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REVIEW

NEURONAL NETWORKS AND ENERGY BURSTS IN EPILEPSY

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Abstract—Epilepsy can be defined as the abnormal activities of neurons. The occurrence, propagation and termination of epileptic seizures rely on the networks of neuronal cells that are connected through both synaptic- and non-synaptic interactions. These complicated interactions contain the modified functions of normal neurons and glias as well as the mediation of excitatory and inhibitory mechanisms with feedback homeostasis. Numerous spread patterns are detected in disparate networks of ictal activities. The cortical–thalamic–cortical loop is present during a general spike wave seizure. The thalamic reticular nucleus (nRT) is the major inhibitory input traversing the region, and the dentate gyrus (DG) controls CA3 excitability. The imbalance between γ-aminobutyric acid (GABA)-ergic inhibition and glutamatergic excitation is the main disorder in epilepsy. Adjustable negative feedback that mediates both inhibitory and excitatory components affects neuronal networks through neurotransmission fluctuation, receptor and transmitter signaling, and through concomitant influences on ion concentrations and field effects. Within a limited dynamic range, neurons slowly adapt to input levels and have a high sensitivity to synaptic changes. The stability of the adapting network depends on the ratio of the adaptation rates of both the excitatory and inhibitory populations. Thus, therapeutic strategies with multiple effects on seizures are required for the treatment of epilepsy, and the therapeutic functions on networks are reviewed here. Based on the high-energy burst theory of epileptic activity, we propose a potential antiepileptic therapeutic strategy to transfer the high energy and extra electricity out of the foci.

Key words: epilepsy, networks, GABAergic inhibition, glutamatergic excitation, energy burst, antiepileptic.

Contents

INTRODUCTION

Epilepsy is a common neurological disorder characterized by abnormal discharges in the brain. Based on our clinical observations, the paralyzed limbs of stroke patients have the capability for movements during a seizure, suggesting that the energy generated during epileptic activity is much greater than subjective wishes. Epileptic activity can be regarded as a burst event of excessive energy resembling an earthquake or a volcanic eruption. By comparing the seismic waves in 81,977 earthquakes and the brain waves in 16,032 epileptic seizures, these two events exhibit patterns that are highly similar, suggesting that seizures can be metaphorically thought to be earthquakes in the brain (Osorio et al., 2010). Electrical energy bursts during seizures can be observed through electroencephalograms (EEGs) and magnetoencephalography (MEG), and are characterized by highly elevated frequencies and amplitudes of both electrical and magnetic signals (Nishida et al., 2008; Widjaja et al., 2013). These high-frequency neural oscillations require elevated energy (Lord et al., 2013).

A seizure is a process of amplification and synchronization of neuronal firing, which involves the interaction of GABAergic inhibitory mechanisms and

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Abbreviations: AEDs, anti-epilepsy drugs; CT, corticothalamic; DBS, deep brain stimulation; DG, dentate gyrus; EEGs, electroencephalograms; HFS, high-frequency stimulation; IPSPs, inhibitory post-synaptic potentials; LFP, local field potential; mEFP, mean extracellular field potential; NMDA, N-methyl-D-aspartate; nRT, thalamic reticular nucleus; SE, status epilepticus; SLEs, seizure-like events; SNpr, substantia nigra pars reticulata; TC, thalamocortical; tDCS, transcranial direct current stimulation; VNS, Vagus Nerve Stimulation.

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glutamatergic excitatory mechanisms. In extracellular field potential recordings on hippocampal slices, the high electrical energy results in spontaneous activity and is characterized by a negative shift from an increase in high-frequency electric activity at seizure onset to low-frequency electrical activity (Gluckman et al., 2001). Bursts of high biological energy result from increased electrical energy during this epileptic activity. This high biological energy results in an increased requirement for blood flow, oxygen, glucose and ATP as well as an increase in glycolysis (Lord et al., 2013). The process of energy generation requires an integral neuronal network that is related to the mechanisms of seizures. This paper reviews the mechanisms involved in the epileptic network and the relationship with therapeutic management. We also propose a new anti-epileptic management strategy: to transfer the high electrical and biological energy out of the seizure foci to relieve the discharges.

DEVELOPMENT OF A SEIZURE

The essence of epileptic activity is the abnormal discharge of brain neurons accompanied by the disruption of the normal order of electrical rhythms that is caused by neurons discharging inappropriately; resulting activities are then synchronized among a large population of neurons. Epileptic bursts are all-or-none behaviors and depend on the threshold of the firing frequency as influenced by the recovery from the former burst. Increased supra-threshold firing and higher firing rates before a burst can advance a burst onset; in contrast, reducing either cellular excitability or the functioning of excitatory synapses can abolish population bursts. It has been suggested that epileptiform activity can spread through the network only when the excitatory glutamatergic transmission is fast enough to counteract GABAB-mediated inhibition (de la Prida et al., 2006).

After the initiation of a cortical epileptic discharge, the discharge is propagated from a limited cerebral cortex to larger areas and subcortical structures via projection through fibers of cortico-cortical projecting neurons and multiple brain circuits (Morimoto et al., 2004). In epileptic models, the synchronization of neuronal activity is increased while inhibition is decreased, and thus, the threshold for excitation or synchronization is lowered to facilitate seizures (Bertram, 2013; Hall and Kuhlmann, 2013). The epileptiform activity is initiated and promoted by a positive feedback mechanism with cortical neurons through local axonal collaterals (McCormick and Contreras, 2001). The speed of propagation is inversely correlated with the number of restrained depolarizing shift (RDS) cycles, indicating that the numbers of recruited networks in epileptic activity affect propagation speed. The more the discharges that are recruited from the abutting territory, the more time the wavefront progression needs, and the slower the speed. Epileptic activities generally propagate more slowly than action potentials. The mechanisms are determined by the action potential conduction and recurrent excitation via excitatory synapses leading to positive feedback, electrotonic coupling and non-synaptic interactions (Hall and Kuhlmann, 2013; Trevelyan and Schevon, 2013).

Epileptic seizure is not a uniformly hyper-synchronous state. Synchronization is the largest at ictal onset and termination, and gradually decreases during seizure progression. In the middle of the seizure, the networks are no longer synchronous. The propagation time of the field potentials decreases progressively after the onset of a seizure, while long-range synchrony increases and reaches its maximum at the end of the seizure, possibly through de-synchronization (Kramer et al., 2010; Jiruska et al., 2013). Simulation models of reduced inhibition show that low extracellular [Mg^{2+}] results in slowly propagating waves (0.1–20 mm/s), while a GABA-antagonist elevated excitation model shows faster propagation with speeds of 10–100 mm/s (Hall and Kuhlmann, 2013). Therefore, the speeds of propagation differ relative to different inhibitory mechanisms. Epileptic activity propagates faster in elevated excitation models and slower in decreased inhibition models, suggesting that the tremendous energy generated during the excitation process can propel seizure propagation. Moreover, longer stimulation results in a longer duration of discharges, indicating that with enough energy and neurons to drive the abnormal electrical activity, the seizure could last for a longer time (Sanchez et al., 2006).

Synchrony reaches its peak as the seizure comes to an end, suggesting that both disrupting and enhancing synchronization may facilitate seizure termination. Epileptic seizures stop when nothing is left to excite (Jiruska et al., 2013). Thus, terminating the supply of the energy may stop the seizure. The mechanisms of termination include massively increased membrane conductance and disrupted synaptic integration, which results in decreased transmission efficacy, inhibitory transmission (Pavlov et al., 2013), and the changes in the surrounding environment (Jiruska et al., 2013).

NEURAL NETWORKS IN EPILEPSY

Epilepsy originates from the aberrant dynamics of neuronal networks. Neuronal networks are composed of various types of cells in the nervous system that are connected through synapses and whose activities are mediated by the extracellular environment. Modifications in the structure of neuronal networks can induce epilepsy, and chronic epileptic activity can contribute to the abnormal structure of nervous system. For example, increased extracellular GABA in status epilepticus (SE) contributes to the progressive loss of inhibition at both ipsilateral and contralateral sides (Karunakaran et al., 2012). In the normal hippocampus, over 70% of synaptic inputs into interneurons are excitatory (Gulyas et al., 1999) and have a major constitution of GABAergic neurons (Cossart et al., 2000). Chronically disinhibited networks can reduce the efficacy of anticonvulsants compared with acutely disinhibited epileptic networks (Sabolek et al., 2012). Additionally, the size of the synchronously firing neuronal population can become larger and lead to the oscillation of neurons at higher frequencies in chronically epileptic tissue (Köhling and Staley, 2011).

During a single discharge, the generation of hyperexcitability involves multiple changes in synaptic transmission, gap junctions, ionic concentrations and electric fields.

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