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A hypothesis of series resonance in the white matter for understanding the mechanism of spike-wave seizures

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ABSTRACT

Generalized epilepsy is accompanied by large-amplitude synchronized spike-wave discharges on electroencephalography. The condition rapidly and synchronously involves most regions of the brain, but the mechanism underlying this global involvement remains unclear. Here I attempt to clarify this phenomenon by hypothesizing a series resonance in an equivalent electric circuit for the white matter. This hypothesis is based on the ideas that the electric conduction along an axon is due to the displacement current, and the unit structure composed of a node of Ranvier and the next node can be regarded as a capacitor or an inductor, depending on the geometry and the substance around the nodes. The flash-visual evoked potentials at various flash repetition rates were measured in generalized epilepsy patients, and compared with those for healthy controls and focal epilepsy patients. The P_{100} amplitude plotted against the flash repetition rate had a maximum peak at a certain flash repetition rate only for each of the generalized epilepsy patients. The observation of a peak in the P_{100} amplitude was inferred to reflect the series resonance phenomenon in the white matter. I speculate that patients with generalized epilepsy have large regions of white matter with similar resonance frequencies.

1. Introduction

What are the precise differences between focal epilepsy and generalized epilepsy? In the case of generalized epilepsy, it is considered that there is some epileptogenic focus in the centrencephalic system (or the brainstem and thalami, in the current nomenclature), as suggested by Penfield [1]. However, it remains uncertain whether this is a truly representative model for generalized epilepsy, or indeed, whether a focus such as a tumor or an infarction in the brainstem will induce generalized epilepsy, as the model predicts.

Animal models have provided evidence that absence seizures, which are one of the forms of generalized epilepsy, are initiated by a cortical focus with a secondary involvement of the thalamus [2,3]. Similar results have been observed in human patients with absence seizures [4]. However, if there is an onset focus in the cortex, how different is generalized epilepsy from secondary generalized focal epilepsy? Moreover, the onset focus of spike-wave discharges is likely to vary in the cortex [2–6].

Carbamazepine, which is recommended as the first-line medicine for focal epilepsy, can worsen seizures if it is given to patients with certain types of generalized epilepsy [7]. This suggests that there are essential differences between focal epilepsy and generalized epilepsy.

Generalized epilepsy is accompanied by large-amplitude synchronized spike-wave discharges on electroencephalography (EEG). A typical spike-wave discharge is a 2–5 Hz periodic wave complex which has much larger amplitude than that of the background activities. In the normal brain, the thalamus is believed to play the role of a pacemaker supplying the periodic wave on EEG [8–11].

Despite the prior efforts, it remains unknown how most parts of the brain are synchronously and rapidly involved in epileptic spike-wave discharges in patients with generalized epilepsy.

Here I present a hypothesis that may explain how spike-wave discharges occur. The essence of my proposal is that the large amplitude of spike-wave discharges in generalized epilepsy is based on the resonance phenomenon of the electric circuits in the white matter.

2. Theory

2.1. The mechanism of electric conduction along an axon

Hodgkin-Huxley's model can explain how an action potential occurs [12–14], but this model does not address the phenomenon of the signal propagation along the axon. That is, when the voltage-gated sodium channels on the axon membrane open, the sodium ions flow from the

Abbreviations: VEP, visual evoked potential; EEG, electroencephalography; CK, creatine kinase; AED, anti-epileptic drug; VNS, vagus nerve stimulation; VPA, sodium valproate; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; PB, phenobarbital; JS, Jeavons syndrome

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outside to the inside of the axon through the ion channels in the cell membrane. This brings about the action potential, but it does not necessarily mean that the signal is propagated along the axon by the charged particles.

Most of the pertinent textbooks describe that propagation of the action potential is caused by a "local circuit" of current flow from the depolarized areas of the membrane to the adjacent resting membrane areas [15,16]. Many researchers seem to believe that this current flow is carried by the positive ions. However, if this model is accurate, does the current flow carried by the positive ions initiate the action potential at the next node of Ranvier in the case of myelinated fibers?

Signal propagation in the brain system is an electric phenomenon. It thus seems useful to adapt the principles of electromagnetics to the signal conduction in the brain. Maxwell's equation (i.e., rot $\mathbf{H} = \mathbf{i} + \partial\mathbf{D}/\partial t$, where $\mathbf{H}$, $\mathbf{i}$, and $\mathbf{D}$ denote the magnetic field, the electric current carried by the charged particles, and the electric flux density, respectively) shows us that an electric current is not only transferred with such charged particles as electrons or ions ($\mathbf{i}$), but also with the time-derivative of the electric flux density ($\partial\mathbf{D}/\partial t$), which is called the displacement current [17].

In this investigation, I assume that the electric conduction along an axon is not mediated by $\mathbf{i}$, but by $\partial\mathbf{D}/\partial t$. With this assumption, it is easy to understand why the saltatory conduction is faster than the continuous conduction. This is because the conduction of $\partial\mathbf{D}/\partial t$ along an axon is much faster than the conduction of ions.

The electric current from a node of Ranvier to the next node can be compared to the current through a capacitor in an electric circuit. A capacitor has a structure consisting of an insulator between two electrodes (Fig. 1A, *left*). Only variable current can be conducted through a capacitor, because $\partial\mathbf{D}/\partial t$ is zero for constant current. Even if the upper electrode in Fig. 1A (*left*) is revolved to the position next to the lower electrode, it is still expected to work as a capacitor (Fig. 1A, *middle*). This structure is considered to be a depolarized node of Ranvier and the next node, although the displacement current $\partial\mathbf{D}/\partial t$ between the two nodes is conducted through the curved path in the insulator outside and even inside of the axon (Fig. 1A, *right*). When an action potential occurs at a node of Ranvier, the density of the sodium ions is decreased on the outside of the axon and increased on the inside. This density change makes $\partial\mathbf{D}/\partial t$ non-zero and enables the current to conduct to the next node of Ranvier. This displacement current opens the voltage-dependent sodium channels of the next node, and the depolarization process continues periodically with the periodic current supplied by the thalamus.

The "curved" capacitor is also regarded as an inductor, because the path for the current is curved and the paths outside and inside of the axon form a complete loop (Fig. 1A, *right*). Whether the unit structure is regarded as a capacitor or an inductor depends on the capacitance of the capacitor C and the self-inductance of the inductor L, and the angular frequency of the electric current ω, as follows.

Assuming the current is a sine wave; i.e.,

$$I = I_0 \sin \omega t,$$

the voltage for the capacitor V_C is expressed as

$$V_c = \frac{1}{C}\int Idt = -\frac{I_0}{\omega C}\cos \omega t,$$

and the voltage for the inductor V_L is expressed as

$$V_L = \mathrm{L}\frac{\mathrm{dI}}{\mathrm{dt}} = \omega \mathrm{L} I_0 \cos \omega t.$$

The unit structure is regarded as a capacitor, if

$$|V_L| < |V_C| \quad \text{i. e. ,} \quad \omega \mathrm{L} < \frac{1}{\omega C}.$$

And it is regarded as an inductor, if

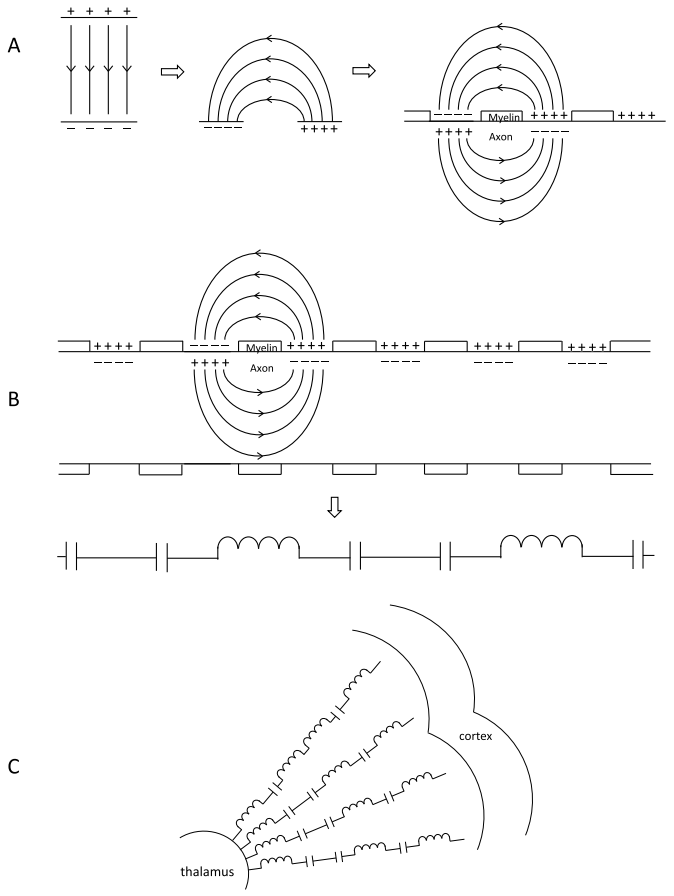

Fig. 1. Equivalent circuits for axons and the white matter. A: *Left*: A schematic of a capacitor. The upper horizontal line shows the positive electrode and the lower horizontal line shows the negative electrode. The vertical lines with arrows show the displacement current $\partial\mathbf{D}/\partial t$. *Middle*: The upper electrode of the *left* capacitor is revolved toward the right side of the lower electrode. The displacement current runs through the curved path. *Right:* A unit structure on a myelinated axon with the depolarized node of Ranvier at the left side. The displacement current through the curved path can be found not only outside but also inside the axon. This is also regarded as an inductor as well as a capacitor. **B:** A myelinated axon (*upper*) and its equivalent electric circuit (*lower*). Depolarization is found at the second-from-the-left-end node of Ranvier. **C:** A schematic of white matter with the thalamus and the cortex. Similar but slightly different equivalent electric circuits are found between the thalamus and the cortex in a certain brain area.

$$|V_L| > |V_C| \quad \text{i. e. ,} \quad \omega \mathrm{L} > \frac{1}{\omega C}.$$

The magnitude of C or L is determined by aspects of the geometry and the substantial characteristics around the nodes—specifically, the geometrical relation between the two adjacent nodes as well as the dielectric constant and the magnetic permeability in the extracellular and cytoplasmic sides of the nodes.

The behavior of a capacitor and that of an inductor for the alternative (variable) current are known to be opposite in a sense. That is, the phase of voltage is retarded compared to that of the current by $\pi/2$ for a capacitor and advanced by $\pi/2$ for an inductor, because $(-\cos \omega t)$ is retarded by $\pi/2$ compared to $(\sin \omega t)$, and $(\cos \omega t)$ is advanced by $\pi/2$ compared to $(\sin \omega t)$. In other words, the unit structure with the nearest two nodes can be regarded as a capacitor when the voltage phase is retarded, and it can be regarded as an inductor when the voltage phase is advanced.

An axon has many nodes of Ranvier, each of which plays the role of an electrode. Therefore an axon can be equivalent to an electric circuit with many capacitors and inductors chained in a serial manner (Fig. 1B). In this article, I call this hypothesis the "displacement current model".