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A combined astrocyte – G-lymphatic model of epilepsy initiation, maintenance and termination

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ABSTRACT

Although epilepsy afflicts numerous people worldwide, its dynamics are still controversial. Especially seizure termination is relatively unidentified. Here we suggest a coherent explanation to all stages of epilepsy, its genesis, seizure initiation and termination. We present biophysical features that could account for the phenomenon: all phases of epilepsy can be related to the brain's "waste disposal" systems. Although problems in the astrocytic system have already been suggested as a major player in this malfunction, the termination phase is not really understood. Here it is assumed to arise from a G-lymphatic clearance system.

Our biophysical mechanism provides a coherent explanation of the phenomenon, offers support for the previously published mathematical model, and can shed light on the conflicting results encountered in norepinephrine measurements in epilepsy treatment.

Introduction

In a recent paper [1], a *mathematical* model of epilepsy based on five state variables was introduced and shown to depict seizure dynamics. The model treats the bifurcations and especially the separatrix (threshold) involved. We would like to consider a hypothetical biophysical mechanism, which could be accountable for such dynamics.

We assert that all stages of epilepsy can be explained by the accumulation of wastes in the brain fluid and their clearance or lack thereof by the two waste-disposal systems, the astrocytic and the G-lymphatic ones.

The brain includes two kinds of cells, neurons and Glia. The neurons, which are surrounded by a brain fluid (called interstitial fluid, ISF), perform brain functions that we are aware of, such as controlling movements, senses and feelings, learning, memory etc. The function of the Glia-cells is mainly to take care of the neurons, to provide them with nutrients, energy and other needed working substances, to regulate the environment of the neurons and to clear the wastes originated by them, sometimes replacing those by needed materials. One of the tasks of Glia, which is our main concern here, is waste disposal of the fluid surrounding the neurons. This task is carried out by a part of the Glia-cells called astrocytes. In addition to the astrocytic system of waste disposal, this task of ISF clearing is carried out by another mechanism, namely the G-lymphatic system (see below). Astrocytes clearing operates continuously, while clearing by the G-lymphatic system occurs mainly during sleep. We would like the reader to bear in mind that this function arises a short time after a subject started to sleep [2].

Neuron cells are composed of a basic unit, the cell body (soma), a set of incoming cables called dendrites and a cable or multiple cables (axons), carrying the information out of the neuron. Information passage within the cell is accomplished by electricity (action potential), while communication between cells is done by synapses. Chemical molecules passing between its two sides accomplish the synaptic communication. There are mainly two types of neurons, excitatory and inhibitory. The excitatory neurons use a substance called glutamate in their synapses to convey to the neurons on the other sides of these synapses, the directive to function. The inhibitory neurons use a substance called GABA in the synapses to deliver the command not to function. The receiving neuron, getting information by its dendrites from both types of sending neurons, decides to function if the difference between the instructions from the excitatory and the inhibitory neurons is higher than a certain level.

The astrocytes, residing in the glia surrounding the neurons, are the agents that maintain *constant* homeostasis in the brain [3] by absorbing molecules and ions emitted by the neurons during their operation, and specifically by enveloping neural synapses and up-taking excess substances transmitted between the pre and post synapses [4].

The general system that takes care of the waste disposal in almost

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the entire mammalian body is composed of an arrangement of combined lymphatic and blood vessels [5]. However, the brain does not have a lymphatic system and uses the lymphatics of the brain's cover (meninx) for this purpose [6]. This brain system, called the G-lymphatic system cleans the ISF in the brain from all excess molecules accumulated there. This task is fulfilled by exchanging the ISF with a flow of the so called Cerebrospinal fluid (CSF). In contrast to the astrocytic system, the G-lymphatic one operates mostly during *sleep* or under *anesthesia* (see Ref. [2]).

These dual waste-disposal systems are therefore responsible for the elimination of unwanted substances in the ISF. Two such materials, which are important to this work, are ions of Potassium (K^+) [7] and Glutamate [8].

K^+ is emitted by the axon in the regular process of its action potential transfer. And the axon reabsorbs these ions while repolarizing back to its quiescent state. K^+ concentration in the space outside the neurons, $[K^+]_o$, influences the threshold of the neuron to function (to yield action potential). If this concentration becomes too high, this threshold drops and it becomes much easier to invoke this function.

Glutamate (Glu) is the substance transferred in the synapses in order to excite receiving neurons into action. In a healthy brain performance, an excess of Glu reaching the ISF is absorbed by the astrocytes, which in turn convert it into Glutamine and send it back to the neurons. The latter can alter it back to Glutamate or to GABA and use it accordingly for exciting or inhibiting target neurons. If Glu concentration in the ISF becomes too high, there is an increase of excitability in the neural synapses [9].

Model and discussion

We adopt the claim that the proxy that could cause epileptic illness initiation is the impairment of either the K^+ [10] or the Glutamate [11] clearance by astrocytes at a certain brain part. Glutamate concentrations could thus increase in the ISF (see Fig. 1) up to 5 times the normal homeostatic one. The glutamatergic mechanisms of such an impairment are numerous (see e.g. Ref. [12] in which the implication to epilepsy is discussed). A high constant level of $[K^+]_o$ or of glutamate in the ISF leads, in fact, to low inhibition (similar either to a low percentage of inhibitory neurons or to the lowering the threshold of action potential activation). This situation of constant high concentrations is the marker of the interictal period of epilepsy. A seizure could develop above a certain K^+ or Glu concentrations, which could arise by an excessive casual local neuronal operation. Such a function releases additional amounts of these materials there. Note that, above such threshold (separatrix, see Ref. [1]), the process can become a positive-feedback one. Thus, ictal initiation, possibly by causing an enhancement of local neural functioning, increases in turn the emission of K^+ and Glutamate, whose excess leads to an increased excitatory behavior causing functioning enhancement, etc. The seizure intensifies (See increase of Glu concentration in Fig. 1) and can transfer to other brain parts.

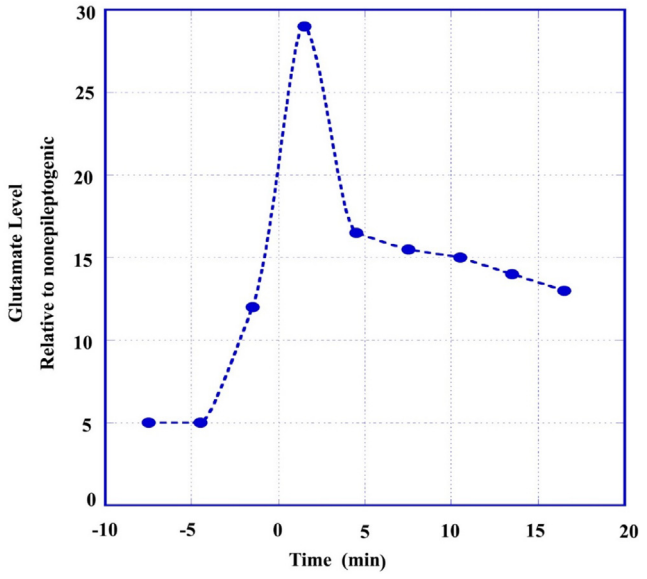

Fig. 1. (Adapted from Eid T et al., Glutamate and astrocytes-key players in human mesial temporal lobe epilepsy, Epilepsia 49 (Suppl. 2) 42–52, (2008)). Extracellular Glutamate concentration during all stages of an ictal. Glu levels-relative to non-epileptic state (where it is = 1). Time of seizure start: t = 0. Note that the Glu level measurement referred to is the only such thorough measurement carried out.

During a tonic-clonic ictal, the body stops functioning and the patient's behavior resembles sleep. We postulate that, under such circumstances, the brain, identifying sleep, is set into action causing *the G-lymphatic system to operate,* which clears the fluid and gets rid of the excess wastes. The process lasts several minutes into the ictal/sleeping mode (Ref. [2]), causing *seizure-termination*.

The ISF, cleaned by this CSF waste-disposal system, resets the brain to normal. The inter-ictal period starts. Since the basic impairment of the astrocytic system is not alleviated, disturbing substances begin to accumulate and the levels reach the “epileptic homeostatic” height. When these concentrations exceed the threshold, an additional seizure would occur.

Glutamate concentration changes during interictal, seizure and following seizure termination were measured [13] (see Fig. 1 and Note), showing indeed that the Glu level of an epilepsy patient is ~5 times higher than normal, it jumps to ~30 times higher than normal within the seizure itself and drops sharply at termination.

A major argument against the model of the ictal termination by the G-lymphatic system is that the duration of its nightly “cleaning” operation is lengthy, of the order of 30 min. to 1 h. (in mice) [14] and humans [15], while seizures usually last much shorter times (1–5 min.). The answer to this criticism can be: A. G-lymphatic clearance duration is not a constant. It crucially depends on body signals such as brain delta waves and heart rates, as measured [16] for different anesthesia substances, and B. terminating a seizure does not mean that the glutamate clearance is complete. A partial concentration decrease, which can also occur only at the specific location of the ictal-focus, can suffice to briing Glullug or K^+ concentrations below the threshold to maintain seizures.

Under this assumption, sleep deprivation should encourage seizures. This in fact is a well-known situation [17,18]. Children having epileptic seizures show less efficient sleep [19], but higher percentage of REM (rapid eye movement) sleep perhaps as a protective mechanism [20]. It also seems that inducing sleep in epilepsy-patients could help in preventing seizures.

In a very informative recent paper [21], the conflicting impacts of norepinephrine (NE) on epilepsy were reviewed and the influences of NE on several neural mechanisms were analyzed in order to try to resolve this discrepancy. NE is known to induce contradictory effects on epileptic seizures. On the one hand, pharmacological agents increasing NE levels have anticonvulsant effects [22–25]. In addition, NE concentrations are reduced following an ictal [26]. On the other hand, high levels of NE may increase the risk of seizures [27–29]. There are different attempts to explain such a behavior. We here would like to suggest an alternative view on this problem.

NE is possibly the most important substance controlling the sleep-wake cycle [30]. Its level is increased during waking hours and decreases during sleeping time. Let us assume that the brain “considers” epileptic seizure as a state of sleep of the body (SSB). This assumption alone can explain the conflict stated above:

1. In order to prevent seizures (SSB), the body should be kept in a waking mode hence NE administration will be advantageous in this respect.

2. In order to terminate a seizure, the brain, sensing an SSB, recruits a G-lymphatic clearance of the brain, as discussed above. This process gets rid of all substances in the ISF, which initiated the ictal. To impose a continuous SSB, the brain has to lower the NE level. Hence, its level drops following a seizure.
3. If the circadian mechanism finishes the body's waking period and "wants" to start an SSB mode, a high NE concentration would be decremental to this process and a resort to an SSB simulation, a seizure, could be invoked.

Summary

In summary, the waste disposal assumption can explain the whole sequence of epilepsy: the epileptic disease generation and the interictal high Glu (or K^+) level-by a damage to the astrocytic clearing [12], the ictogenesis [31,32] by a random surge of local neuronal activity and the seizure termination-by the G-lymphatic rinsing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109384.

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