receptor (TLR) signalling in astrocytes and neurons has been proposed as a crucial event for initiating brain inflammation and decreasing seizure threshold (Maroso *et al.*, 2010). HM6B1 is considered to be a danger signal released from injured or stressed cells to alert the microenvironment of an immediate or ongoing injury. Its interaction with cognate TLR4 triggers innate immune

mechanisms in tissue and activates the related inflammatory events. Penetration into the brain parenchyma of leukocytes has also been described after seizure occurrence (Turrin and Serge, 2004) [6], likely as a consequence of activation of innate immunity in the brain (i.e., microglia and astrocytes derived inflammatory mediators) and upregulation of adhesion molecules in endothelial cells of the BBB. Investigation of the pattern of expression of cytokine receptors in seizures has given information on the cell populations targeted by the cytokines. IL-IRI, which mediates the biological responses to 1L-10, is rapidly increased in neurons after seizures, as well as later in astrocytes (Ravizza *et al.,* 2008), thus indicating both paracrine and autocrine actions of IL-1β acting as a soluble mediator of glioneuronal communications in epileptogenic tissue. Strong IL-I b and 1L-1R I immunoreactivity is found also in perivascular astrocytes and in endothelial cells of the microvasculature; these changes are associated with evidence of albumin extravasation in brain tissue reflecting BBB breakdown. Cytokines can indeed affect the permeability properties of the BBB via disruption of the tight-junction organization or production of nitric oxide and activation of matrix met-halloproteinases in endothelial cells. Alterations in BBB permeability favours neuronal hyperexcitability, by resulting in albumin extravasation and its astrocytic uptake; this phenomenon compromises astrocytes ability to buffer extracellular K^+ and to reuptake extracellular glutamate. The extent of BBB leakage positively correlates with the frequency of spontaneous seizures in rats suggesting a reciprocal cause-effect relationship (Vliet *et al.,* 2014) [9].

Inflammation in Human Epileptic Brain

The activation of both innate and adaptive immune systems has been described in human epilepsy. The analysis of brain specimens from drug-refractory epileptic patients showed upregulation of IL-1β and HMGB1 and their receptors IL-1R1 and TLR4, in glia and neurons in epileptogenic tissue. This suggests that the activation of these signalling pathways occurs in human epilepsy (Iyer *et al.,* 2010). Moreover, upregulation of complement system and COX-2 were also shown in parenchymal brain cells (Phillis *et al.,* 2006). Noteworthy, in epilepsy associated with malformations of cortical development, a positive correlation was found between the percentage of IL-lb-positive brain cells and the frequency of seizures prior to surgical resection. Cells of adaptive immunity were detected in some but not all types of epilepsy; for example, a notable absence of lymphocytes was described in temporal lobe epilepsy specimens and this is clearly different from Rasmussen's encephalitis or from epilepsies associated with malformations of cortical development where these cells were found often in close apposition with degenerating or dysmorphic neurons. The finding that inflammatory events persist during epileptogenesis in experimental models thus outlasting the initial precipitating event (e.g., status epilepticus, prolonged febrile seizures) suggest that inflammatory processes may precede the onset of epilepsy in humans, possibly playing an etiopathogenetic role in the occurrence of spontaneous seizures. The use of transgenic mice overexpressing TNF-α or IL-6 indicates that a chronic inflammatory state in the brain can indeed predispose to the occurrence of seizures (Campbell *et al.,* 2010). Further, long-term increase in brain excitability was demonstrated in rodents after systemic administration of lipopolysaccharide (LPS), a proinflammatory reagent mimicking bacterial infection that induces both systemic and brain inflammation (Riazi *et al.*, 2010) [8].

Role of Cytokines in Neuronal Excitability

In addition to the classical induction of NFkBmediated gene transcription described during peripheral inflammation, nonconventional intracellular signalling pathways are activated by proinflammatory mediators in the epileptogenic tissue. These novel mechanisms are likely to contribute to neuronal hyperexcitability underlying seizures, mediating at least part of the inflammation related glia neuronal interactions that have a role in decreasing seizure threshold. For example, recent evidence demonstrates that IL-1β activation of neuronal IL-1R I induce Src kinase mediated tyrosine phosphorylation of the NR2B subunit of the N-methylD-aspartate (NMDA) receptor, a key glutamate receptor involved in seizures. As a consequence of this action, NMDA receptor-mediated Cat' influx into neurons is enhanced by IL-1 β, and this effect plays a role in promoting excitotoxicity (Viviani *et al.,* 2003) and seizure generation. This mechanism is also shared by HMGBI, another proinflammatory molecule that is implicated in experimental seizure precipitation and recurrence. Activation of other kinase families (e.g., MAPK, PKA, PKC) by pro inflammatory molecules has been implicated in rapid posttranslational changes in voltage-dependent Ca^{2+}, Na^+, and K^+ ion channels with significant impacts on neuronal excitability. IL-Iβ can also inhibit the astrocytic reuptake of glutamate and increases its glial release possibly via TNF-α production, resulting in elevated extracellular glutamate levels. It has been recently reported that the astrocytic glutamate release may have a role in the genesis or strength of seizure-like events (Fellin *et al.,* 2006) [10].

P2X7 receptor in epilepsy

The P2X7 receptor is an ATP-gated non-selective cation-permeable ionotropic receptor selectively expressed in neurons and glia in the brain. Activation of the P2X7 receptor has been found to modulate neuronal excitability in the hippocampus and it has also been linked to microglia activation and neuroinflammatory responses. Accordingly, interest developed on the P2X7 receptor in disorders of the nervous system, including epilepsy. Studies show that expression of the P2X7 receptor is elevated in damaged regions of the brain after prolonged seizures (status epilepticus) in both neurons and glia. P2X7 receptor expression is also increased in the hippocampus in experimental epilepsy. Recent data show that mice lacking the P2X7 receptor display altered susceptibility to status epilepticus and that drugs targeting the P2X7 receptor have potent anticonvulsant effects. Together, this suggests that P2X7 receptor ligands may be useful adjunctive treatments for refractory status epilepticus or perhaps pharmaco-resistant epilepsy (Engel *et al.,* 2012).

Neurochemical mechanisms underlying epilepsy

a) GABA

The GABA hypothesis of epilepsy implies that a reduction of GABAergic inhibition results in epilepsy whereas an

enhancement of GAB Aergic inhibition results in an anti-epileptic effect. Inhibitory postsynaptic potentials (IPSPs) gradually decrease in amplitude during repetitive activation of cortical circuits. This phenomenon might he caused by decreases in GABA release from terminals, desensitization of GABA receptors that are coupled to increases in CI^- conductance or alterations in the ionic gradient because of intracellular accumulation of (Wong and Watkins, 1982). In case of intracellular accumulation of passive redistribution is ineffective. Moreover, Cl^- K^+ co-transport becomes less effective during seizures as it depends on the K.4 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 autogenesis and intricate 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. In stiff-man syndrome, a disease associated with epilepsy and diabetes mellitus, auto-antibodies to GAD were demonstrated. A reduction of 3H-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. Reduced GAD levels were revealed in the substantia nigra of amygdala-kindled rats. Significant alterations in GABA and benzodiazepine binding have been shown in the substantia nigra of genetically seizure-prone gerbils. Mice with a genetic susceptibility to audio genic seizures have a lower number of GABA receptors than animals of the same strain that are not seizure prone. Several endogenous (guanidine compounds) and exogenous (e.g. bicuculline, picrotoxin, penicillin, pilocarpine, pentylenetetrazol) convulsant inhibit GAB Aergic transmission through inhibition of GABA synthesis or through interaction with distinct sites at the postsynaptic GABAA receptor. Convulsant agents that block synaptic GABA-mediated inhibition, amplify the dendritic spike-generating mechanism that involves $Ca^{2+.}$ 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, and valproate) or facilitate postsynaptic effects of GABA. However, a study evaluating dose-dependent behavioral effects of single doses of vigabatrin in audio genic sensitive rats, suggests that the antiepileptic properties of vigabatrin not only depend on GAB Aergic neurotransmission but might also be explained by decreased central nervous system levels of excitatory amino acids or increased glycine concentrations (Engelborghs *et al.,* 2000) [11].

b) Glutamate

Glutamatergic synapses play a critical role in all epileptic phenomena. Activation of both ionotropic and metabotropic postsynaptic glutamate receptors is pro-convulsant. Antagonists of N-methyl-D-aspartate (NMDA) receptors are powerful anti-convulsant 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. Changes in metabotropic glutamate receptor function may also play a key role in epileptogenesis (Szczurowska and Mares, 2013). Epileptic seizures and epilepsy form frequent complications of uraemia. As a possible underlying mechanism, we have demonstrated the accumulation of a series of uremic guanidine compounds which were shown to inhibit GABAergic neurotransmission. One of these endogenous agents was in addition shown to be an agonist at the excitatory NMDA receptor. In patients with absence seizures, plasma glutamate levels were found to be significantly increased (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/R1J rats spontaneous spikewave (SW) discharges accompanied by behavioral abnormalities) provides evidence for an interaction of glutamatergic and serotonergic mechanisms in the triggering and maintenance of epilepsy.

c) Catecholamine

Abnormalities of CNS catecholamine have been reported in several genetic models of epilepsy. In spontaneous epileptic rat, dopamine was decreased in the nucleus caudate whereas noradrenaline was increased in midbrain and brainstem. Decreased levels of dopamine have been found in epileptic foci of epilepsy patients. In animal models of absence epilepsy, seizures are exacerbated by dopamine antagonists while fits are alleviated by dopamine agonists (Cortez *et al.,* 2015). 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. Recent data indicate that the serotonergic system regulates epileptiform activity in a genetic rat model of absence epilepsy as intraperitoneal or intra cerebral ventricular administration of 8-OHDPAT caused marked and dose-dependent increases in number and duration of SW discharges (Gerber *et al.,* 1998).

Alterations of Ionic Environment

Inherited disorders of voltage-gated ion channels are a recently recognized aetiology of epilepsy in the developing and mature central nervous system. Two human epilepsy syndromes, benign familial neonatal convulsions and generalized epilepsy with febrile seizures plus, represent K^+ and Na^+channel path, and other newly defined syndromes

have now been mapped to chromosomal regions that are rich in ion channel genes. Experimental mouse models promise a resolution of their intriguing pathophysiology, which includes a diverse array of cellular phenotypes consistent with the differential contributions of individual channels to excitability in neural networks (Steinlein and Noebels, 2000).

a) Potassium channels and epilepsy

The first human idiopathic epilepsy syndrome to be mapped from a single pedigree, benign familial neonatal convulsions (BFNC), was reported exactly one decade ago by (Leppert *et al.,* 1989), and the long-awaited cloning of this gene eloquently illustrates how genetic analysis of epilepsy is contributing not only to our understanding of the disease but also to the basic molecular neurobiology of the brain. BFNC syndrome is caused by mutation of either of two genes that encode novel voltage-gated potassium ion channels of the KQT subfamily (Hahn and Neubauer, 2009). Linkage analysis of pedigrees with similar clinical phenotypes has revealed genetic heterogeneity (EBN 1 on chromosome 20q 13.2, EBN2 on chromosome 8q24), leading to identification of the KCNQ2 and KCNQ3 ion channels. These proteins are similar to the 6TM domain KCNQI channel that is mutated in one variant of the cardiac long QT syndrome. KCNQ2 and KCNQ3 channels are expressed diffusely in brain and persist in adulthood, although seizures associated with BFNC typically disappear by 6 months of age. Co-expression of KCNQ2 and KCNQ3 leads to a large increase of the potassium current, suggesting that the proteins interact as heterodimers. As the predicted loss of this current in these short-lived epilepsy syndromes represents a dominant gain of function, it will be of great interest to learn whether this current is subsequently restored, or whether other cellular plasticity mechanisms must be sought to account for the age-dependent disappearance of the seizure phenotype. Mice deficient in this delayed rectifier die young, and those that survive display a severe seizure disorder in adulthood. Analysis of both behavioral and immediate-early, gene indicators of brain excitability in the heterozygous and homozygous Kv1.1 mutants reveals preclinical neuronal hyperactivation at a young age before spontaneous seizure activity appears, indicating that brain maturation magnifies, rather than alleviates the loss of this channel type (Sabbadini and Yost, 2009).

b) Sodium channels and epilepsy

A sodium channel mutation that is linked with epilepsy provides a second example of a partially penetrant human epilepsy phenotype with variable regional brain excitability alterations. In 1998, a large pedigree displaying a variety of seizure phenotypes, including those related to fever was linked to a point mutation of the sodium channel β1 subunit gene located on chromosome 19q13.1. This regulatory transmembrane 01 subunit is believed to interact with any of the 10 pore-forming α subunits found in brain and to modulate sodium channel kinetics. There is recent evidence of other gene loci for this clinical entity, called `generalized epilepsy with febrile seizures plus's ($GEFS^+$), in a region on chromosome 2q21-q33 (Baulac *et al*., 1999) that, intriguingly, contains genes encoding five different a subunits of the voltage-gated sodium channel family, the calcium ion channel β4 subunit and a potassium ion channel gene KCNJ3. The human β1 mutant subunit prolongs neuronal depolarization under steady-state conditions when co-expressed in vitro with a rat brain sodium channel a subunit RBII: however, there is still little insight into how the sodium channel defect gives rise to the phenotypically diverse seizure patterns seen within a single $GEFS^+$ pedigree. Seizures in some affected individuals also occurred during a febrile episode, but most of these events were found to persist beyond the age of 6 years, which is the commonly used diagnostic cut-off for the clinical syndrome classified as febrile seizures. In febrile seizures, 90% of cases show seizures in the first 3 months of life, and less than 10% develop afebrile seizures at a later age. Interestingly, a locus (FEB3) for febrile seizures occurring only before the age of 6 years has also been localized to the region of 2q23-q24, again in the same vicinity of the ion channel cluster noted above. Evaluation of these candidates will clarify the genetic heterogeneity of these overlapping clinical phenotypes. A new candidate sodium channel gene for epilepsy was also proposed this year after the discovery that it is selectively expressed in the limbic system of the brain, giving new meaning to the term 'positional cloning'. The cardiac sodium channel SCN5A gene, which is localized to chromosome 3p24, was previously believed to be expressed only in heart tissue on the basis of results from northern blot assays-, however, mRNA for this channel has now been identified in the brain piriform cortex and amygdala using in situ hybridization and PCR techniques. These limbic networks have been long known to possess the lowest threshold for epileptogenesis of any brain region. In the heart, several mutations in this channel have been described that prolong sodium currents, depolarize cells and cause prolonged cardiac QT intervals, tachyarrhythmia and lethal ventricular fibrillation. It is thus likely that a similar defect expressed within limbic neurons represents a molecular mechanism for the epileptic seizures that have been repeatedly observed in the prolonged QT syndrome patient population (Xiaoxue *et al.,* 2013) [14].

c) Calcium channels and epilepsy

Although mutations in calcium channels in humans produce episodic or persistent cerebellar ataxia, hemiplegic migraine and stationary night blindness (Heyes *et al.,* 2015), no seizure phenotype has been linked to a calcium channel gene in human pedigrees. In sharp contrast, four spontaneous mutations with generalized absence epilepsy and cortical spike-wave discharges have been identified in mice (tottering, lethargic, stargazer, and ducky), and these overlapping mutant phenotypes are linked to mutations in genes encoding four separate subunits that together form the tetrameric voltage-gated calcium channel complex (Phillips *et al.,* 2014) [7]. Calcium channels are important modulators of membrane excitability, transmitter release and gene expression. Several findings have been reported in the past year that shed light on how each of the mutations could alter calcium channel entry, but the main downstream events that translate these complex channel paths into mechanisms of epileptogenesis remain unidentified. Synaptic transmission problems, and presumably the neurological phenotype, therefore arise preferentially in circuits for which alternative calcium channel subunits are less available. How could a hyperexcitability phenotype arise from decreased calcium currents in any neuron, much less a restricted few? The

answer to this apparent paradox presumably lies in understanding the behaviour of the affected circuit, as well as the individual presynaptic terminal. Oscillations within the thalamus cortical system are sensitive to small changes in either excitation or inhibition, and population imbalances at specific synapses may lead to increased network synchrony (Huntsman *et al.,* 1999). If release at inhibitory synapses is modulated differently to that at excitatory ones, as found in the tottering neocortex and thalamus, a hyperexcitable phenotype may arise. The converse issue appears in the Kv1.1 mutant, where loss of membrane repolarization enhances both GABA-mediated inhibitory as well as excitatory activity, and appearance of an epileptic phenotype must depend on the threshold for this balanced amplification in specific circuits (Zhang *et al.,* 1999) [15].

Role of oxidative stress in epileptic seizures

Oxidative stress resulting from excessive free-radical release is likely implicated in the initiation and progression of epilepsy. Therefore, antioxidant therapies aimed at reducing oxidative stress have received considerable attention in epilepsy treatment. However, much evidence suggests that oxidative stress does not always have the same pattern in all seizures models. Thus, this review provides an overview aimed at achieving a better understanding of this issue. We summarize work regarding seizure models (i.e. genetic rat models, kainic acid, pilocarpine, pentylenetetrazol and trimethyltin), oxidative stress as an etiologic factor in epileptic seizures (i.e. impairment of antioxidant systems, mitochondria' dysfunction, involvement of redox-active metals. arachidonic acid pathway activation, and aging), and antioxidant strategies for seizure treatment. Combined, this review highlights pharmacological mechanisms associated with oxidative stress in epileptic seizures and the potential for neuroprotection in epilepsy that targets oxidative stress and is supported by effective antioxidant treatment.

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