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Review Article

Brain Network and Homeostatic Influences in Epileptogenic Spreading

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Abstract

After stroke, epilepsy is the second leading brain impairment, affecting over 50 million people worldwide. Its persistent seizures often cause various sequelae such as momentary deviations in perception and behavior, mild convulsions, and temporary loss of consciousness, which are due to the spread of epileptogenesis to various brain regions. Among the multifactorial influences contributing to the variation in the spread of seizure foci are particular domains affected, mechanisms of spatial distribution, and the nature of the disturbance eliciting seizure foci. Unlike the influence of homeostatic perturbations, these latter are likely to involve operational and global structures of cognition, that is, top down as opposed to bottom up influences that affect seizure distribution in complex ways. Current studies suggest that these mechanisms could entail the interaction of both ictal and extra-ictal electrical events with global oscillatory activity that mediates higher order cognitive events.

Keywords: *Brain; Homeostatic; Epileptogenic; Consciousness Disorders; Temporal Lobe epilepsy; Global Workspace Model; General Epilepsy*

Introduction

Epilepsy is a widely occurring, common neurological disorder. After stroke, it is the second leading brain impairment, affecting over 50 million people worldwide [1]. Its high incidence in geographical settings of lower economic status is indicative of environmental factors that feature prominently in its occurrence and that can exacerbate its prevalence in regions of relatively lesser medical care.

The International Bureau for Epilepsy (IBE) defines epilepsy as a disorder of the brain characterized by an enduring predisposition to generate at least one epileptic seizure and by the neurobiological, cognitive, psychological and social consequences of this condition [2]. Persistent seizures may also cause various sequelae such as momentary changes in perception and behavior [3], mild convulsions [4], and temporary loss of consciousness [5,6], which are related to the origin of seizure foci and the intensity of ictal episodes. The etiological basis for these sequelae is currently unknown. On the other hand, it is known that epileptogenesis affects brain areas well beyond the epileptogenic foci [7,8]. The domains affected, mechanisms of spatial distribution and nature of disturbance eliciting seizure foci are thus likely to be significant factors in generating the variability observed in epilepsy's symptoms.

The often profound changes in states of consciousness occurring during epileptic episodes, for example, are likely to involve major networks outside the region of seizure origin. Consistent with such observations, functional connectivity is impaired in large scale brain networks in focal as well as general epilepsies that extend bilaterally and via subcortical structures [9]. For recurring seizures, large-scale interactions are thus major pathogenic factors contributing to symptom severity [10,11].

How extra focal interictal and ictal activities emerge in the epileptic brain is still unknown. However, since many of the causes of eliptogenesis, e.g., trauma and stroke, are likely to affect homeostatic mechanisms, it has been suggested that the etiological factors are chiefly related to impaired preservative or homeostatic processes [12]. Fasting, for instance, has long been associated with anticonvulsant activity, and the discovery in the 1920's that its anticonvulsant effects was due to ketosis led to treatments with strictly modified diets that replicated these effects. The so-called ketogenic diet, with its low carbohydrate, high fat ratios and moderate-to-low protein levels, was shown to reproduce the major metabolic effect of fasting, while minimizing convulsions in both children and adults [13]. Consistent with these observations of dietary influence, conditions that can precipitate epilepsy such as traumatic brain injury, and diseases in which epilepsy can be comorbid, such as Alzheimer's disease, have since been shown to be accompanied by a chronic loss of homeostatic function. Moreover, the loss of energy homeostasis associated with epilepsy is found acutely during the seizure or precipitating event, as well as chronic processes of epileptogenesis. Accordingly, since such mechanisms are likely to exert global influence, a principal factor contributing to the spread of epileptic foci is that of underlying homeostatic impairments in energy maintenance.

On the other hand, the variability of epileptogenesis in its manifestation and the distribution of seizure foci, suggest that homeostatic mechanisms are not the sole factors contributing to etiology and that non-uniform factors may also be substantially involved in the globalization of epileptogenesis. Unlike the influence of homeostatic perturbations, these likely relate to operational and global influences of cognition, that is, top down as opposed to bottom up influences that affect seizure distribution in complex ways. Recent studies, for instance, suggest that the former mechanisms may involve global brain states that couple to ictal and extra-ictal events. How these relate to impaired homeostatic influences and how they may assist the spread of epileptogenesis outside initial seizure zones are discussed in this short review.

Impaired energy homeostasis and the globalization of epileptic activity

Adenosine and ATP

It is increasingly evident that epilepsy entails a global dysregulation of metabolic function [14]. During seizures the rate of glucose and oxygen consumption increases [15], requiring more energy than generated from oxidative phosphorylation via the TCA cycle, with the replacement of glycolysis as the main supply of neuronal ATP. The activity of enzymes involved in the TCA cycle, such as aconitase, malate dehydrogenases, and succinate dehydrogenases, notably decrease in epileptic seizures, whereas metabolites produced by the enzymes involved in anaerobic glycolytic metabolism, such as phosphofructokinase and glucose kinase, increase. The latter increase in activity has the effect of elevating lactic acid production, where it is used by neurons as an alternative energy supply [16] via its conversion to pyruvate and entry into glycolysis. The reduction of oxygen that follows on neuronal activity during epileptic events also induces the expression of hypoxia-inducible factors (HIF). These factors amplify the inhibition of the mitochondrial TCA cycle and the resultant activation of glycolysis. Such energy resources are generally insufficient to sustain the hypopolarization needed to prevent spontaneous axonal firing due to reduced sodium-potassium-ATPase activity. Na^+/K^+-ATPase malfunctioning, for instance, is known to be associated with neuronal hyperexcitability, is a key mechanism for post-seizure extracellular K^+ clearance and has been reported in neonatal seizures [17]. It is also decreased both in the rat cortex and hippocampus in the first few minutes after transient focal ischemia [18] and in experimental traumatic brain injury [19]. Hence, the reduction but not the elimination of Na/K ATP activity is thought to lead to repeated seizure episodes. Significantly, ketobodies cannot be converted into glucose, unlike glycogen and lactate and so cannot fuel the anaerobic pathway, thereby preventing the increased neuronal firing caused by a partial restoration of hyperpolarization.

The role of energy metabolites in seizure events is, nonetheless, not simply due to a reduction in ATP availability. With epileptic seizures there is a rapid drop in ATP levels, resulting in the generation of adenosine levels that can exceed the baseline level more than 40 times [20]. The intracellular concentration of ATP, for example, is nearly 50 times higher than that of AMP and about 10,000 times higher than that of adenosine [21]. Minor decreases in intracellular ATP, therefore, lead to a large rise of intracellular adenosine level [22].

Accordingly, adenosine acts as a key bioenergetic network regulator for energy homeostasis of a cell. Adenosine's universal metabolic role suggests in fact that an early evolutionary principle was to conserve energy through a rise in adenosine due to ATP depletion and to use the increase in adenosine as a negative feedback regulator to attenuate cellular activities that consume energy. In line with this, the rise in adenosine has been shown to act as a negative feedback regulator to attenuate cellular activities that consume ATP, including processes related directly to neural function.

Adenosine, for instance, can have powerful receptor-mediated effects on synaptic transmission in the brain [23]. Presynaptic adenosine-1 receptors (A1R) inhibit synaptic release of most neurotransmitters, particularly those used for excitatory transmission. Thus, if adenosine levels are raised sufficiently, synaptic transmission can be blocked altogether. Further, A1Rs hyperpolarize postsynaptic receptor membranes by opening inwardly rectifying K^+ channels. Together, the A1R effects strongly dampen synaptic transmission, suppressing brain activity [24].

Adenosine also participates in adenosine receptor-independent regulatory functions, which involve mitochondrial bioenergetics, prevention of ATP consuming biochemical reactions, and epigenetic functions. For example, adenosine interacts directly with ATP generating processes. Intracellular adenosine is dephosphorylated from AMP by cytosolic 5-nucleotidase and is converted back to AMP via adenosine kinase (ADK). The adenosine-AMP cycle is thereby linked to ADP and ATP through adenylate kinase within the cell, coupling it tightly to energy metabolism. However, after ATP is dephosphorylated, adenosine is also retrieved from the extracellular into the intracellular space by nucleoside transporters [25]. Adenosine-AMP cycles and bidirectional adenosine uptake and release via nucleoside transporters help to maintain adenosine homeostasis. Therefore, changes in extracellular adenosine due to adenosine and/or ATP release also alter adenosine receptor signaling [26], yielding a complex series of intracellular and extracellular processes that lead to the stimulation of mitochondrial bioenergetics and energy metabolism [27].

Significantly, astrogliosis, which is a pathological hallmark of epilepsy, has been consistently associated with overexpression of ADK and its resulting adenosine deficiency [28]. Consistent with this observation, a fall of 25% in adenosine levels has been observed in epileptogenic zones with microdialysis measurements [20]. Furthermore, increased ADK expression results in the spontaneous occurrence of seizures, whereas the transgenic reduction of ADK in cortex and hippocampus of mice confers resistance to seizures and epileptogenesis. Together, impaired adenosine metabolism, in conjunction with a reduction in aerobic energy metabolites, appear to constitute key factors underwriting epileptogenesis in the brain.

Metabolic impairment as a mechanism for distributing epileptogenesis

An important aspect of the generation of epileptic seizures is the recruitment of substantial regions of cortical tissue into pathological activity. Based on a general model of spreading metabolic impairment, which is suggested from the adenosine related effects, recruitment can be expected to consecutively engage nearest neighbor circuits. On this basis Wang., *et al.* [29] notably posited a model of arrays of interacting minicolumns distributed across a cortical tissue sheet, which sequentially evoke epileptogenic activity. Using this model localized occurrences of hyperactivity were observed within the simulated sheet, an observation consistent with micro periodic epileptiform discharges that are seen during interictal intervals [29]. Locations where high activity occurred recruited neighboring and, subsequently, distant sites to the abnormal activity, eventually resulting in the participation of the whole sheet in abnormal activity; that is, as a globally excited state. The time required for the recruitment of the whole sheet depended on the number of hyperexcitable clusters, with earlier recruitment occurring when more clusters were present. Moreover, cluster size was also shown to influence recruitment time, with smaller clusters resulting in longer intervals to global excitation. Together, the model's predictions were consistent with some notable observations of epileptogenic events.

Synchronization patterns are inconsistent with nearest neighbor recruitment

Among the mechanisms likely to account for the extended activation seen in these results are those involving spike timing dependent plasticity, where neighboring units experience localized and synchronous depolarizations coinciding with the depolarization of ictal foci [30]; that is, in regions where epileptogenesis occurs, units neighboring the seizure foci become depolarized in synchrony with the depolarization of the units located within the seizure zone. According to this hypothesis, epileptogenic activity would be expected to generate focal synchronous activity, which would progressively advance to larger and larger cortical areas. Indeed, it has been presumed that ictal episodes lead to recruitment through processes of synchronization [31].

Synchronization of excitation, in fact, has been shown to occur during late phases of seizure discharge. However, seizure initiation and interictal epileptiform events are not consistently associated with an enhancement of synchronous, excitatory network interactions. One of the most common neurophysiological patterns observed in focal seizures is characterized by low-voltage fast activity at seizure onset, followed by irregular spiking that progressively develops into periodic bursting, interspersed with post-burst depressions. This pattern is nearly always observed in human temporal lobe epilepsy [32,33], in focal epilepsy of neocortical origin [34], and in acute models of focal seizures [35]. Also occurring is low amplitude, fast activity, which frequently fragments with the substitution of background rhythms.

Interictal events of various amplitude, morphology and duration, which are characterized by spikes, sharp waves, and short spike bursts, with rhythmic activity in theta/delta frequency range, can also be recorded between seizures with intracranial electrodes positioned within the epileptic zone in the cortex and around the zone. Neural correlates of interictal and ictal patterns in human epileptic brains, in fact, showed that synchronization and enhanced excitation were not likely to occur in specific phases of ictogenesis and synchronous neuronal bursting was not observed during interictal spikes and seizures [36]. Rather, intracranial human recordings performed during the early phase of a seizure showed that neurons in the epileptic zone and the surrounding areas reduce their firing activity and synchronization as measured by a spiking heterogeneity index [37].

Microelectrode recordings, moreover, also showed increased firing synchrony only after several seconds of seizure onset, suggesting that action potential synchronization within the epileptogenic network is not required to initiate a seizure [29,37]. Indeed, non-linear correlation analysis between activities intracranially recorded during human focal seizures demonstrated a desynchronization of the epileptogenic region during and just ahead of seizure onset [38]. As a group, these studies show that synchronization builds up and becomes prominent in the late phase of seizures close to seizure termination and so is unlikely to be a mechanism by which adjoining cortical regions are enlisted for epileptic activity; that is, transitions into seizure due to a localized, synchronous enhancement is relatively rare.

Globalization of epileptogenesis

Accordingly, the several different classes of results - the variability of patterns, temporal and spatial non-uniformity, and lack of synchronous recruitment in zones neighboring foci - are caveats to explanations that invoke metabolic impairments alone and so implicate additional functional mechanisms that underlie seizure appearance. Indeed, it is not only likely that multiple factors contribute to the non-uniform globalization of epileptogenesis, but that these factors include interactions with structured cognitive activity. Global brain state phenomena, for instance, entail various networks that underlie higher order cognition that could both be influenced by epileptogenesis and, in turn, influence its appearance elsewhere in the brain. Two such states are considered here, consciousness, and default mode network activity associated with task positive and task negative states. Both have been shown to be impaired in epilepsy.

Relating alterations in consciousness to globalization of epileptogenesis

In the most frequent type of chronic drug resistant partial epilepsies, the temporal lobe epilepsies (TLE), alterations of consciousness (AOC) are a particularly dramatic clinical manifestation, as well as a potential source of injury. In fact, video-EEG recordings have revealed that some 60% - 80% of patients suffering from TLE have AOC during their seizures [39]. In line with this, the international classification

of epileptic seizures has made impaired consciousness a framework within which the main categories of partial seizures, simple and complex, are distinguished. The association between epilepsy and consciousness, a higher order and generally posited global, cognitive state, suggests that specific processes associated with consciousness are factors that may contribute to the manner by which epileptogenesis spreads to various brain regions.

Seizures in TLE are characterized by epileptic discharges originating from one or several regions of the temporal lobe (often from the mesial temporal regions) and propagating through an interconnected network within both cortical and subcortical structures. Different hypotheses have been proposed to explain how those seizures could impair consciousness [40]. In one case, intracerebral EEG recordings have suggested that alteration of consciousness could be related to the spread of epileptic discharge to cortical structures contralateral to the origin of the seizures and be more frequent in seizures affecting the dominant hemisphere [41]. In another, bilateral involvement of the temporal lobe is a factor that has been suggested to explain memory and so consciousness loss although it has also been shown that AOC may occur during apparently unilateral TLE seizures [42].

Mechanistic features that might contribute to spreading have been shown to involve a specific increase of neural synchrony, with regions distant from the sites of origin of the seizures [43]. In a study of patients having intracerebral recordings of cortical and subcortical structures two groups were distinguished on the basis of the severity of their loss of consciousness, with one group displaying complete loss of consciousness and the other only partial loss. Measurements of synchrony within the temporal zone alone were not markedly different between the two groups during seizure occurrence. However, synchronization differed significantly when measurements were also made of regions outside the temporal lobe and included the thalamus and parietal cortex. In the group having complete loss of consciousness there was a specific increase in synchronization between the distant regions and the temporal lobe during epileptogenesis, whereas enhanced synchronization was not seen in individuals with a partial loss of consciousness. These results thus suggest that extra-temporal structures are associated with increased synchrony during AOC.

Measurements of synchrony, moreover, were found to be correlated with the degree of thalamo-cortical and corticocortical synchrony, with the transition between consciousness and loss of consciousness obeying a sigmoid curve, indicative of a bi-stable system. A leading model of consciousness, the global workspace model (GW), notably postulates the integration of cortical and subcortical modules, with the 'broadcasting' or sharing of information between modules comprising the physical aspects of the consciousness state [44] Such information sharing is thought to occur via synchronization and is described by the communication by coherence theory [45]. Accordingly, abnormal synchronization between subcortical and cortical modules composing the GW, could constitute a core mechanism of AOC in TLE, a process that could be mediated by epileptogenesis and underly its spreading within the brain.

Alterations in default mode network and epileptogenesis

The default mode network (DMN) is a major resting state brain network that is intimately involved in task related activities, enabling the brain to shift between task negative and task positive roles. DMN activity is anticorrelated with task positive states, which are mediated by the executive fronto-parietal network and which engage the basal ganglia (BG) through the putamen. Significantly, the DMN has been shown to be altered in various neurological impairments, including epilepsy [46]. The BG form a very complex group of nuclei and pathways and may act as an integrated system due to the unidirectional character of the major connections and the information being transformed and transmitted from the cortex via the BG and back into the cortex. It is known to exercise distant control over widespread cortical areas that may influence cortical epileptic activities. Several experimental and clinical studies, for instance, show that the putamen and other BG nuclei are likely to be involved in the modulation of epileptic seizures.

Based on these observations, functional connectivity between putamen and cortical zones has been assessed during ictal episodes [47]. The results from these studies show the presence of significant differences within nuclei of the DMN in patients suffering epilepsy,

even during rest; that is, when the DMN is in a task negative state. Specifically, the left superior, frontal gyrus, left postcentral gyrus, and the right superior temporal gyrus, i.e. the connectivity within the DMN, was decreased in patients with epilepsy as compared with normal controls. Conversely, in epileptic patients as compared with controls, the DMN component was significantly increased in the left lingual gyrus, left and right putamen, right insula/inferior frontal gyrus, and left inferior frontal gyrus; i.e. the connectivity between the DMN and basal ganglia regions was no longer anticorrelated as in controls. In controls, the putamen displayed significant negative connectivity values within the DMN component while in extra temporal and temporal epilepsy these values were non-significant and even slightly positive. Thus, the putamen appears to operate relatively independently from the DMN during epilepsy; that is, it is not significantly engaged within the DMN in epileptic patients. Although these studies do not show the emergence of ictal episodes in the DMN per se, taken together they show that epileptogenesis mediates significant functional alterations at long distance from seizure sites that appears to involve a specific global network.

Brain oscillations and cross coupling

Mechanisms by which global networks may contribute to the spread of epileptogenesis at long distances from seizure foci are for the most part unknown. However, the prominence of electrical events during ictal episodes makes it very likely that these strongly interact with other electrical activity that enables normal brain function. Such interactions could enable the spread of epileptogenesis beyond initial focal zones.

Among the fundamental electrical signatures unifying brain activity are brain oscillations, which synchronize regional activities with global cognition [30]. Oscillations are thought to enhance neuronal spike probability by defining, through repetitive cycles periods of higher excitability, where neurons are sensitive and more responsive to incoming trains, and periods of reduced sensitivity, where spike occurrence is less [45]. By adjusting spike timing, particularly, it is thus possible to enhance intrinsic tendencies toward synchrony where oscillators can properly align and their frequencies then resonate in unison, or, conversely, to weaken their association leading to decoherence.

Consistent with this expectation, recent studies have found that electrical activity specific to ictal events interacts with global oscillatory activity, leading to the appearance of epileptic activity signatures in loci widely separated from seizure origin. These studies exploited an electrical biomarker that characterizes experimentally induced epilepsy, fast ripples. Fast ripples (FR) are high frequency waveforms that are associated with experimental epileptogenesis, which is induced by kainite injection [48]. Following injection the frequency of occurrence of these waveforms notably increases some 40 fold. Investigation into the waveforms revealed that they did not occur in a "random" background, but were associated with a specific ongoing activity, involving slow oscillations [49]. Specifically, fast ripples were shown to associate with two oscillatory bandwidths, a slow oscillation (3 - 5 Hz) surrounding the FRs and one associated with interictal epileptic episodes located at 20 - 30 Hz. Phase-amplitude coupling during these transient epileptic events occurred at 4.5 Hz frequency for phase and 27 Hz frequency for amplitude, the occurrence of which was 2.1 times higher than during baseline.

An examination of the frontal cortex and left and right hippocampi showed specific increases in power at 3 - 5 Hz in all three regions suggesting an increase in synchronization across regions. Furthermore, the increase in synchronization converged toward a common value, revealing that the distribution of phase differences tended to converge and was significantly more concentrated during the period of interest than during baseline at these specific frequencies, coinciding with the slow oscillation between regions. Significantly, synchronization with the frontal cortex was delayed with respect to the two hippocampi, and causal influences by Grainger analysis were shown to occur from the hippocampi to the frontal cortex. Altogether, these data reveal that cross-frequency coupling between the slow oscillation and FR constrains epileptogenesis, beginning in the bihippocampal network and then spreading across the network before frontal cortex expression.

Conclusion

Spatial and temporal epileptogenic variability is a common feature of epilepsy that likely relates to the variety of its pathogenic manifestations. Its etiological basis is unknown, but is unlikely to be due solely to impairments in energy homeostasis. Existing studies suggest that major symptoms like the loss or alteration of consciousness and the inhibition of widespread functional connectivity are likely to involve a distribution of epileptogenic activity via global brain networks. These disruptions may be due to a modulation of oscillatory activity that transmits epileptogenesis to spatially distant loci.

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