Epilepsy & Behavior 59 (2016) 28–41

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Review

Rapid chain generation of interpostsynaptic functional LINKs can trigger seizure generation: Evidence for potential interconnections from pathology to behavior

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ARTICLE INFO

Article history:
Received 17 January 2016
Revised 7 March 2016
Accepted 8 March 2016
Available online 14 April 2016

Keywords:
Paroxysmal depolarization shift
Interpostsynaptic link
Seizure generation
Aura
Hallucination
Consciousness
Semblance hypothesis

ABSTRACT

The experimental finding that a paroxysmal depolarizing shift (PDS), an electrophysiological correlate of seizure activity, is a giant excitatory postsynaptic potential (EPSP) necessitates a mechanism for spatially summating several EPSPs at the level of the postsynaptic terminals (dendritic spines). In this context, we will examine reversible interpostsynaptic functional LINKs (IPLs), a proposed mechanism for inducing first-person virtual internal sensations of higher brain functions concurrent with triggering behavioral motor activity for possible pathological changes that may contribute to seizures. Pathological conditions can trigger a rapid chain generation and propagation of different forms of IPLs leading to seizure generation. A large number of observations made at different levels during both ictal and interictal periods are explained by this mechanism, including the tonic and clonic motor activity, different types of hallucinations, loss of consciousness, gradual worsening of cognitive abilities, a relationship with kindling (which uses an augmented stimulation protocol than that used for inducing long-term potentiation (LTP), which is an electrophysiological correlate of behavioral makers of internal sensation of memory), effect of a ketogenic diet on seizure prevention, dendritic spine loss in seizure disorders, neurodegenerative changes, and associated behavioral changes. The interconnectable nature of these findings is explained as loss of function states of a proposed normal functioning of the nervous system.

1. Introduction

By developing a framework for an operation that can explain a large number of pathological findings at various levels, it may become possible to understand a disease process. This is particularly viewed as important in seizure disorders [1,2]. The existence of a wide variety of seizure types makes it seemingly hard to understand the common denominator that initiates seizures [3]. Identifying a cellular mechanism that allows the interconnection of different findings at the biochemical, cellular, electrophysiological, systems, imaging, and behavioral levels in seizure disorders remains a challenge and an opportunity to understand both the normal operation of the system and its potential pathologies. Even though many genetic aspects of the seizure disorders have been identified and abnormalities in the function of ion channels that lead to hyperexcitability of the neurons can explain motor aspects of the disease, several other features of seizure disorders remain elusive [4]. The primary reason for this is attributed to our lack of understanding of the normal operation of the nervous system itself [5]. Therefore, a reasonable expectation is that various findings in seizure disorders can serve as pieces of a large puzzle, which in turn, will allow us to understand the normal operational mechanism of the system.

The simultaneous loss of consciousness that blocks perception and memory along with the generation of a self-reinforcing cycle of motor activity synchronized over a large area of the motor cortex requires a mechanistic explanation. A unified model of the dysfunctions of the normal operations is also expected to explain the cognitive impairment and neurodegenerative changes associated with seizure disorders. The interconnectable aspect of the investigative approach is of paramount importance in identifying the exact nature of the basic pathology, which in turn, is required to develop therapeutic methods to prevent the disease progression. In these contexts, it is reasonable to expect that examination of any proposed mechanism that can explain both the generation of internal sensation of different higher brain functions

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; dendritic spine, spine or postsynaptic terminal or postsynapse; DHA, docosahexaenoic acid; ECM, extracellular matrix; EEG, electroencephalogram; EPSP, excitatory postsynaptic potential; GABA, gamma-aminobutyric acid; GluA1, AMPA receptor subunit A1; HCN, hyperpolarization-activated cyclic nucleotide-gated; IPL, interpostsynaptic functional LINK or LINK; islet, islet of inter-LINKed postsynaptic terminals; LC-PUFA, long chain polyunsaturated unsaturated fatty acid; LINK, interpostsynaptic functional link (IPL); LTP, long-term potentiation; MECP2, methyl CpG binding protein 2; meq/L, milliequivalents per liter; n-3 PUFA, omega-3 polyunsaturated fatty acid; MRI, magnetic resonance imaging; NMDA, N-methyl-D-aspartate; PDS, paroxysmal depolarizing shift; Postsynapse, postsynapse terminal or dendritic spine or spine; SK channels, small conductance calcium-activated potassium channels; SNARE, SNAP (soluble NSF (n-ethylmaleimide-sensitive fusion attachment protein) receptor) proteins; VDCC, voltage-dependent calcium current.

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http://dx.doi.org/10.1016/j.yebeh.2016.03.014
1525-5050/

and behavioral motor activity may provide valuable information about the pathogenesis of seizure disorders. In approaching this challenge, primarily, an examination of the diverse findings in seizure disorders from different levels is made with an aim to lay out what must be explained by the pathology of an ideal operational mechanism of the system. The following is a list of features that a unified model is expected to answer.

1.1. Clinical features

The aura of different hallucinations, focal and generalized tonic or clonic motor activity, and loss of consciousness observed in different seizure disorders require an interconnectable mechanistic explanation. Different studies indicate that repeated seizure activity produces altered functional reorganization of the motor cortex [6,7]. The expansion of seizure spread along the motor strip in one study [8] indicates that the cellular mechanism responsible for seizures is capable of spreading laterally. Even though motor activity during seizures can be observed by third persons, the first-person internal sensations of hallucinations during aura and loss of consciousness that cannot be accessed by the observers make it difficult to understand an interconnectable pathological mechanism from a third-person view.

1.2. Electroencephalogram (EEG) findings

The key intracellular electrophysiological correlate of epileptiform activity is paroxysmal depolarizing shift (PDS) [9], which is a discharge recorded in interictal EEG. Similar depolarization shifts were also observed as abnormal intrinsic dendritic events, when inhibitory postsynaptic potentials were suppressed [10]. The hypothesis that PDS is a giant excitatory postsynaptic potential (EPSP) [11] was confirmed by experimental verifications [12]. Scalp EEG recording of a focal interictal epileptiform spike or a sharp wave is thought to occur when PDSs are synchronized sufficient to spread over an area of 6 cm^2 of the cerebral cortex. The observed PDS raises several questions. What is the origin of the cellular mechanism that leads to the observed PDS? What possible mechanism can give rise to such a giant EPSP at the postsynaptic terminals (dendritic spines), has the propensity to propagate, and is also capable of reversing back after an interval of time? If they occur from dendritic events, then it is reasonable to expect an additional mechanism for the lateral spread of activity to the adjacent areas of the cortex.

1.3. Kindling and seizures

Hippocampal kindling is a commonly used model for human seizures in animals by inducing afterdischarges [13], which requires higher stimulation intensity than that is used for inducing LTP. In kindling models of epilepsy, kindling reduces the afterdischarge threshold for inducing a seizure [14]. In an experiment to study the difference in cellular changes between the repeated stimulations that induce LTP and afterdischarges, it was found that spatial memory errors were significantly higher in the ten afterdischarge-kindled group than in other groups after the first and fourth weeks [15]. This indicates that kindling results in cellular changes that are a direct accentuation of changes induced by LTP. This leads to the following questions. What type of a cellular change occurring during LTP can transition towards the kindling effects? Can such changes take place in an irreversible manner? Can such cellular changes explain the relationship between kindling and LTP?

1.4. Effect of repeated seizures

It was found that repeated stimulation lowers the threshold for more seizures to occur [16]. What cellular changes can occur in an additive fashion, most of which can be maintained stably, that lowers the seizure threshold for future stimulation events?

1.5. Cognitive impairment

Memory problems have been found even at the early stages of seizure disorders. Cognitive defects are reported in pediatric patients, even those with new-onset seizures [17]. Studies showing that cognitive–behavioral deficits can precede seizure onset [18] have raised the question of whether there is a bidirectional relationship between the cognitive deficits and seizures. In this context, questions were raised whether patients with cognitive impairment also have a higher risk of developing epilepsy [19]. How can cognitive impairment possibly relate to seizures? The question may be reframed as the following. What cellular changes induced by seizures can lead to an impaired internal sensation of retrieved memories?

1.6. Electrolyte changes

During seizure activity, it was found that the extracellular concentration of Ca^{2+} decreases and K^+ increases [20–22]. A simultaneous reduction in Ca^{2+} and an elevation in K^+ in the extracellular matrix (ECM) volume to the levels observed during seizure can prevent action potential propagation along the axons [23]. In spite of these ionic changes that are in favor of stopping the propagation of activity, seizure generation continues to takes place. Therefore, mechanisms other than synaptic transmission are expected for short-range synchronization [24]. What extrasynaptic mechanism can mediate seizure propagation?

1.7. Hyponatremia-induced complex seizures

When serum sodium drops below the concentration of 120 meq/L, the probability of triggering generalized seizures increases. What cellular mechanism can explain this? Since the generalized seizures occurring in this condition cannot be differentiated from primary generalized tonic–clonic seizures, examination of the role of hyponatremia may provide information regarding the cellular mechanisms leading to seizure generation.

1.8. Association with viral infections

Seizures are a common clinical feature of acute infections with herpes simplex virus and flaviviruses [25]. What cellular mechanism can be evoked by these viruses to induce seizures?

1.9. Ketogenic diet and seizure susceptibility

A ketogenic diet rich in lipids is used as a therapeutic method for treating seizures in pediatric patients [26,27]. Clinical, animal, and *in vitro* studies suggest that several long chain polyunsaturated fatty acids (LC-PUFAs) may be beneficial in reducing seizure susceptibility [28–33]. This indicates that lipid-driven molecular–cellular changes have a direct role in reversing the pathological changes that lead to seizures. How can a ketogenic diet contribute to a common mechanism that can also explain all the above findings?

1.10. Effect of anesthetic agents on seizure

In refractory and status epilepticus, anesthetic agents are used in controlling seizures. What possible cellular mechanism can lead to the stoppage of seizure when using anesthetic agents? Similarities in the loss of consciousness by complex seizures and anesthetic agents may provide a common mechanism from which the mechanism for seizure generation and propagation may be understood.

An examination of the events during seizure activity is carried out with the expectation that certain loss-of-function states of the normal operation will be able to explain all the diverse findings such as the initiation of seizure activity through PDS, a mechanism for the rapid lateral spread of activity that enables synchronized hyperexcitation across the